## TABLE OF CONTENTS

## DAY TWO AFTERNOON SESSIONS

Friday, February 9, 2018

### Session 2F
### *Examples of Medical Success*

Moderator**: Brian Cordery**, Bristows LLP, London
Presenters:
**François Houÿez**, Director of Treatment Information and Access, Policy Advisor, EURORDIS, Paris
**Prof. Michelle Petri**, Director, Hopkins Lupus Cohort, Baltimore
Panelist**:**
**Dr. Bruce Bloom**, CEO, Cures Within Reach, Chicago

### Session 2G
### *Should the U.S. System be Changed?*

Moderator**: Paul Ainsworth**, Sterne, Kessler, Goldstein & Fox PLLC, Washington, D.C.
Presenter**:**
**Prof. Erika Lietzan**, University of Missouri Law, Columbia
Panelists**:**
**Dr. Hans Sauer**, Vice President for Intellectual Property, Biotechnology Innovation Organization, Washington, D.C.
**Kurt Karst**, Director, Hyman, Phelps & McNamara PC, Washington, D.C.
**Brian Hirsch**, Vice President, Global IP and Legal Head North America, Glenmark Pharmaceuticals, New York
**Dolly Judge**, Vice President of Government Affairs, Teva Pharmaceuticals, McLean

### Session 2H
### *The Impact of Technology and Large Databases on the Development of New Medicines from Existing Drugs*

Moderator**: Dr. Felix Frueh**, OpusThree, San Diego
Panelists**:**
**Dr. C. Anthony Altar**, Chief Scientific Officer and Senior Vice-President, Verge Genomics, Inc., San Francisco
**Dr. Iris Grossman**, VP, Head of Earl Stage Development, Global R&D, Teva Pharmaceuticals, Petah Tikva

## Session 2I:
## *Judges' Panel*

Moderator**: Karl-Heinz Metten**, Boehmert & Boehmert, Frankfurt am Main
Panelists**:**
**The Hon. Arthur Gajarsa**, Former Judge of the Court of Appeals for the Federal Circuit, Washington D.C.
**The Hon. Roger T. Hughes QC**, Former Judge of the Federal Court of Canada
**Prof. Robin Jacob**, University College London
**Judge Rian Kalden**, Senior Judge, Court of Appeal, The Hague

## Closing Remarks

**Prof. Robin Jacob**, University College London

# University College London | Georgetown University Law Center

# CLINICAL INNOVATION:
# Fair and Effective Incentives for New Uses of Established Drugs

*Georgetown University Law Center*
*600 New Jersey Avenue NW*
*Gewirz Student Center*
*Washington, D.C.*
*Friday, February 9, 2018 – 1:30 p.m.*

## Session 2F:
## Examples of Medical Success

***Moderator:***
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***Presenters***
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*CEO, Cures Within Reach, Chicago*

* * *

MR. CORDERY: Welcome to the first session of this afternoon, Examples of Clinical Success.

Before we get going with this session, I just want to make two very small comments, one from my experience as a UK citizen — which I wish I wasn't, but I am — and one from being a UK lawyer.

My experience as a UK citizen concerns our mainstream press, the *Daily Mail*, *Daily Mirror*, *Sun* sort of newspapers. Most of the time they are announcing secret plans to derail Brexit on the part of the liberal lefties; but when they are not doing that, almost every month the papers announce a headline "Statins to Treat Alzheimer's," "Beta-Blockers to Treat Cancer." They really publish a lot of that. But then, one or two days later, the same journalist will

express outrage when the same drug is priced higher for the new indication. This is something that Bob Armitage alluded to early on, and it really chimed with me. I think there is a "hearts and minds" job to be done, at least in the United Kingdom. I do not know if it is reflected across the rest of Europe and the world.

My experience as a lawyer is that I have been very lucky to be involved in several second medical use projects, and I have spoken to physicians who have told me stories of patients whose quality of life, even duration of life, have been enhanced by new uses. I think there are stories to be told, and if these stories were told, hearts and minds would be won over, perhaps even *The Daily Mail*. I don't know.

This session is all about clinical success.

With that very short introduction, the only person I need to introduce is Michelle because she has not been on a panel previously.

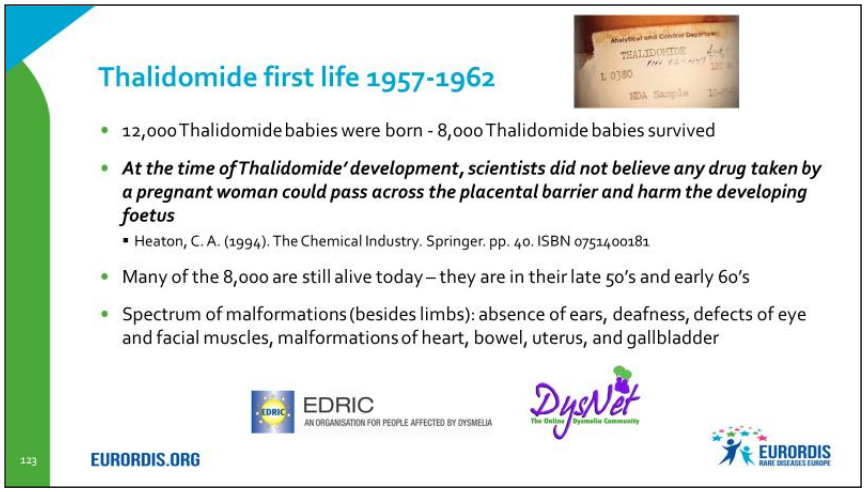
Michelle, welcome to the conference, first of all.

PROF. PETRI: Thank you.

MR. CORDERY: I understand that you are a Professor of Medicine at Johns Hopkins University, which is quite near here. You are focused, among other things, on lupus disease.

If you would like to begin, François, that would be great.

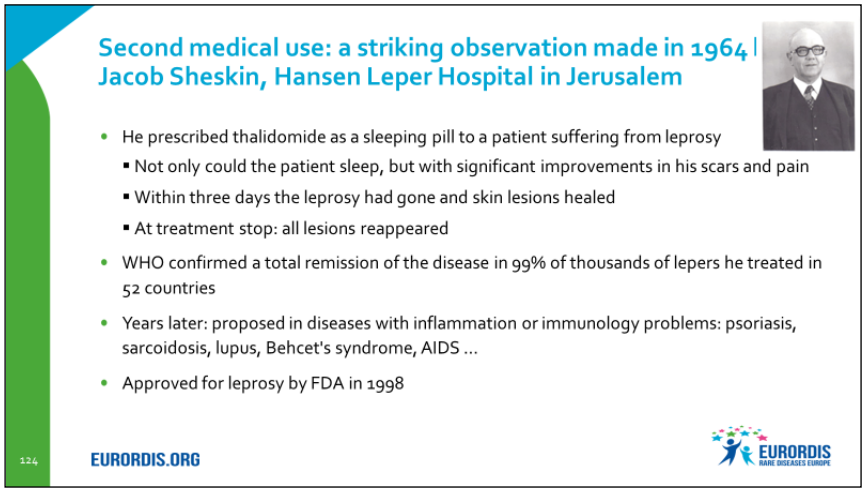
MR. HOUŸEZ: Good afternoon again. I would like to tell you the story of the reintroduction of thalidomide in Europe, particularly highlighting the role of patients and victims of thalidomide that made this return possible.




As you all know, thalidomide was first authorized in the late 1950s as a pill to induce sleep. At that time, science ignored the fact that pharmaceuticals could pass across the placental barrier. Some 12,000 babies were born that had been exposed to thalidomide, of whom 8000 survived.

You must realize that, even if the product was withdrawn from the market in 1962, these 8000 people who survived now are in their fifties and sixties and they have medical conditions that nobody knew before and they need extra attention. The catastrophe linked to thalidomide is not completely over for them. They suffer from all kinds of other conditions, like malformations of heart.

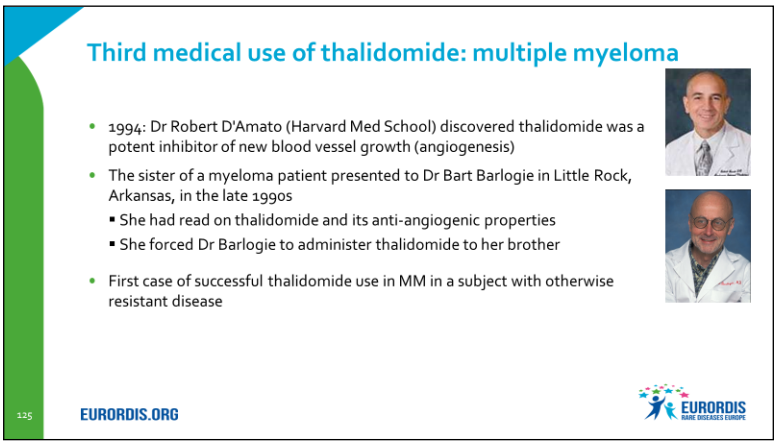
In Europe, there are only three specialized centers that know how to treat these patients: one in Sweden, one in the United Kingdom, and one in Germany. These patients have to organize themselves to help other patients to travel to these countries to receive the care they need.



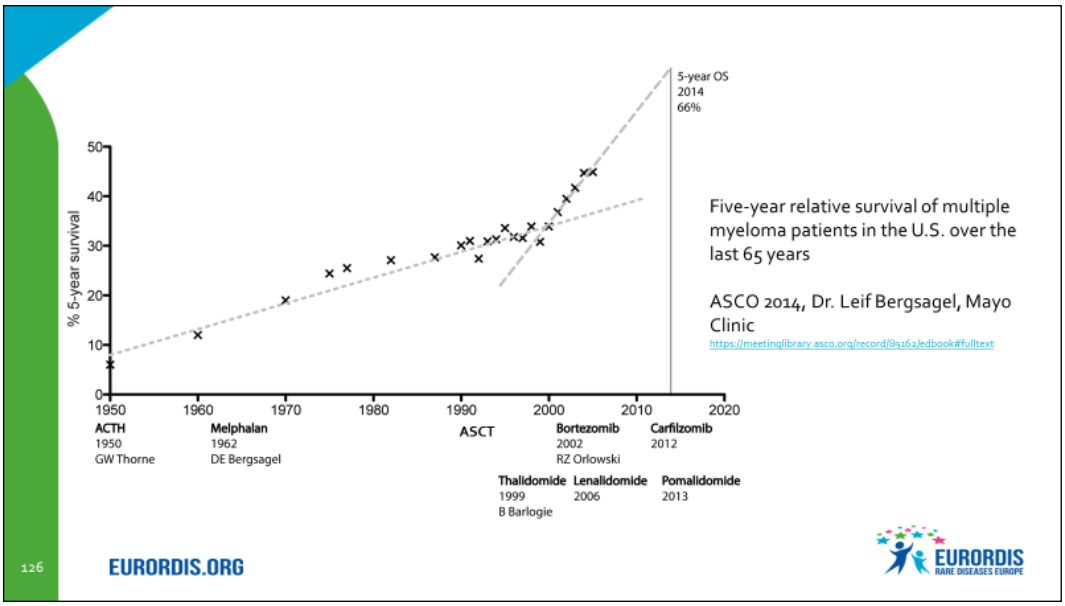

Shortly after the thalidomide catastrophe, because there were some boxes and packages of thalidomide still in some pharmacies, there was this observation by Dr. Sheskin in Israel, who prescribed thalidomide as really a last-resort product for a patient who had leprosy and who could not sleep because of pain. The next day, not only could the patient sleep for the first time in many days, but there were significant clinical improvements of his scars and pain. Within three days all lesions were gone, and when he stopped treatment, because that was the only box the doctor had left, the lesions reappeared. Then clinical research started in many different countries which confirmed the high efficacy of thalidomide to treat leprosy.

Years later, this property of thalidomide to treat leprosy was explored for many different inflammatory conditions and immunological problems, even for AIDS patients with severe arthrosis, and it was used under its marketing authorization — for example, in France in a large compassionate use program where patients with AIDS could access thalidomide to treat arthrosis.

It was approved by FDA in 1998 to treat leprosy. That was the first second medical use for thalidomide.



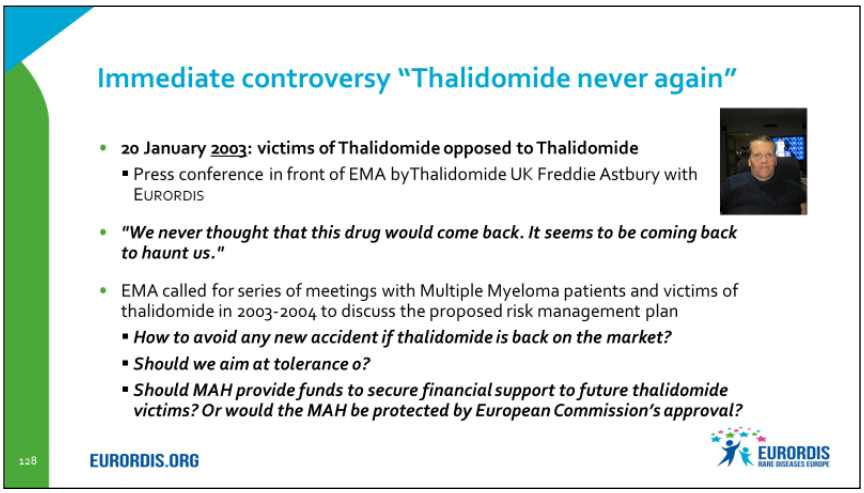
A third use of thalidomide was proposed following, first, research by Dr. D'Amato, who discovered that thalidomide was a very potent antiangiogenetic product. Then, the sister of a patient with resistant refractory multiple myeloma visited Dr. Barlogie and requested him to prescribe thalidomide to her brother because she had read about the antiangiogenetic properties of the product. He first did not want to use it because he did not see the relation between multiple myeloma and antiangiogenesis, but then he did. That was, in fact, the first case of successful thalidomide treatment to treat multiple myeloma.




On this slide you see the great improvement in relative survival of patients with multiple myeloma over several decades with, first, ACTH and Melphalan, with a slight increase; and then, later, with autologous stem cell transplantation.

But it was really thalidomide becoming largely prescribed in multiple myeloma that led to following products like lenalidomide, which is thalidomide repurposed. Lenalidomide has a similar structure to thalidomide, with the same typhogenic properties, developed by the same company, but adapted, so it is repurposed. You see that by 2014 the five-year relative survival is about 66 percent, much higher than it was in the 1950s.

How did this happen? The history is that in 2001 five entities in Europe had obtained an orphan drug designation for thalidomide and were considering applying for a marketing authorization: in France the company that was providing the product for compassionate use for AIDS aphtosis was Laphal; and then the Pharmacie Centrale des Hôspitaux, which is a hospital pharmacy dispensing and manufacturing products for hospitals; Kendle International Ltd., a UK consultant company; Chemie Grünenthal in Germany, the originator manufacturer of the product; and Pharmion, a U.S. company also obtained orphan drug designation. Two companies submitted marketing authorization applications in 2002, Pharmion and Laphal, which was then acquired by Pharmion.




Then, immediately, the victims were shocked when the news was announced that there was this marketing authorization application for a product they never thought could be considered again for market authorization. Thalidomide UK immediately organized a press conference in front of the European Medicines Agency (EMA) in London.

EURORDIS was there because we wanted to understand their concerns. Their comments were everywhere in the press, not only in the United Kingdom but in Europe, because they thought it was really an offense to what had been living with.

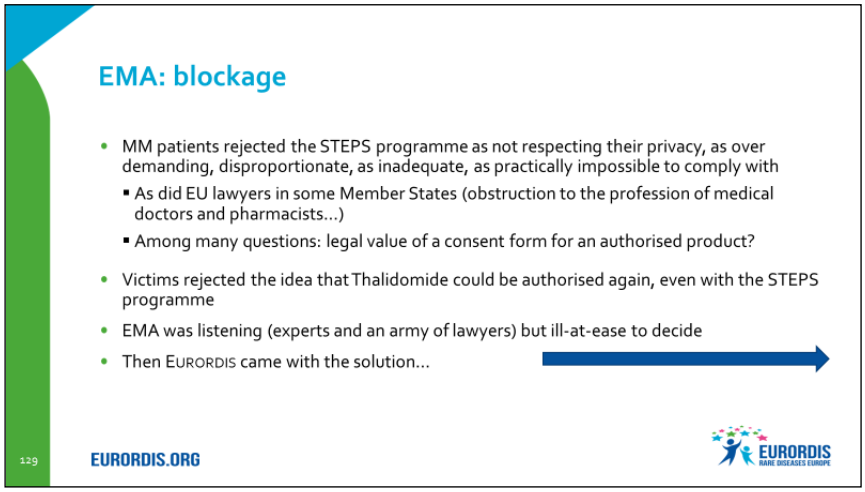
The EMA was very smart. The EMA organized meetings with patients with multiple myeloma and the victims to discuss under which conditions both parties could agree on how to safely introduce thalidomide on the market again. These were the three main questions:

• How to avoid any new baby would be born with abnormalities;

• Should we aim at tolerance zero, and how to reach that level;

• And, in case new babies would be born with abnormalities again, who would be responsible to support them financially? Should the manufacturer, even if there is no defect in the product, bear the responsibility for that, or should it be the European Commission and EMA for authorizing that product knowing the potential problems it could cause?

You understand from these questions how important it was to also have lawyers consulted in these meetings.

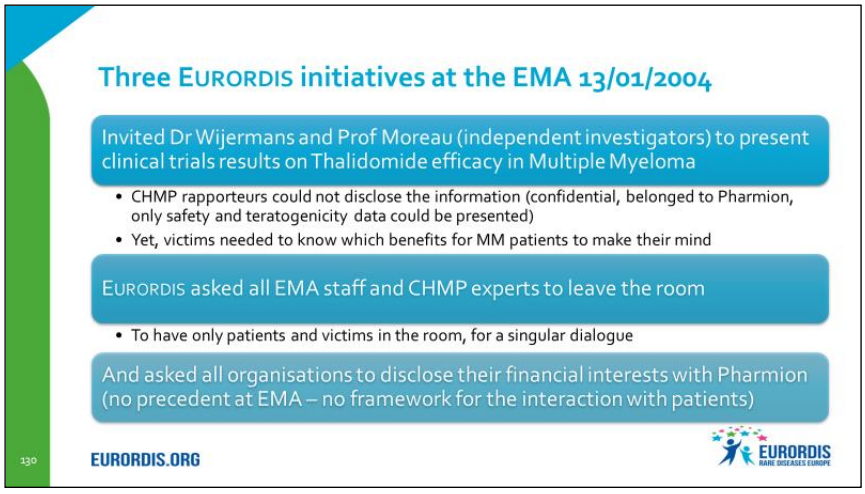



But there was a blockage. The situation was completely put on hold because the company came with a risk management program developed by Celgene in the United States which was impossible to implement in Europe. For example, a person with multiple myeloma — it did not matter how old you were; even at seventy — still had to call a computerized system every month and report their sexual activity during that month. If the computer detected a risk that a pregnancy could have started, your pharmacist would not receive the thalidomide package you would need for the next month.

That was one of the many measures that was imposed by the System for Thalidomide Education and Prescribing Safety (S.T.E.P.S.™) program that the patients completely rejected. It was not practical. It could not be implemented this way.

But the victims of thalidomide said we needed to impose very strict measures — "and even with very strict measures we do not trust the system" — that could guarantee no baby could be born with abnormalities.

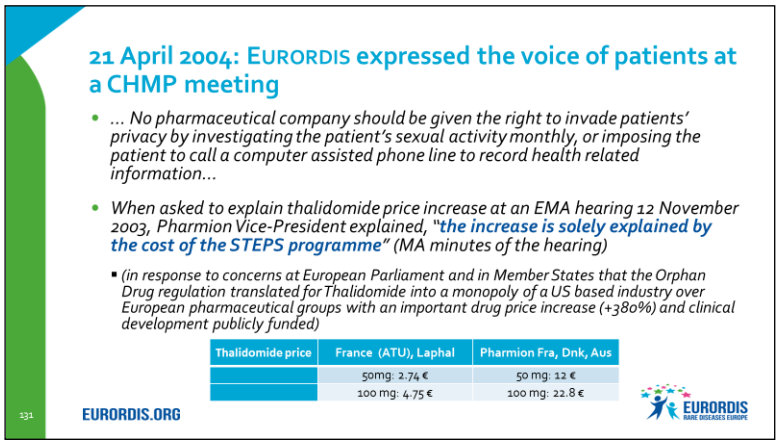
This was the situation, and we had different meetings with the same status quo.



At the end of the day, in January 2004, we invited independent investigators, who were not bound by confidentiality as the EMA experts were, to explain the results of their studies. One particular characteristic of this dialogue is that the EMA experts were not authorized to tell us anything about the benefit of the product, because the company only had lifted part of the confidentiality, only on the safety but not on the benefits. Therefore, you can understand that it was not possible for the victims to understand for which reason thalidomide could come back on the market if it was impossible to explain to them the efficacy of thalidomide for multiple myeloma.

Also, we asked all EMA staff and all EMA lawyers — I must say I have never seen as many lawyers from the EMA in a meeting, apart from this space — to leave us for two hours to talk behind closed doors. That is what we did. We started from a blank page and we wrote together a risk management plan and a pregnancy prevention program that could please both the multiple myeloma patients and the victims. And it worked. At the end of the two hours, we had a common position agreed to by all.

I think it is extremely important to have face-to-face meetings because the patients could explain to the victims: "You see, we have this product Now you know the potential efficacy. It can prolong our lives by two to three years or even more. We understand your concerns, but maybe we can work together and find a way to make it happen." For the victims it changed. It moved from an abstract disease in people with multiple myeloma that they did not know to these five or six patients in front of them asking them, "Can we maybe work together and find a solution?"




Then we expressed the voice of patients at the Committee for Medicinal Products for Human Use (CHMP) meeting, explaining why we were rejecting completely the S.T.E.P.S.™ program.

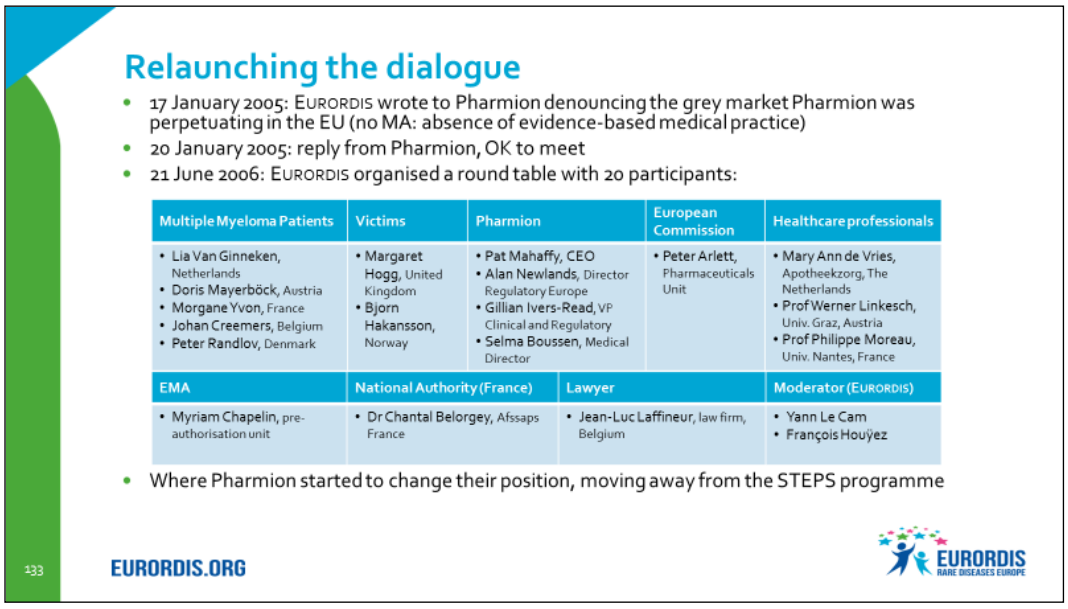
That is an add-on to this topic. It is about the price. During one of the meetings, we invited also the company to explain the price difference between the price proposed by the U.S.-based company compared to the price of thalidomide available through different pathways, like the Laphal company in Europe. There was a fourfold-to-sevenfold price increase, which I will say the company thoroughly explained was the cost of the S.T.E.P.S.™ program. So once you

reject the S.T.E.P.S.™ program, you reject the explanation why the price was increased.

We passed that information on to payors after the marketing authorization, telling them, "Do not accept the price increase because it is no longer justified."

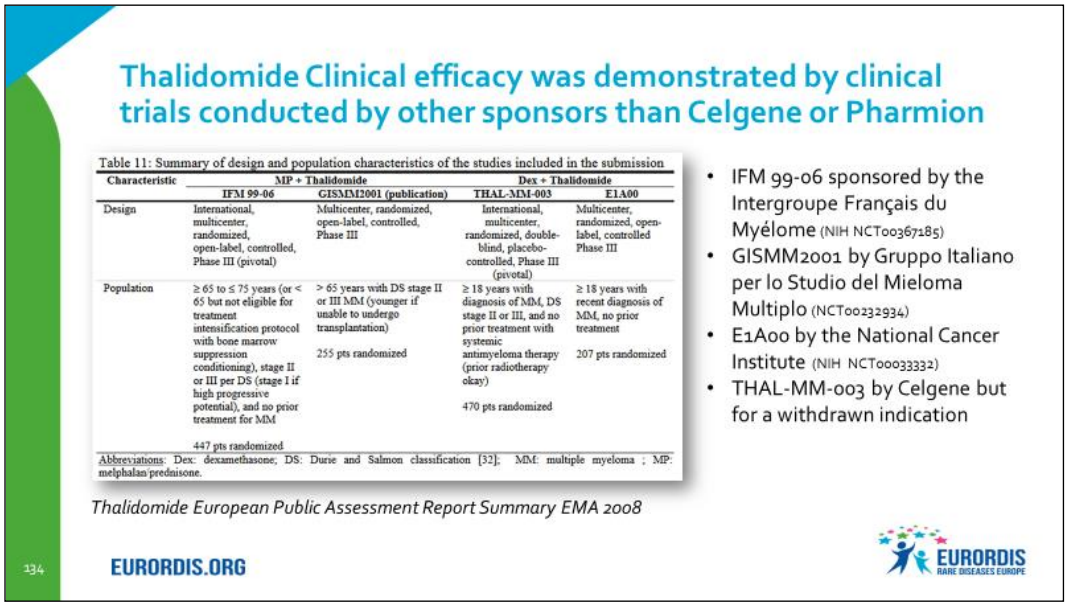
The only response we got from the payors was to the patients' organizations that contacted them: "Well, you know, this is none of your business. Let us negotiate the price and let us do our work," which we found was a missed opportunity because patient organizations rarely advocate for price reductions, but in that case I think they had a good case to use with the payors.


Then, because the S.T.E.P.S.™ program was rejected, Pharmion withdrew the marketing authorization application because they had a contract agreement with Celgene under which Celgene would not authorize Pharmion to market thalidomide if the S.T.E.P.S.™ program could not be implemented. We discussed this with Pharmion at the General Assembly with our members in Cork, but nothing really came out of this.

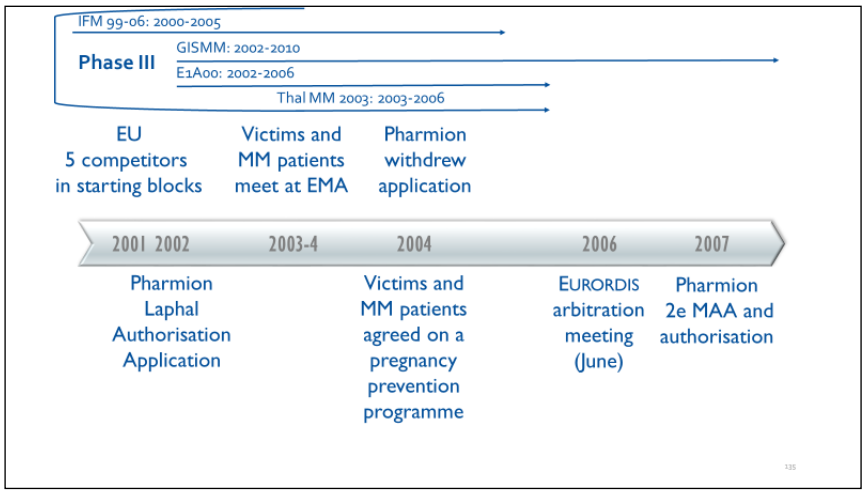


Finally, in January 2005, we insisted that Pharmion restart the dialogue. It was only one year later that we could organize a meeting, the kind of meeting that cannot happen anymore, but it was extremely important. All parties were invited, even the lawyers. So we had victims, patients, the company, the European Commission, the EMA, national agencies, and healthcare professionals.

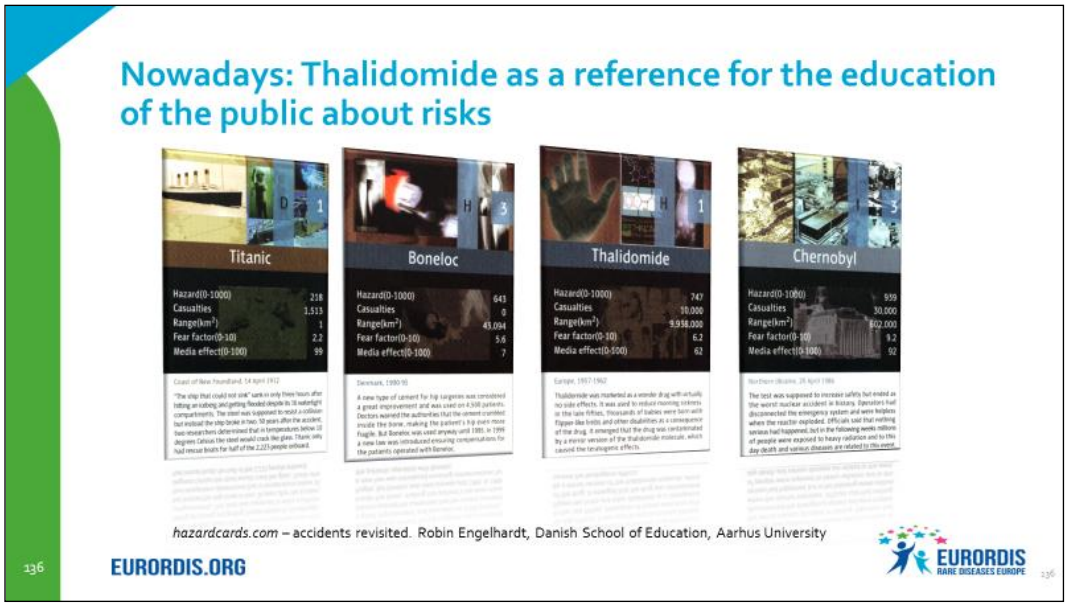
At the end of the day, Pharmion agreed to abandon the S.T.E.P.S.™ program, agreed to file a marketing authorization application using the pregnancy prevention program as agreed by the patients and the victims, and said that they would stop the agreement with Celgene or amend it, but they said they were confident that Celgene would accept it.



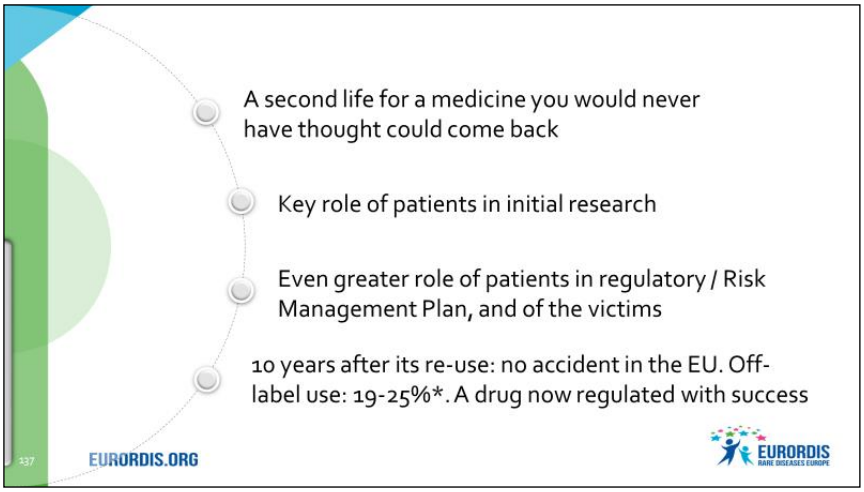

Of note, the clinical studies considered for the marketing authorization applications were not conducted by Pharmion or Celgene. They were driven by independent investigators, one from the Intergroupe Francophone du Myélome (IFM), one from an Italian independent network of investigators, and one from the National Cancer Institute (NCI) in the United States, and only a supportive study was submitted by the company.



To sum up, we had first five competitors in starting blocks and then we had two that submitted a marketing authorization. We had the meetings with victims and patients at EMA, who agreed on the program to prevent pregnancies in 2004; that is when the company withdrew the application. Then we had the arbitration meeting; and then again the company filed for a new application once they had the okay from Celgene to proceed with the marketing authorization.




Nowadays the thalidomide case is part of many educational tools to educate the public about the concepts of risks and benefits. Just as an example here, hazard cards were developed by a university in Denmark that explain the different risks related to human activities, explaining the human factor, the fear factor, and the media effect. I think thalidomide is still a very educative example of something that can be regulated.



To conclude, it is a second life for a product you would never have thought could come back, with the key role of patients initiating the research with Dr. Barlogie, and most of the initial research was funded by the International Myeloma Foundation created by patients and their families. There was an even greater role of patients and victims at the time of the regulatory activities, defining together how they would regulate, or at least define, the pregnancy prevention program.

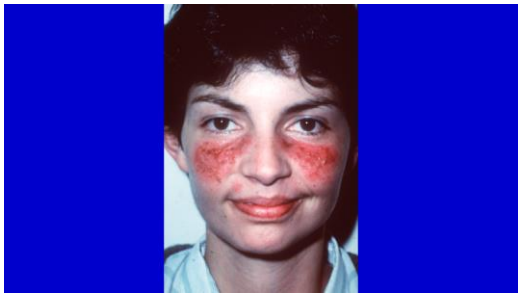
The lesson is that ten years after its reuse no baby has ever been born in the European Union with abnormalities. Off-label use is still frequent. All these other inflammatory diseases are treated with thalidomide. In terms of patients, it is 19−25 percent, but in terms of total patient exposure, because it is for short periods, it is no more than 4 percent of the market. Reimbursement agencies or healthcare systems can live with an additional 4 percent off-label use that is fully reimbursed. It does not represent such a big impact on their budgets. So this is now a drug regulated with success.

Thank you.

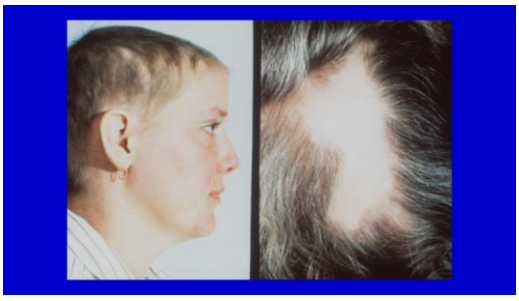
MR. CORDERY: I think that was a fascinating story. You read about it, the terrible events that happened and how it has been resolved. I think it is fantastic.

We will move on now to Michelle.

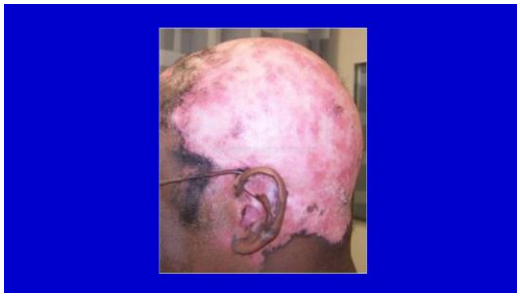
PROF. PETRI: Thank you very much for inviting me. You have heard I am the "lupus lady from Baltimore," and I am actually happy to be in a room full of lawyers. This will never happen to me again!



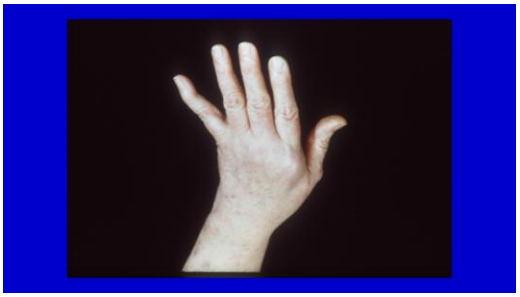
I want to draw your attention to why we should all care about lupus, not just me. This is called the "butterfly rash," but butterflies are beautiful. Lupus rashes are not.



Lupus patients have such fragile hair that they end up looking like chemo victims. Can you imagine looking like this? This is the worst lupus rash. It is called discoid lupus.



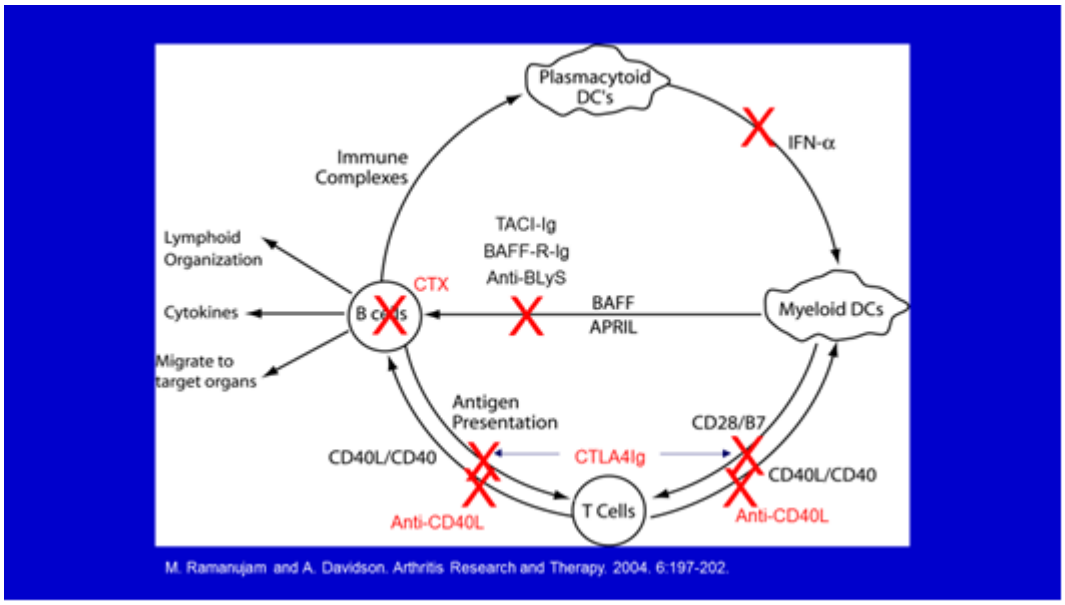
This woman will have to wear a wig the rest of her life, but she will have these same disfiguring lesions on her face and her arms. One of my patients was hounded out of her housing development because her neighbors thought that she had leprosy.



There is this terrible deforming arthritis as well. Those are the visible manifestations.

It turns out that 50 percent of Caucasians with lupus and 75 percent of African Americans develop lupus kidney disease; and, if they develop it as one of their presenting signs of lupus, over 25 percent will go into endstage renal failure. Please remember these are people in their twenties. For lupus patients who live beyond their twenties, one out of six will be dead by the age of thirty-six.

So this is a disease with many unmet needs.

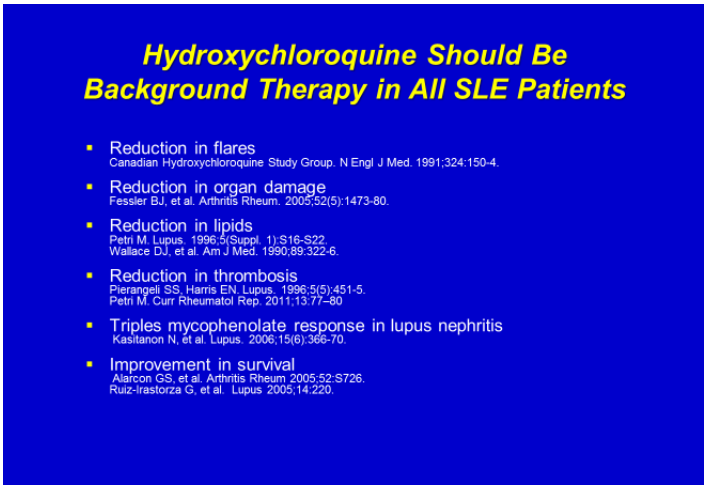



Now don't panic. This is immunology. It is confusing even for physicians. This is to show you that there are many different pathways that contribute to the activity of lupus. No one of these pathways is universally the issue in an individual lupus patient.

You can think of this as an example of a disease with multiple opportunities. But, very much as in cancer — we do not treat lung cancer anymore; we treat the pathway that is active in the lung cancer — that is what is going to happen in rheumatology, and particularly in lupus.

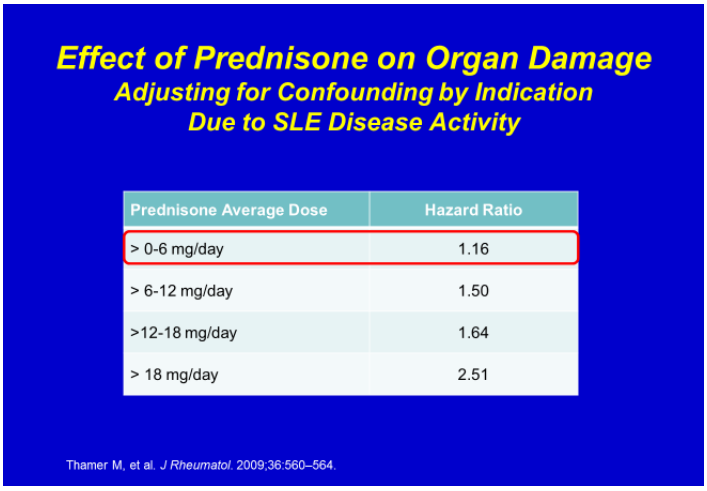
What are our current treatment approaches?

Our very first treatment was an accident. It happened during World War II. The soldiers and sailors who were serving in the Pacific were given an antimalarial called chloroquine. Some of these soldiers and sailors had lupus or rheumatoid arthritis and their disease was getting better on the antimalarial. They came back to the States after the war and they begged their doctors to keep prescribing the antimalarial.




The antimalarials are still used. They are part of our standard of care. They are FDA-approved, and we are into the seventieth year of using them.

Why? The current antimalarial hydroxychloroquine helps the skin and joint manifestations that you saw on those slides. They also prevent the renal disease, and they are the only drugs that we currently use for lupus that have been demonstrated to improve survival.

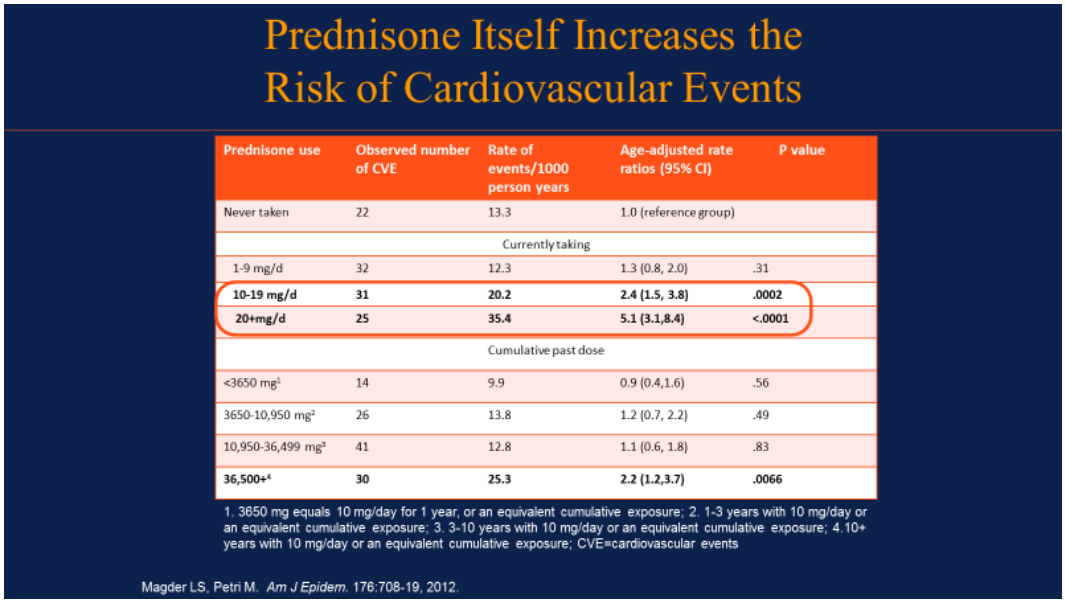



The second treatment was "borrowed" from rheumatoid arthritis. It is cortisone or the current version, which is prednisone. It led to a Nobel Prize for Dr. Hench, the doctor at the Mayo Clinic who developed it.

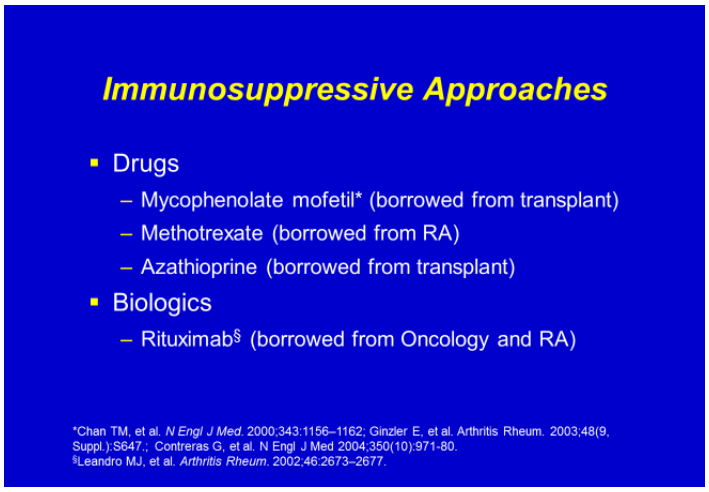
But it is the treatment that we currently hate. When I lecture to primary care doctors, I tell them "the P in prednisone stands for poison" to try to stop them from using it, because in lupus 80 percent of the permanent organ damage is from prednisone, not lupus.

If anything more than a minuscule dose of prednisone is used, there is over a 50 percent increase in permanent organ damage. And, if the prednisone dose is 10 mg, which is considered low-dose, there is a 2.4-fold increase in cardiovascular events, which turn out to be the major cause of death in lupus.

Can you imagine how schizophrenic this is? One of the major therapies is leading to many of the bad outcomes.



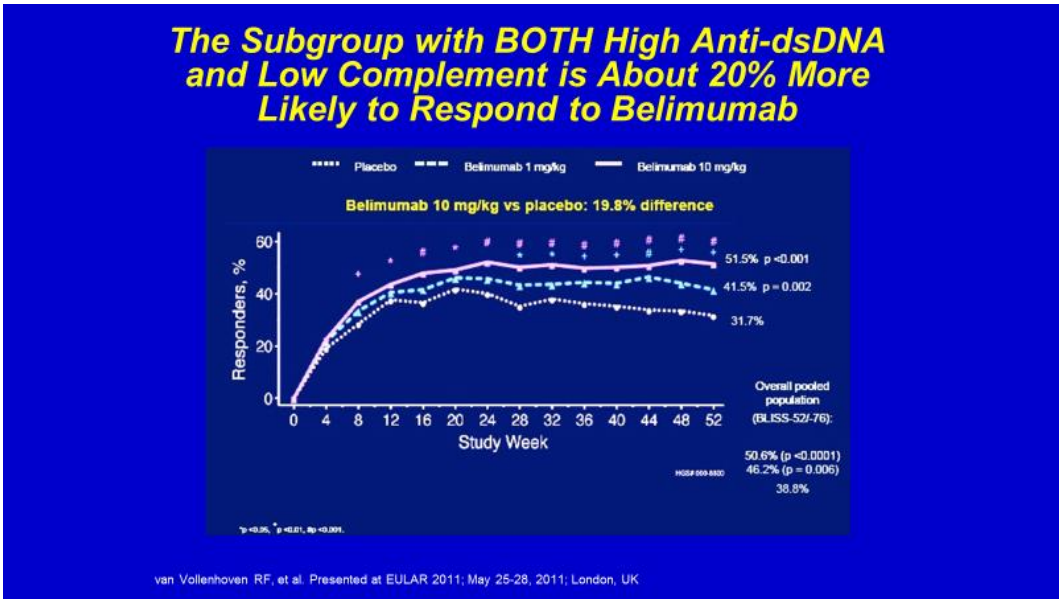

The next treatments were all borrowed, and they were borrowed so that we could limit how much prednisone we use to treat lupus.



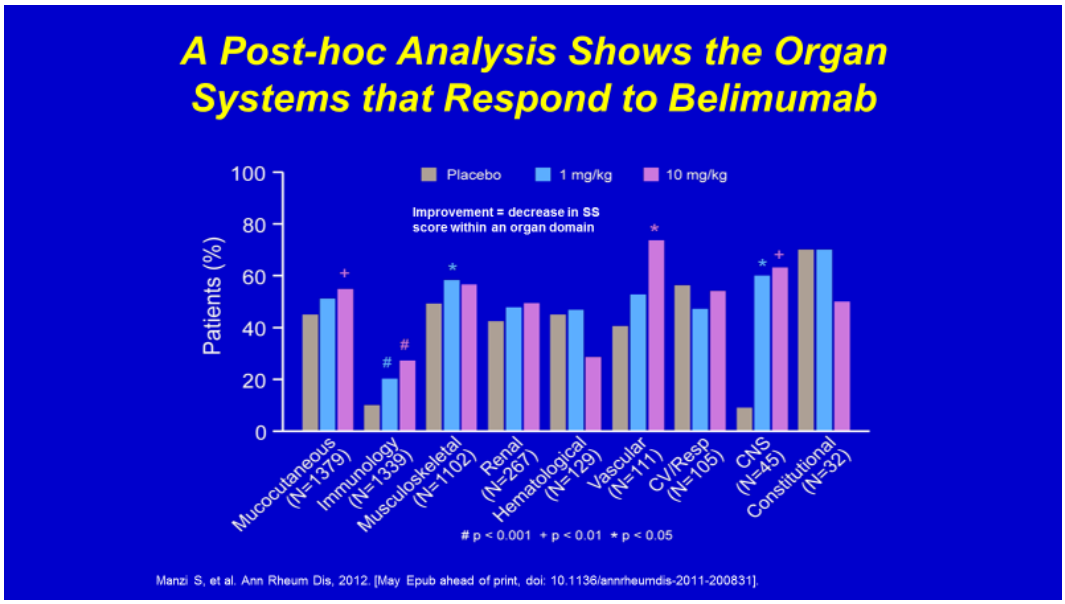

The first three were borrowed not using any rocket science. These are general immunosuppressive drugs, so they will work for any autoimmune disease. None of these are FDA-approved, and all of them come with a lot of baggage, because if you suppress the entire immune system, you increase infections, you increase cancer, and it turns out the second leading cause of death in people with lupus is infection.

The last one on this list, rituximab, is also not FDA-approved, but it is a targeted therapy. It only targets the B cells which make the lupus antibodies. Everyone thinks targeted therapies are smart. They are not necessarily that smart. Rituximab hits all the B cells, so of course it ends up increasing infection.

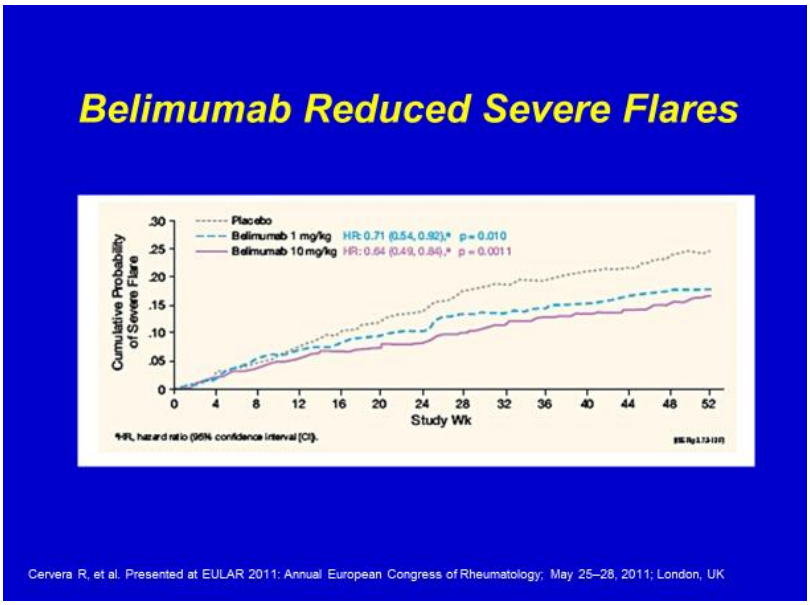
Here I am, the chief of the Lupus Center at Johns Hopkins, and if I want rituximab for a lupus patient, how often would you guess I am successful in getting insurance approval? Fifty percent in a good week. But if I were in Europe, I would be able to get it without question. So it just shows you the lack of uniformity for the exact same product.



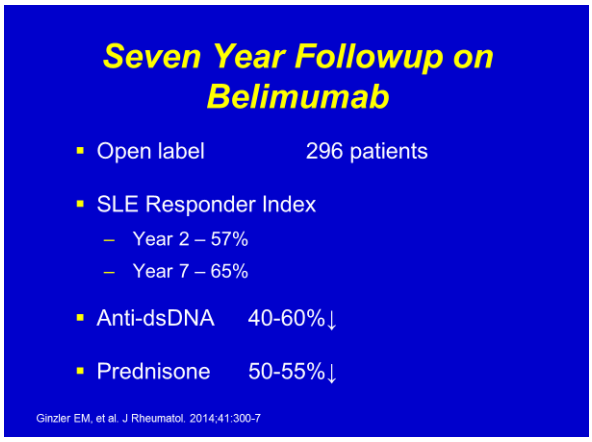

Finally, we have a designer treatment for lupus! This came from the recognition that there was a protein called B lymphocytic stimulator (BLyS) or B-cell activating factor (BAFF) that was necessary for autoimmune B cells to make lupus antibodies. A company developed a monoclonal antibody that could attack this protein. It is called belimumab; Benlysta is its brand name.




It does not work for everybody with lupus. That is not a surprise to me, but it was a disappointment. But in people who have some markers, there could be a 20 percent delta over standard of care.

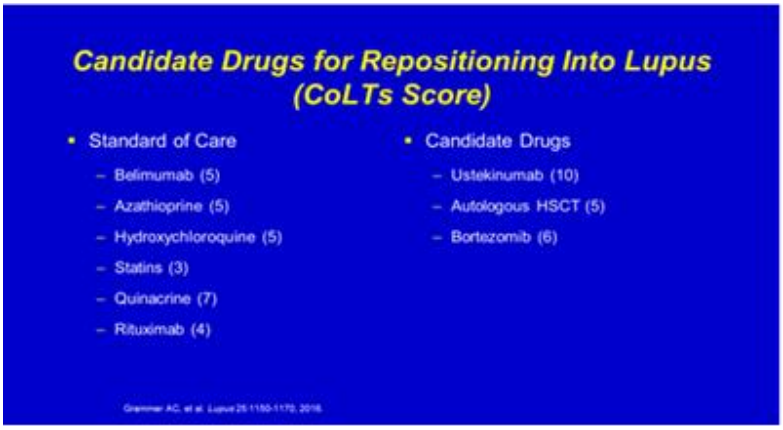



It does work for skin and joints, and it does reduce flares of lupus.



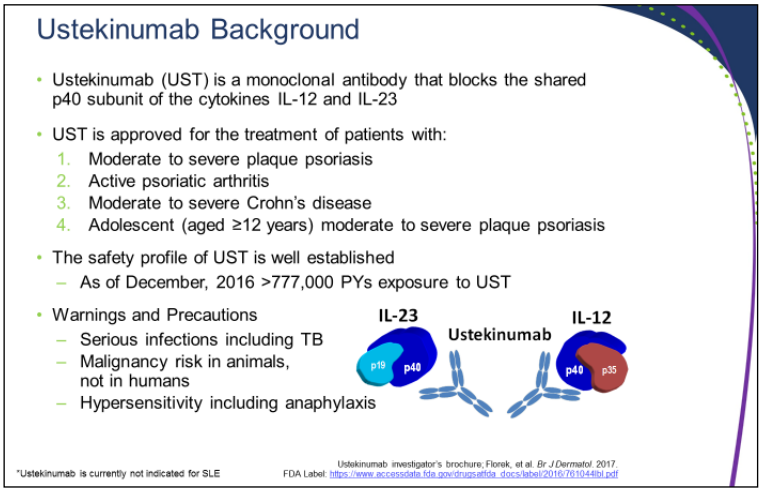

It is well tolerated over many years, with maybe a minuscule infection signal and a minuscule malignancy signal — nothing nearly as scary as the other drugs we have been using. But remember, it is only helping a subset.

What is happening that I think is very exciting is that there is now a scientific approach to drug repositioning specifically for lupus. This started out with a company run by Peter Lipsky, who used to be a rheumatologist at the National Institutes of Health. Using first literature mining and crowdsourcing and then adding gene expression data to get those pathways, they reviewed hundreds of potential new drugs for lupus.



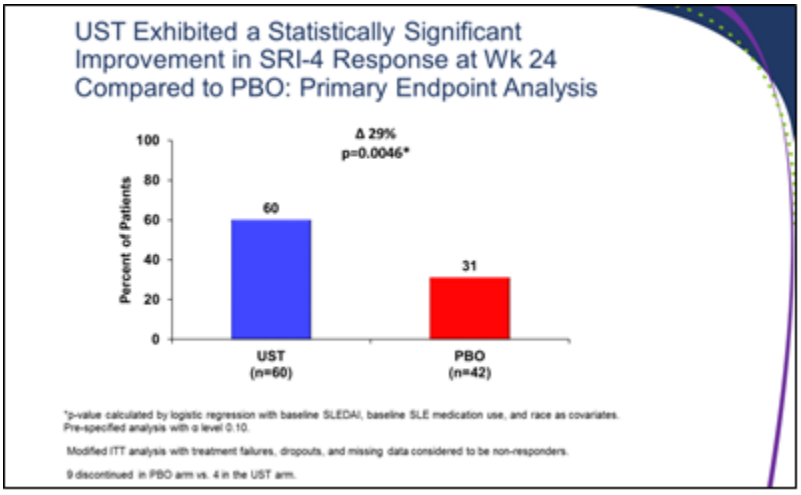

They came up with the Candidate Drugs for Repositioning into Lupus (CoLT) score. I want you see some of the ones we have already discussed: belimumab/ Benlysta got a 5; azathioprine, one of those general immunosuppressive drugs, got a 5; hydroxychloroquine, the antimalarial, got a 5; rituximab (which I can only get 50 percent of the time) got a 4. So that is where we are with the general standard of care.

Now look on the right-hand side at some of the highest candidates. You see one called ustekinumab got a 10, twice the ones we are already using; stem cell transplant got a 5; and bortezomib, which you saw on those multiple myeloma slides, got a 6. Pay attention to that top one, ustekinumab. That is sort of exciting, twice what we currently have.[1]



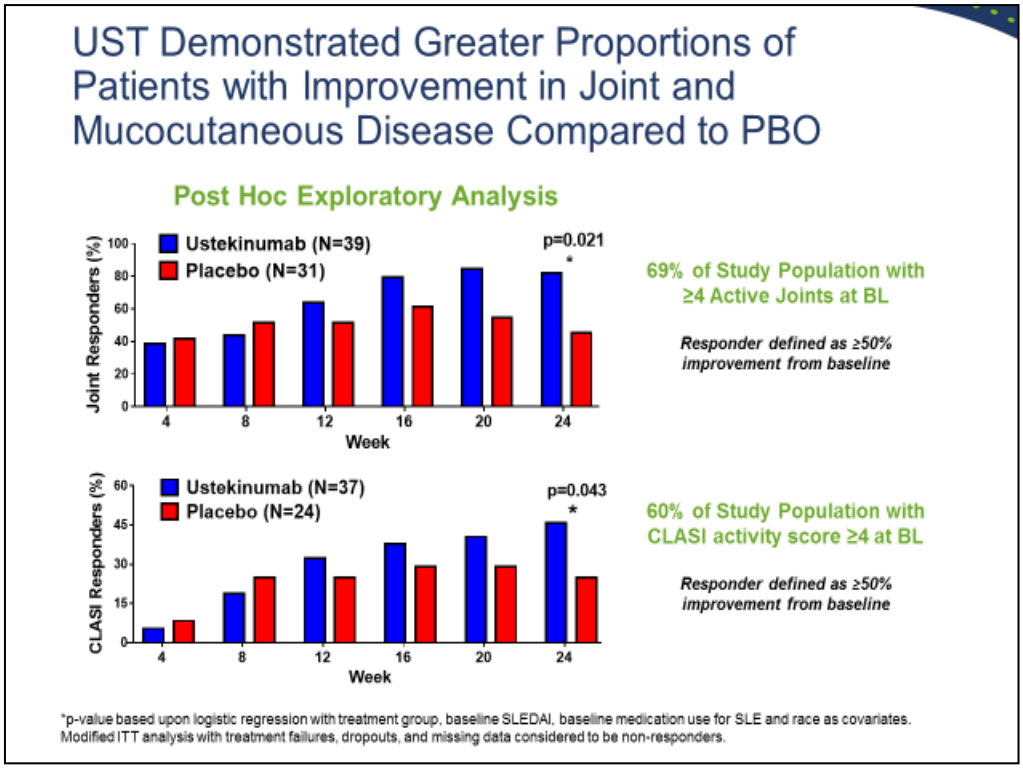

Ustekinumab, which is called Stelera®, is already FDA-approved for psoriasis and Crohn's Disease, etc. And it is targeted; it blocks two immune molecules, interleukin 12 and interleukin 23. It turns out that is a pathway that is active in a subset of systemic lupus erythematosus (SLE) patients. The gene expression pathway data support this.

[1] A.C. Grammer et al., *Drug Repositioning in SLE: Crowd-sourcing, Literature-mining and Big Data Analysis*, LUPUS 25 (10), 1150−170 (2016), *available at* https://www.ncbi.nlm.nih.gov/labs/articles/27497259/.




But what happened? Janssen actually did a Phase II study that was wildly successful. In lupus we do not have a lot of successful Phase II studies. By the way, we do not have very successful Phase III studies either. You can see here the delta was 29 percent, which is much better than the delta of 20 percent in that subset for belimumab. And it was very well tolerated. Of course, because it has been around for a while for psoriasis and Crohn's, physicians would feel very comfortable with this.

Of course, it is not going to get FDA-approved until there is a Phase III trial. That is the rule in lupus. Just to give you an idea of what a hurdle this is, one Phase III trial often has to have 800 patients in it. This is terribly expensive, very difficult to do.




Remember I showed you those slides of how bad the skin could be, how bad the joints could be? Ustekinumab worked for both skin and joints, which is going to be about 90 percent of lupus patients.


I wanted to end with this slide. There are so many arrows in lupus, so many things that go wrong, there is not going to be one treatment for every patient. There are going to be different side effect profiles for every treatment. We may need to combine. I think of myself as the off-label physician of all time because 99 percent of what I do is off-label.

We have to have some way of making off-label on-label. Remember all of those generalized immunosuppressive drugs that we use all the time in the United States? We are all using them off-label. And we don't want to get in trouble with the lawyers.

Thank you very much for your attention.

MR. CORDERY: Thank you so much, Michelle.

Bruce, would you like to make some observations?

DR. BLOOM: Sure. The first thing is it is amazing how the repurposing community is connected. Our nonprofit funded the first thalidomide trial in the United States in 1999, so we are connected to François's story; and we worked with the lupus group around 2010−2011 to help them think about using repurposing instead of or in addition to *de novo* research, and also I referred a patient to Michelle not that long ago, although the patient has not gotten there yet because she has been sick with severe lupus. So, we are all connected up here.

I have a couple of comments about clinical successes. These are two really important clinical success stories. There are many more.

I want to make a comment in response to a question that Dr. Banerjee asked earlier, which is, does Cures Within Reach work on neglected diseases? If you have an unsolved medical condition these days, you think you have a neglected disease, so if any of you have a condition or know somebody in your family, and you don't have a medical solution, it feels like a neglected disease. There are no non-neglected diseases if you do not have an effective treatment.

The idea that there are so many opportunities out there to repurpose generic drugs or nutraceuticals or combinations, alone or with devices, to solve these things, that they can be done quickly and inexpensively, is really critical.

We are in the nonprofit business of repurposing. In the last seven years, our funders have funded over sixty clinical trials. We have thirteen treatments that we have validated through these clinical trials. Ten of those are being used off-label based on the published results. Three are moving toward commerciali-

zation. I just want to tell you quickly about three of them.

One is a drug repurposing. We funded repurposing of the drug sirolimus in a rare pediatric autoimmune disease called autoimmune lymphoproliferative syndrome, a white blood cell disease where white blood cells never die; they just build up in the body until they crowd out the healthy spaces and the kids die. The drug sirolimus flips the switch in those cells and all the accumulated cells die and all the new cells go through a normal cell death cycle.

For under $300,000 and in less than three years, we helped build a mouse model, tested the drug on the mice, then did a clinical trial where 85 percent of the patients were in remission in less than 90 days. All of those children are still on the same dose of the drug and still in remission now, over seven years later.

The accumulated cost savings: for the patients who have moved off of all of their unsuccessful drugs, a lot of which were prednisone — poison — and where they were hospitalized up to 50 percent of the time, all those kids are now leading basically normal lives on two pills a day. The total cost per year of that treatment is about $2500, a savings per patient per year of almost $100,000.

It is a rare disease. There are maybe a thousand kids in the United States, and half of them are refractory and need to go on sirolimus. It creates about $50 million of potential cost savings a year for a $300,000 investment, with a very low cost and known safety profile for the patients, which is a much better return on investment for the patients and the payors versus *de novo* drug development.

We also did a similar thing funding nutraceutical research. Many nutraceuticals are just like drugs in the ways they impact disease processes, although they have never been approved as drugs. The first difference between a drug and nutraceutical is the approval process. The second is making sure that you get the right chemical at the right dose — in a drug you do; in a nutraceutical you are never sure.

However, things like epigallocatechin gallate (EGCG), vitamin E, and vitamin K have very strong biological impacts in the body. In a disease called familial dysautonomia, another pediatric rare deadly disease, a combination of six different nutraceuticals up-regulates the gene or corrects a splicing defect in the defective protein so that these kids can have 100 percent of their circulating protein. Again, it saves their lives using a combination that costs about $25 a week, a considerable health cost saving.

The other interesting thing is that if a mother who is pregnant with a baby who has the gene defect takes the nutraceuticals during gestation, her baby will be born with a normal autonomic nervous systems instead of a damaged autonomic nervous system. It is remarkable work that has been done at Fordham University and is saving lives.

So there is a drug example and a nutraceutical example.

We have also been involved in repurposing devices. We supported research that took a laser device that was used for removing liver cysts and repurposed it for treatment of early prostate cancer. It is basically an outpatient procedure that eliminates the chance of the side effects of incontinence, impotence, or bowel perforation based on how it is used.

All of these repurposing clinical trials were completed in three years or

less at very low cost. We currently have over 180 clinical trials up on our CureAccelerator™ platform all ready to go repurposing generic drugs, devices, and nutraceuticals that could help patients with diseases that have unmet medical needs.

There is a lot of repurposing research opportunity out there.

I want to thank the sponsors of this conference because the brain power that is here is really important. I told Sir Robin that when I got the floor this afternoon I would make a pitch to not leave here without encouraging all of us to work together so that when we come back in a year or two we have actually made some progress on some things.

As you heard me mention, at Cures Within Reach we are working on social finance. We are also working on a couple of other initiatives. I am happy to work with any of you.

The Armitage fourteen-year patent proposal is a great thing to get behind if you are interested in that, and there are several others David mentioned yesterday. He was the first one to talk about a year of additional exclusivity.

So, there are some things that are potentially moving forward, and I bet there are some other ideas, and I think we should find a way to work together to move forward. I have just been really pleased at the enthusiasm that this group has shown toward really thinking through this process.

MR. CORDERY: Thank you, Bruce. Powerful words indeed, and I agree with every one of them.

Michelle, you mentioned ustekinumab. Two Phase III trials have to be carried out; is that right? How long is that going to take?

PROF. PETRI: One Phase III trial will be needed. This is going to take, on average, a year to a year and a half to enroll, another year to complete the twelve months in the Phase III trial, and, depending on how swiftly a company can do it, three to six months to clean and analyze the data. Because so many patients have to be enrolled, it means that most of the enrollment will be outside the United States, and if all the enrollment is outside the United States, this is going to be a major problem for the FDA.

MR. CORDERY: Do you think that is a proportionate task for a company to have to undergo to get this medicine approved?

PROF. PETRI: Well, it's ridiculous, isn't it? Part of the problem is that lupus is a heterogeneous disease. Our outcome measures are not perfect. Some of the patients who come into trials may not even have real lupus.

There are a lot of things in study design that could be fixed. However, we have to be able to have a meeting of the minds. You cannot require 800 patients for each Phase III trial. It is not ever going to be a long-term solution.

MR. CORDERY: Final question: who is going to pay for these trials?

PROF. PETRI: That is a huge problem because only the pharmaceutical companies have the hundreds of millions of dollars.

For mycophenolate, which is our standard of care for lupus renal disease, there were three pivotal trials. All three were published in the *New England Journal of Medicine*, which will give you an idea of their quality. But two out of the three did not come from a pharmaceutical company.

You have heard about issues of good clinical practice, etc., but these were superb trials, three trials published in *New England Journal of Medicine*, but it could not get FDA approval. I do not know if we have a feasible pathway toward drug approval in the United States that does not involve pharmaceutical companies.

MR. CORDERY: Does anyone in the audience have any questions?

QUESTION [Peter Waibel, Novartis]: For these types of studies, would it be easier for the physicians to just do these like an Investigational New Drug (IND) phase that is really not meant to end? So you are not looking for a final approval, but there is enough data there to support the off-label use so that other physicians will just use it — not to avoid the clinical trials, but to avoid the structure of the clinical trials, to have the access for patients and to have it work?

PROF. PETRI: If you are asking about investigator-initiated studies to create interest in an off-label use, our problem is still going to be will we ever get patient access to it, because the insurance companies will block access when it is off-label.

QUESTIONER [Mr. Waibel]: If it is an IND phase-type study that is just open for a long time, you may be able to partner with the pharmaceutical companies. I do not know if that is an alternative to trying to get a full Phase III study going to get it on-label. Keep it as an IND phase that doesn't end, but build a literature of support for it and the use behind it. So the focus shifts from trying to get it on-label, and the system setup doesn't really help you do that for these unique diseases.

PROF. PETRI You are well aware that the IND mechanism requires a huge amount of paperwork and time and review, and it is usually one investigator in one university. So it does not allow dissemination of a promising therapy.

QUESTIONER [Mr. Waibel]: I don't mean you use the current IND system itself.

PROF. PETRI: But something similar, novel?

QUESTIONER [Mr. Waibel]: Absolutely, because your goal is not to actually get it on-label. Your goal is to get the information out there for patients to have access to it so that you can keep building on that knowledge, without trying to bring it within a Phase III trial, especially in those cases where it is either nonexistent or not very effective.

MR. BLOOM: You are suggesting a workaround to the approval system, which is to get key opinion leaders and other people together and say: "Look, we need to figure out if this works and we need to find a mechanism of proving it. Let's create a widespread trial so lots of patients can enroll, see where the data take us, and eventually, maybe, we will just all use it this way. And, if we have enough data and get the FDA convinced, maybe we will get it on-label."

I think Michelle's issue is, how do you get the payments for that, especially if this particular biologic is expensive? But it is an interesting suggestion.

QUESTION: I have a quick question for Michelle. You mentioned that interesting CoLTs program, where gene expression data in lupus tissue was used

to discover drug candidates. Could you elaborate on that a little bit more? Who the investigator was who led that effort?

PROF. PETRI: Peter Lipsky led the effort.[2] He asked me and several other lupus researchers to basically give him our gene expression data. So his company has it, but there is no reason why any company couldn't have my gene expression data. I will give it to anybody who asks.

The bottom line is, why are we doing this company by company? Shouldn't it be sort of a universal program, perhaps under the FDA, where we could have everyone's data in one place and every company could have equal access to it?

MR. CORDERY: We have time for one question from Sir Alasdair, then one from François, and then we will break.

QUESTION [Sir Alasdair Breckenridge, Former Chair of MHRA, UK]: Michelle, are you not making a very good case for the use of real-world data to make it into real-world evidence?

PROF. PETRI: Of course.

QUESTIONER [Sir Alasdair Breckinridge]: What the FDA is now leading Europe in — and we spoke about this a bit yesterday — is beginning to use real-world data which is out there for licensing purposes. It is already doing this for orphan drugs and for rare diseases. My suggestion would be that you have discussions with the FDA about extending their program to diseases like you are taking about.

PROF. PETRI: Absolutely. Groups like The Lupus Foundation are trying. But remember, the FDA is bound by U.S. government regulations, so a lot of this has to come through Congress.

MR. CORDERY: Let me say thank you very much to this fantastic panel.

[Session adjourned: 2:47 p.m.]

[2] See Lupus Research Alliance Announces Published Data Showing Effective Approach to Drug Repositioning, *available at* https://www.lupusresearch.org/lupus-research-alliance-announces-published-data-showing-effective-approach-drug-repositioning/.

**University College London | Georgetown University Law Center**

# CLINICAL INNOVATION:
# Fair and Effective Incentives for New Uses of Established Drugs

*Georgetown University Law Center*
*600 New Jersey Avenue NW*
*Gewirz Student Center*
*Washington, D.C.*
*Friday, February 9, 2018 – 2:30 p.m.*

## Session 2G:
## Should the U.S. System be Changed?

***Moderator:***
**Paul Ainsworth**
*Sterne, Kessler, Goldstein & Fox PLLC, Washington, D.C.*

***Presenter:***
**Prof. Erika Lietzan**
*University of Missouri Law, Columbia*

***Panelists:***
**Dr. Hans Sauer**
*Vice President for Intellectual Property, Biotechnology Innovation Organization, Washington, D.C.*

**Kurt Karst**
*Director, Hyman, Phelps & McNamara PC, Washington, D.C.*

**Brian Hirsch**
*Vice President, Global IP and Legal Head North America, Glenmark Pharmaceuticals, New York*

**Dolly Judge**
*Vice President of Government Affairs, Teva Pharmaceuticals, McLean*

* * *

MR. AINSWORTH: Good afternoon, everyone. My name is Paul Ainsworth. I am a Partner at Sterne, Kessler, Goldstein & Fox, where I focus on intellectual property litigation. I represent both innovators and challengers. Folks ask me who I prefer. I say, "The good guys." They say, "Which ones are those?" I say, "My clients."

We have a fantastic panel here today that I would like to introduce you to. We will be discussing the question of should the U.S. policies be changed in relation to second medical use.

We will first be hearing from Prof. Erika Lietzan, who is an Associate Professor at the University of Missouri Law School. She researches rights on drugs, drug devices, regulatory issues, and intellectual property. Prior to becoming a professor, Prof. Lietzan spent eighteen years in private practice.

Next to Erika is Hans Sauer, who is the Vice President of Intellectual Property for the Biotechnology Innovation Organization (BIO). It is the main trade association, as we all know, for the biotech industry.

Next to Hans is Kurt Karst, who is a Partner at Hyman, Phelps & McNamara, where he focuses on regulatory issues related to FDA exclusivity and intellectual property. Many of us, I am sure, are daily readers of Kurt's FDA Law Blog.

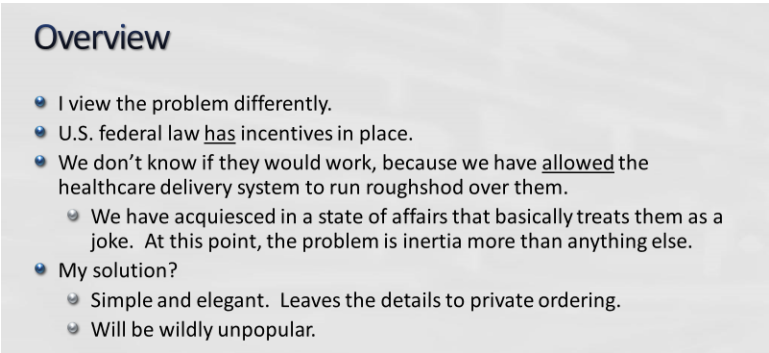
Next to Kurt is Brian Hirsch, who is the Vice President of Global IP and the Legal Head for North America at Glenmark Pharmaceuticals. Brian oversees Glenmark's Global IP team and develops and implements strategy for its U.S. program as well as around the world.

We have a late addition to the panel. We are joined today by Dolly Judge, who is the Vice President of Government Affairs for Teva.

Erika?

PROF. LIETZAN: When I teach class, the first slide that I put up usually has a picture of a reindeer on it to help people remember how to pronounce my last name. It rhymes with the reindeer Blitzen.

I am going to present some ideas that are fleshed out more fully in an article, "Paper Promises for Drug Innovation," which will be published by the *George Mason Law Review* and which you can find on SSRN.[1]




I have been listening to the presentations and discussion over the last two days, and I agree with quite a bit that has been said. But I see the problem slightly differently.

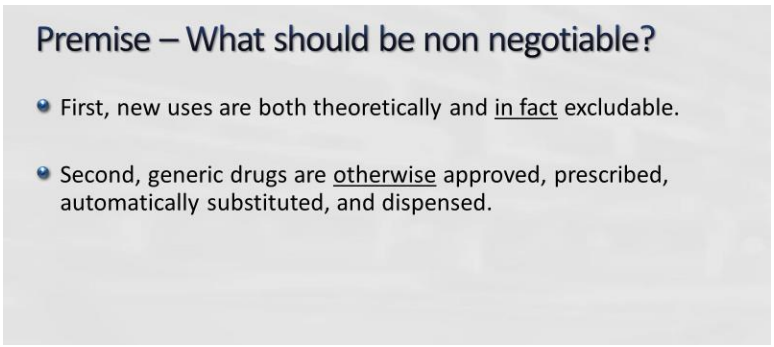
We have incentives in place in the United States. My view is that we do not actually know if those incentives would work because we have collectively acquiesced to a healthcare delivery and finance system that ignores them.

Before we try any of the more creative and aggressive ideas that have been suggested here at this conference — some of which I like a great deal — we ought

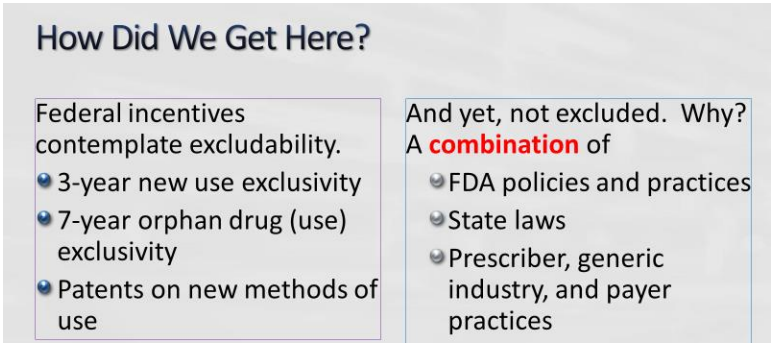
[1] Erika Lietzan, *Paper Promises for Drug Innovation*, 25 GEO. MASON L. REV. (forthcoming), posted Jan. 23, 2018 at https://papers.ssrn.com/sol3/papers.cfm?abstract_id=3103293.

to see if in fact the incentives that Congress has already put in place would encourage new use innovation, if they operated as designed.

Further, as we think about reforms to the law, for instance to repair these incentives, a matter of first principles, I would prefer to let the parties who have skin in the game work out how to structure and order their private arrangements. My preferred solution, which I will describe at the end of my talk, essentially puts the onus on the parties who are in the last best position to prevent dispensing and sale of a product that — under existing federal law — should not be dispensed and sold. For some people, I think my solution, although simple, will be unpopular.

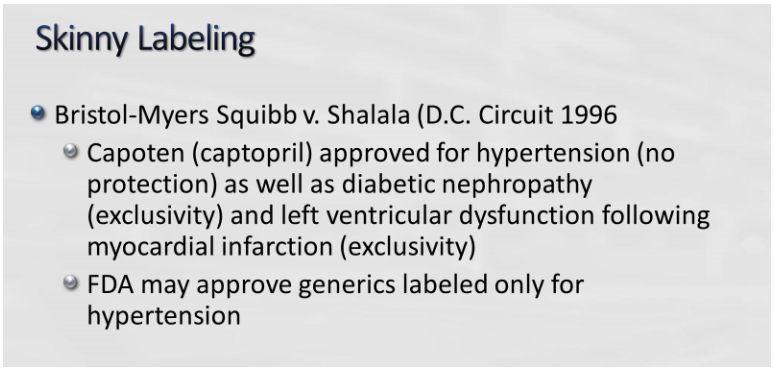



I start from two premises, on which hopefully we can all agree. Even up here on the podium, with one person who represents innovators and one who mainly represents generics, I think and hope that we will have agreement on these two premises. First, in a world where patents and regulatory exclusivity work as designed, new uses are not only theoretically excludable but in fact operate to exclude. Second, except with respect to the new uses that we want to be exclusive, generic drugs should generally be approved, automatically substituted, and dispensed. My position is that it is possible for our health care system to evolve to the point where it respects those two premises. If this is correct, we do not yet need to try any of these more creative schemes that have been discussed here.

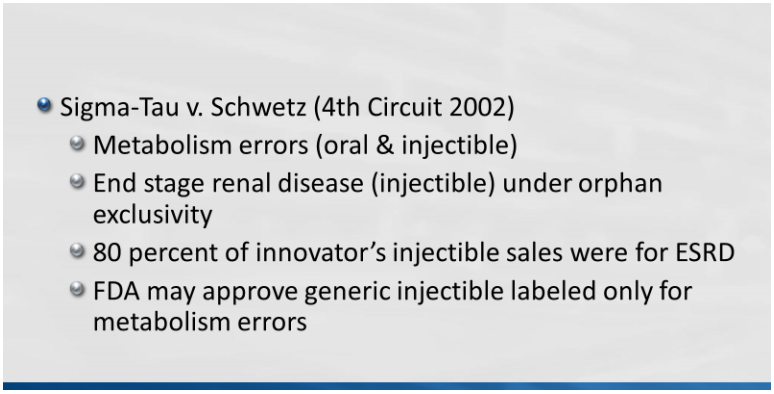



To explain my proposal I must explain why we find ourselves in the situation we are in. I do not need to belabor the incentives that U.S. law has in place to encourage new use innovation. They are on the left-hand side of the screen here. These are legal mechanisms intended to ensure that new uses are excludable.

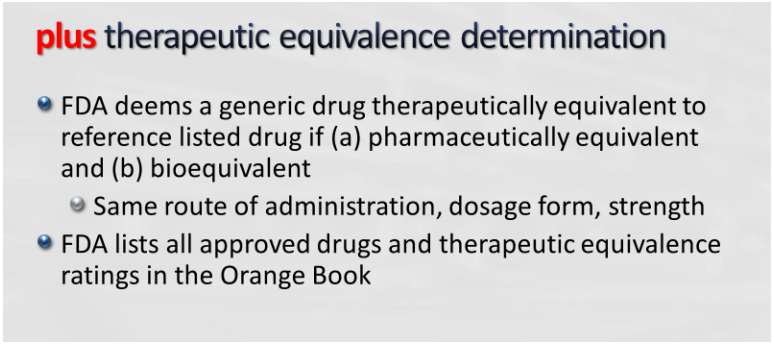
New uses are not in fact excluded due to a combination of factors. Maybe individually these factors would not create the situation we are in now, but they work together and ensure that we are running roughshod over what was intended to be congressionally mandated exclusivity. These factors are as follows.




First, FDA will approve skinny labeling. These two slides explain the court cases that confirmed that FDA may approve generic drugs that have carved out from their package inserts an indication due to exclusivity or a patent held by the reference product sponsor.

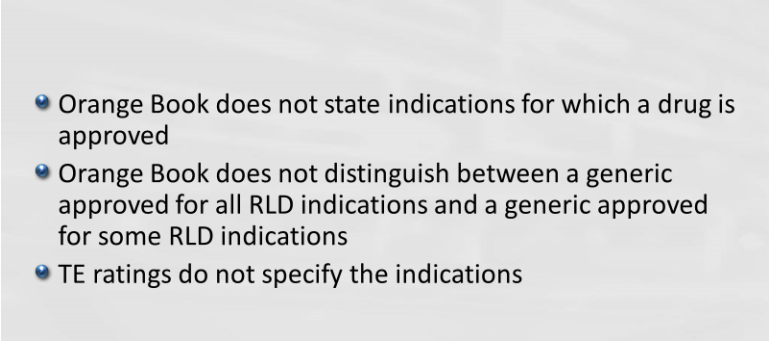



In fact, this second case confirmed that FDA could permit the carve-out even if in fact everybody understood that the vast majority of the generic drug sales would in fact be for the use that was carved out and remained protected under exclusivity. It is well established that FDA may approve skinny labeling. These cases are water under the bridge.

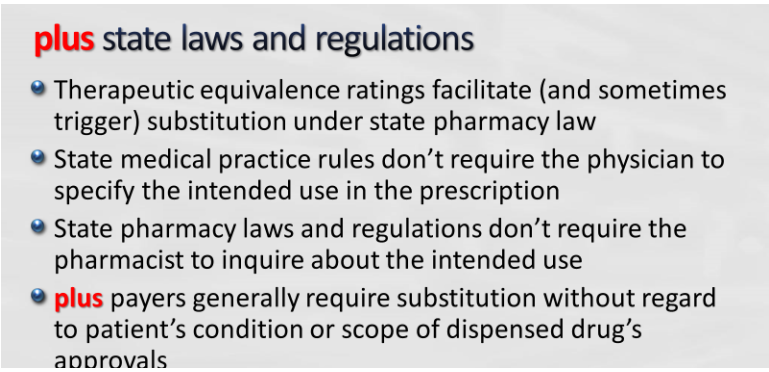



Second, in addition to skinny labeling, FDA issues "therapeutic equivalence (TE) determinations." Under FDA policy the agency will deem a generic drug therapeutically equivalent to its reference drug if the two are pharmaceutically equivalent — same route of administration, etc. — and if they are bioequivalent. FDA does not consider whether the generic drug is approved for some or all of the indications for which the reference drug holds approval.

Third, when FDA publishes this information, it essentially takes an "all or nothing" approach to therapeutic equivalence. The agency publishes a list of all drugs that have been approved for safety and effectiveness, known as the Orange Book. This book also lists these therapeutic equivalence ratings; that is, it indicates which drugs are therapeutically equivalent to which.

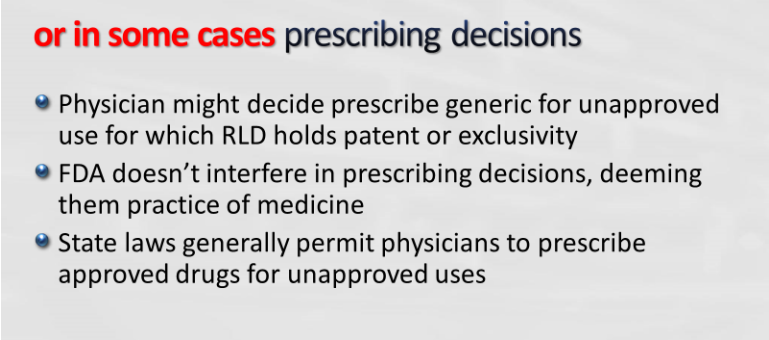



Although the Orange Book lists the drugs, it does not say what they are approved for; it does not distinguish between a generic drug that has all of the reference drug's labeling and a generic drug that has skinny labeling, or partial labeling, as it is sometimes called; and the therapeutic equivalence determinations do not specify the indications for which the drug is approved and therefore therapeutically equivalent. If it is generic and it is approved, even with a skinny label, it is either therapeutically equivalent or not.




Fourth, these therapeutic equivalence determinations by design — this is what FDA intended to do when it set out to publish these in the 1970s — facilitate substitution under state pharmacy law, or even trigger that substitution, depending on how the state's law is written.

The drafting of these state substitution rules varies quite a bit, but the therapeutic equivalence determination from FDA plays a key role in facilitating this next step of automatic substitution at the pharmacy level.

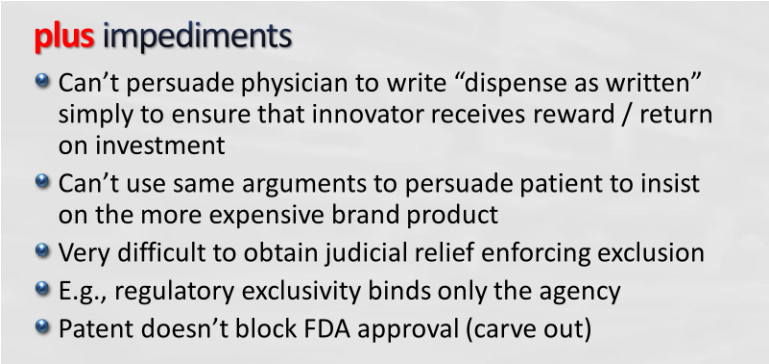



Fifth, state laws governing physicians do not require a physician to record the patient's condition in his prescription; pharmacy laws do not require the dispensing pharmacist to inquire about the indication; and payors generally require substitution with generics or steer patients towards generics with differential co-pays, without paying any attention to the particular condition for which the reference drug was prescribed.

Finally, in some situations, as we have heard, a physician may simply decide to prescribe the generic drug for a use for which that drug is not approved

simply to save the patient money, for example, because the generic co-pay is lower. FDA's practice of medicine policy means the agency will not interfere with these prescribing decisions.

With this list, I am repeating things that you have already heard over the last two days. Nothing I have said is new; everything you have heard before.

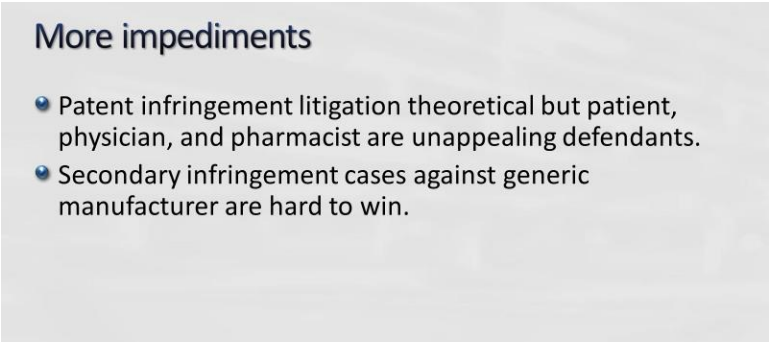



What is new is that I am putting them all together at once. These factors combined mean that the exclusivity for new uses does not work as exclusivity in practice. These factors combine to create a situation in which an innovator may have exclusivity, patent or regulatory, on a new use, a physician writes a prescription for the innovator's drug, and the pharmacy provides the patient with a generic that does not have the indication in its labeling. We all know this happens. It is a given. In fact, we acquiesce in it.

Then there are many impediments to fixing the problem. For instance, those of us who care about this issue will not be able to convince doctors to write "dispense as written" or to ensure the patient get the more expensive drug. This would be a difficult pitch.

Nor could we persuade a patient to insist on the more expensive of the two in order to ensure that innovators to have the incentive to find new uses.

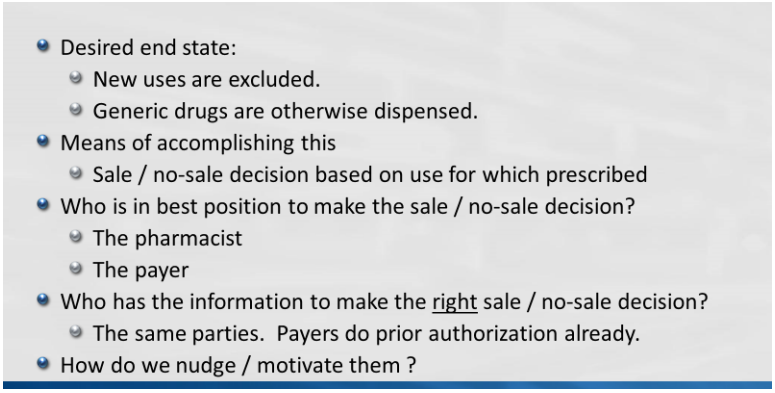
Moreover, it is very difficult for the innovator to get any kind of relief in the courts. For example, the regulatory exclusivity applies to the agency, not the generic company. And, provided FDA does not approve the generic drug with the protected indication, it has complied with the law. The patent does not block FDA approval because of course we are talking about a situation where there is a skinny label.




As we learned yesterday, patent infringement litigation is theoretically possible. But the patient, the physician, the pharmacist, all of whom may play a role in patent infringement, are not very appealing defendants for the pharmaceutical innovator. Secondary infringement cases are very hard to win.


This is the situation in which we find ourselves. We ought to all agree that the patent is meant to convey a right to exclude. That is how it is drafted, and that is how it is intended. Similarly regulatory exclusivity is meant to create a power to exclude. Put another way, the innovator — not the generic company — should be getting those sales. At the same time we want the generic company to benefit from the other sales.

What I want to suggest, at least as an initial starting point, is this: Why don't we see if we can actually get these existing exclusivities to be exclusive — why don't we see if we can get them to work as intended before we try any of the other solutions? Not everyone is going to like how I propose we accomplish that.

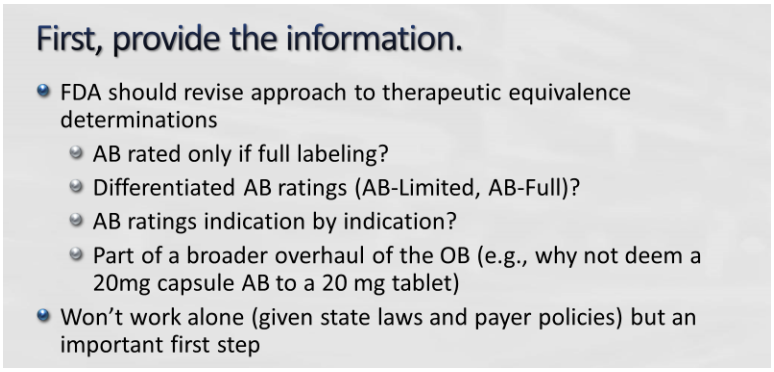



• We want exclusivity.
• We want the generic drugs otherwise dispensed.
• Somebody has to make a sale/no-sale decision based on the use for which the drug was prescribed.

• Who is in the best position to make that green light/red light decision? I think in the end it is the pharmacist, because only the pharmacist knows at the point of dispensing which generic drug the patient is poised to receive. And the pharmacist has access to the labeling of that generic drug, because the companies have to include the labeling with every shipment. The second best positioned entity to make that decision is the payor, because it holds the purse strings.

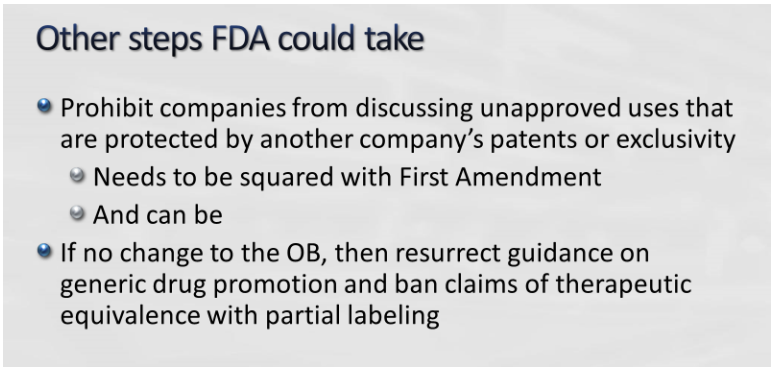
• Who has the information to make the correct yes/no, sale/no-sale decision? Again, I think it is the same parties. As speakers have mentioned already, payors are perfectly capable of putting in place prior authorization requirements that consider the patient's condition before approving a particular company's particular medicine. They do it for some drugs already.

• The question is, how do we motivate these parties?

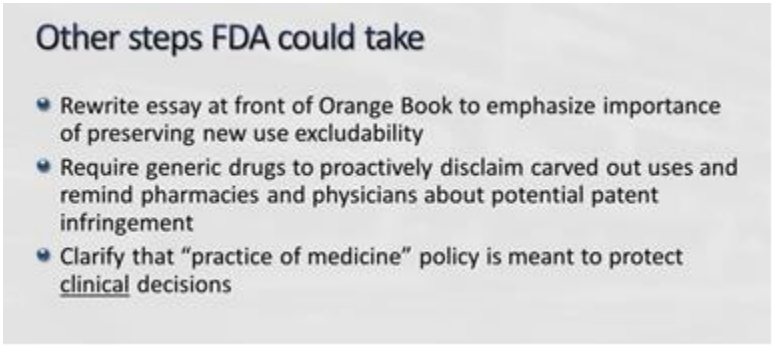



As a preliminary matter, I think we want the information more readily available to everybody. I have some suggestions for changes that FDA should make in the first instance.

FDA should consider revising its approach to therapeutic equivalence determinations. This would be a fair amount of work. But therapeutic equivalence ratings are not statutorily mandated, so the agency could do this without a change in the statute. These are just ideas, but it should be possible, in this age of greater transparency, for the agency to provide access through the electronic Orange Book to information about exactly what a drug is approved for and what it is not approved for, and to make clear that therapeutic equivalence applies only to the things for which it is approved.

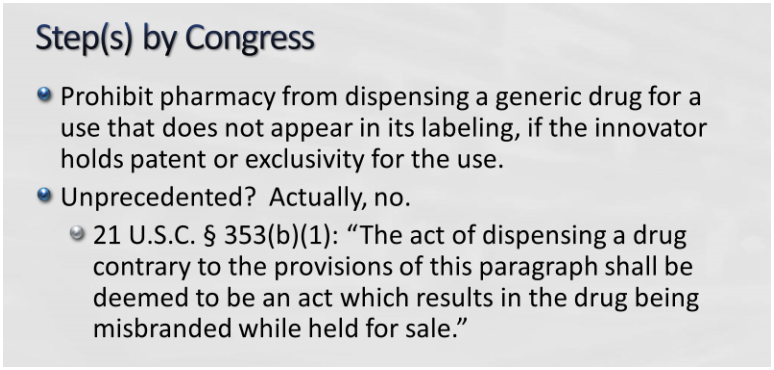



FDA could take other steps as well. To the extent that generic companies engage in any promotional behavior that encourages substitution for uses that have been carved out, FDA could take additional steps. Several of these slides describe steps that FDA could take.



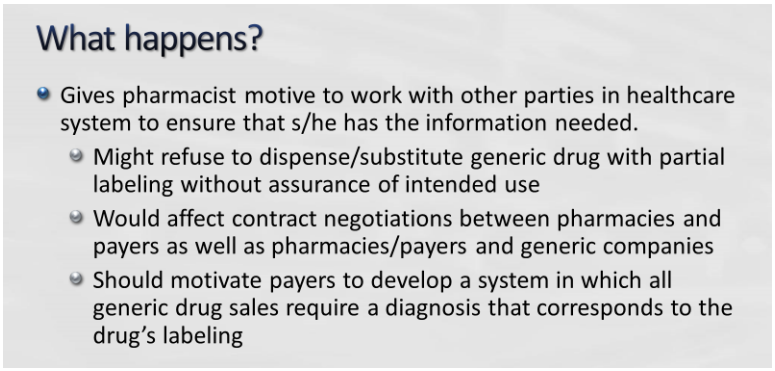

But the key to my proposal is not the changes suggested for FDA. I have three ideas.

First, I suggest we think about prohibiting pharmacists from dispensing a generic drug if the use for which it was prescribed does not appear in the generic drug's labeling and there is patent or exclusivity covering the use.



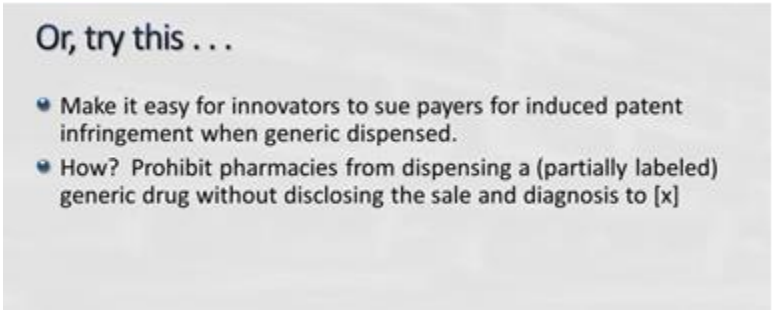

There is already an act of misbranding in the statute that applies to pharmacists. There is a precedent. I quoted it here. That particular provision relates to refills, but essentially it says, "if you dispense contrary to what we just said, that is an act which results in the drug being misbranded while held for sale." My proposal could be tucked in there.

This is a really aggressive idea, but again, the pharmacist is that last, best person to conclude, "I cannot dispense this drug to this person, because of the labeling on the drug which is right in front of me."




That said, I do not envision a legal framework in which we are routinely penalizing pharmacists. Instead, the pharmacists will be highly motivated by this statutory change to say to the payors and the state boards of pharmacy that they simply will not dispense generic drugs with skinny labeling until the parties sort out a system that provides them with the information they need to dispense without fear of liability.

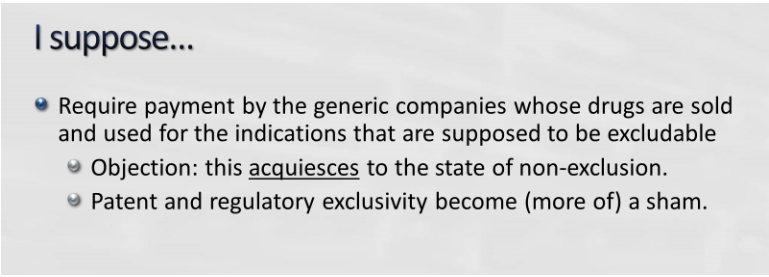
I would like to see a world in which the pharmacists, payors, and generic drug companies work together to develop a system ensuring the sales are indication by indication.




Second, I suggest — echoing Ben Roin's paper — that it be an act of misbranding to dispense a generic drug with skinny labeling unless the pharmacist provides information about the sale and the diagnosis to somebody else. I heard somebody suggest yesterday that it be a neutral third party.

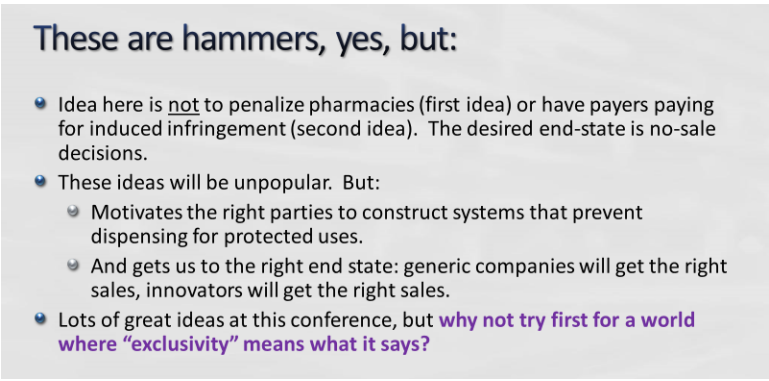
How would the pharmacist have this information in the first place? Again, is if we put this in the law, the parties will be incentivized to work together the set up a system of indication-level prescribing and dispensing.

Again, the payors already require prior authorizations. In these situations, they will not cover a particular drug unless it was prescribed for a particular condition.




Third, I propose requiring payment by generic companies if their drugs are sold and used for indications that are supposed to be excludable. I do not like this solution, because it essentially gives up on exclusion, at least as a theoretical matter. Putting this in the law would be tantamount to announcing that, as a policy matter, we are comfortable with a kind of compulsory license, rather than insisting on exclusion.

But if one wanted to do this, how would one structure it? One possibility is to make the generic company and payor jointly liable for the infringing sales and to assume that the percentage of sales for the omitted indication is the same as the percentage that the innovator enjoys. In other words, if 80 percent of the brand drug's sales are for one indication and 20 percent are for the other, then we would assume that the generic company's sales had the same 80/20 split. We could allow the assumption to be rebutted with data about the actual percentage of sales for the protected use. Such a liability rule would very quickly encourage generic companies to work with the other stakeholders to set up a system that prevented sales for the excludable uses.




In the end, we should have not a system that routinely penalizes pharmacists, and payors and generic companies should not be routinely paying for sale of generic drugs for excludable uses. Instead, we should consider legal reforms that give these entities an urgent incentive to solve the problem. But this proposal has the advantage of not micro-managing the details; the specifics of how to avoid these impermissible sales would not come top-down from the legislature. In the end, ideally, we would have the system we want, in which the generics enjoy all the sales that are not protected but the uses that are supposed to be exclusive are actually exclusive.

MR. AINSWORTH: I have some questions for our panel, but if you have questions there will be time for that as well. To start off, I am going to throw this question out to the group and see who agrees.

MR. KARST: Actually, Paul, I would like to make a comment beforehand.

MR. AINSWORTH: Please.

MR. KARST: I suspected that Erika and I might get into an Orange Book rumble today, so I wore orange glasses. Erika and I are good friends. We are often on opposite sides.

You made one comment to the effect that therapeutic equivalence evaluation ratings in the Orange Book are not by indication. I would actually disagree with that. Generics are approved, if it is a skinny label with carve-outs, as interchangeable insofar as their labeling allows that with the brand product. So a proposal to say full or partial labeling, or whatever the case might be, is already inherently in the therapeutic equivalence rating in the Orange Book because you can only be substituted for that for which you are approved, right? So, at least from an Orange Book perspective, I don't know that any changes are necessary because everything that is needed is already there.

PROF. LIETZAN: Except you cannot tell by looking at the generic listing in the Orange Book which one has a skinny label. So there is no way to tell that a generic drug is not AB rated for every use for which the physician might prescribe the reference drug.

MR. KARST: Right, but one must simply go to the drugs@FDA labeling website and pull up the labeling and you could easily see it, right? If it just said "full" or "partial," it could mean one indication is carved out, or five are, or whatever. So you necessarily have to go to the labeling in any case to know if there is a carve-out or not.

PROF. LIETZAN: I am trying to get to a system where there is a lot more transparency. But I agree. I will note one sentence in the Orange Book about which you and I had some disagreement with last summer.

MR. KARST: It is now gone.

PROF. LIETZAN: Yes, it is now gone. FDA took it out. Let me explain it for the audience. There was a sentence in the Orange Book saying that therapeutic equivalence ratings are not made for unapproved uses. FDA for some reason deleted the sentence out of the 2017 edition.

DR. SAUER: So, if the information is already there, does that make it even easier to implement Erika's recommendation?

MR. KARST: It almost makes it unnecessary because it is already there. If the therapeutic equivalence rating is inherently — "inherently" means you could be substituted for which you are approved vis-à-vis the brand-name product — it is already there.

PROF. LIETZAN: It is. But it could be much clearer to all the participants, all the stakeholders. I believe that many pharmacists see the AB rating and do not realize that it is possible the drug is not approved and not in fact therapeutically equivalent for a particular use.

MR. KARST: Yes, okay.

MR. AINSWORTH: Kurt, in light of your comment, though, let's say the Orange Book was clarified along the lines Erika suggested. Would that actually change the behavior of pharmacists?

PROF. LIETZAN: I don't even claim, myself, it would necessarily have that effect. This is why I explain all the things that contributed to our current situation, because I do not think any one of these solutions is enough. Changing the Orange Book is going to work only if pharmacy practices change as well. This, in turn, may be a function of how the law is written in the particular state and it may be a function of whether we can change state law.

However, with Orange Book changes, no, we are not going to get all the way to our solution. Just as many things are contributing to the problem, many things are part of the solution.

MR. AINSWORTH: Brian, from your perspective, do you think that a change in the Orange Book, or a change perhaps in bringing pharmacists into the enforcement strategy, would alter behavior?

MR. HIRSCH: Before I respond, I should note that my comments are mine and not those of Glenmark.

I think pharmacists are going to have pretty reasonable responses to the proposals that Erika was making that are similar to the types of responses that generic drug manufacturers are going to have, which is that the potential liability on a pharmacist relative to the amount of money that she is going to make for filling a prescription when you compare it against the kind of exposure for patent infringement is really pretty disproportionate liability.

It is a similar problem that generic manufacturers face because the point of different indications and exclusivity that attaches to indications and not to the entire product is to encourage generic competition and lower prices for patients based on indication. So you have need to ensure with whatever approach we were to find to try to encourage second medical uses and patent protections for those to be consistent with reduced liability for generic companies.

Right now there is potential exposure for the interchangeability to the generics when their products are prescribed for purposes that they are not labeled for, and that can be wildly disproportionate to the amount of profit that they are making and deleterious to the incentive for genericizing those indications where associated patents have now expired.

MR. KARST: One potential solution could be, since products in the Orange Book are rated as interchangeable and ANDA versus a particular NDA — so there is a line entry, NDA versus ANDA — if a new use were to be approved under a separate original NDA, it could be pharmaceutically the same product for another use. Of course, it would be easier to brand it separately as well under a new NDA, but it would be a separate line item in the Orange Book that would not carry an interchangeability rating with respect to an ANDA for the different reference-listed drugs. It would cost an extra user fee, but that is not terribly much for many of the brand companies.

PROF. LIETZAN: Yes, I like that.

MR. HIRSCH: Then there would just be the obligation on the innovators to be careful about how they go about deciding what exactly it is they are going to

test under the new NDA. They will have the safety data and there will be a lot of the NDA that they can copy, but if you are going to go under a separate NDA, which will solve a lot of the problems, you also want to make sure that dosing is not purely interchangeable so that you do not have doctors figuring out how to write prescriptions for one strength for the old product and knowing it will work for the new one.

PROF. LIETZAN: Right.

DR. SAUER: I just want to make an observation. To my mind, before we go too deeply down this road of "Oh, innovators could just separately brand a different product under a different NDA," to protect the use, the incentives for which are actually built into the statute, there are particular incentive mechanisms that Congress apparently had in mind which we have already moved off of. Nobody seems to have the will to actually give effect to, for example, three-year new clinical study exclusivity, and the solution instead becomes: "file a separate NDA and brand your product separately."

I do want to return to Erika's proposition, and that is to ask: do we have the will to give these incentives that must have been intended by Congress at some point meaningful effect or not? To my mind, in order to do this, whatever we do, whether we propose new solutions or we want to give effect to the existing incentives, will require a change to the status quo. From the perspective of somebody who works for a trade association, this means going to Congress and arguing for a change of the status quo in the face of an already-established narrative that is very different from the way we have been discussing the issues here, and to enter into debates that have been framed by others.

I have heard policymakers in Congress talk about the new clinical use incentives that are in our statutes. They call them "evergreening." Companies that have pursued these incentives, whether it is three-year new clinical data exclusivity, whether it is orphan drug exclusivity, whether it is pediatric extensions of exclusivity, have been heavily criticized for pursuing these incentives.

The first thing I would do, having learned what I heard at this conference, is to work towards correcting the public narrative and engage in a lot of education. I can tell you, while you all have explained persuasively to me that the existing statutory innovation incentives actually do not operate very well in practice, that is going to be news to a lot of policymakers who believe that these incentives confer powerful monopolies, which they do not.

MS. JUDGE: My perspective obviously is more limited to the Congress and the statehouses. I do think if you look at the bigger picture, when Congress has tried to create incentives — and I would echo a lot of what Hans said — they have tried to create incentives around bioterrorism agents, antibiotics, pediatrics — you get into a fundamental kind of foundational debate between Democrats and Republicans sometimes, and sometimes it does not divide on party lines — but the idea that a lot of this work and this research should be done and should not need rewarding, if you will, and it should not need an exclusivity or a kind of patent protection, that the companies should do this work on their own and because it is the right thing to do. If you look at the costs involved, just looking at

some of numbers involved in the trials, looking at what goes into those, there is a big difference between the practicality of what would be a good incentive and the politics around incentives. So I think that we cannot leave this to Congress alone. I think it is too politicized.

But I do think public-private partnerships and people sitting in rooms like this and coming to consensus around how can we come up with some win-wins is a better alternative. My experience has been there are some things in place now that are not working as well as they could. Creating new incentives is going to be really tough in this environment, but I think the Congress and the administration would be open to ideas that are developed in public-private concert, if you will.

MR. AINSWORTH: A question from the audience?

QUESTION [Dr. David Cavalla, Numedicus]: I have a couple of questions. The first one is addressing your point about obliging the pharmacists to prescribe according to the proper product the proper indication. How do you enforce that system? How would the manufacturer know that things were going properly?

PROF. LIETZAN: I was describing changing the Federal Food, Drug, and Cosmetic Act, to make it an act of misbranding, so it would actually be for the federal government to enforce.

AUDIENCE: Good luck.

PROF. LIETZAN: I hear you.

Again, I don't envision a world in which there is a lot of enforcement against pharmacists. Putting it in federal law as both a civil violation and inherently a crime will motivate pharmacists to immediately say, "We are not going to dispense a generic drug with a skinny label unless we have an assurance that the intended use is a use for which the generic drug is approved" — which will motivate the payors and the pharmacists.

QUESTIONER [Dr. Cavalla]: In a situation where you might have a highly genericized molecule — let's say like metformin, which does not have an innovative brand anymore, and one of those generic companies wanted to develop it for, say, Alzheimer's disease — would that then produce a skinny label for all the other generics? It wouldn't. Then how would that work in that situation? How would you incentivize one out of the ten generic manufacturers of metformin to develop a specific product for Alzheimer's disease?

PROF. LIETZAN: I am focused on situations in which an innovator has added a new use to its own previously approved drug. This solution may not work to encourage all of the new use innovation in which we have an interest.

MR. KARST: You could have ten different generics with ten different labels theoretically.

PROF. LIETZAN: Yes, sure.

MR. HIRSCH: You would file it probably as a B-2. You might file a citizen petition asking for the generic to be designated as a reference-listed drug. But then you would be running clinical trials, at least Phase III, right?

PROF. LIETZAN: Yes, for exclusivity.

MR. HIRSCH: Yes, you would get at least a data exclusivity of three years. So it could be done even repurposing fully genericized products that don't

even have an RLD at this point. But then you would be relying on two things: you would be relying on the data exclusivity, which would at least guarantee you three years, assuming efficacy and FDA approval; and then you would also be relying on your patent department to be able to prosecute some sort of new method-of-use patent, so that hopefully by the time the drug goes to market you have something to list in the Orange Book and maybe you have some exclusivity on top of the three years.

QUESTIONER [Dr. Cavalla]: But this is where the patent method doesn't really work in that particular example. There is plenty of evidence that metformin plausibly has an effect on Alzheimer's disease and is a particularly attractive repurposing project to undertake, and it could be one of the best examples of something that could come out of reformatted regulatory system because it is a cheap generic drug, it is a serious medical condition, and yet there isn't the incentive to do it. Now I think it would be difficult to get a patent for that.

MR. HIRSCH: I would just say that there are finer points that we have not been able to get into about the differences about the equivalent of obviousness in the United States versus Europe. I have heard some people being pessimistic about what would count as a reasonable expectation of success in order to get patentability on a method-of-use claim.

These are patents that can be obtainable in the United States because the Patent and Trademark Office when you go to prosecute these patents usually has a fairly realistic view about what is a reasonable expectation of success. So when you are prosecuting it, you do have a decent chance, even on something old.

But it is fact-dependent. It just depends on what the literature is for that particular product and how much work has gone on in the past and the data. But it is not like it is just a lost cause that you will never get a new patent on a method of use for a new indication if it is sufficiently different in kind on an old, fully genericized molecule. It just depends.

MR. AINSWORTH: Another question?

QUESTION [Prof. Rebecca Eisenberg, University of Michigan]: Erika, it seems to me that there is a disconnect between your aspiration to bring about a system where everybody has skin in the game, and therefore through private ordering they achieve the right outcome, and your remedial focus, which is on top-down government regulatory power moves, like FDA saying products are misbranded. I would think you might prefer a liability rule that imposes damages in order to give potential defendants skin in the game so they will make the moves they need to make to avoid damages liability.

There are some problems in thinking that through, particularly with the incentives of the insurers. The insurers control the money and, therefore, they control the documentation. Just as they require prior authorization, as Ben Roin was saying earlier, insurers could say "We want you to document what use you are making of this product." But they have no incentive to do that. And if you impose damages liability, they may have even less incentive to do that.

Unless the insurers have some skin in the game in the form of facing damages liability, it is hard to imagine this whole thing working because they

would be well served by a system that just fails to document somehow that there is patent infringement going on.

PROF. LIETZAN: I agree. One of the things I mentioned orally but did not include on the slide was the idea of having the payor and generic company jointly liable. Thus, if the brand company has 60 percent sales for unpatented indications and 40 percent sales for indications still under patent, we will assume the generic drug is being substituted in the same proportions and make the payor and the generic company jointly liable for the 40 percent, with the the ability to rebut the presumption with data showing, for instance, that 100 percent of the sales were in fact for unpatented, unprotected uses. That approach provides a liability-based incentive.

QUESTIONER [Prof. Eisenberg]: It seems like there is a problem, though. First of all, I do not know that under the current law the generic would be liable.

PROF. LIETZAN: No. This would have to be a change of statute.

QUESTIONER [Prof. Eisenberg]: You need to change the law, but you are changing the law in a problematic way. If their label is clear enough, then it is not clear that they are subject to secondary liability. It would be a departure from current rules about inducement and contributory infringement.

DR. SAUER: Can I make a quick observation on that before you go on? One of the great things about this conference was listening to my European colleagues yesterday. In the same context in which in the United States we have such problems proving liability for inducing patent infringement, our European colleagues seem to be talking about concepts like "foreseeability," "infringement was predicted," "infringement was known," "the accused party provided the instrumentality for the infringement in the knowledge that it will be used, expecting a certain amount of its profits to come from that." In European courts, that seems to be something that gets you pretty close to liability, and once that is established, courts craft a remedy around that.

In the United States, we have, to my mind, a far more irrational system, where you could have a defendant, whether it is a generic drug company or somebody else, who might say: "Yeah, I know 50 percent or more of the users of my product are going to be infringing your patent, but there is still substantial noninfringing use. I am just supplying product, I am just meeting demand, and I am not actively inducing the infringement because at the end of the day I am not controlling which user is going to use my product in which way, and therefore there is no liability, even though I concede that there will be widespread patent infringement."

If you talk to business people, they would say: "As a commercial proposition this is just not rational, if we can predict and quantify how much patent infringement will happen, and how much commercial damage will accrue? Why are we at a stage where U.S. courts will close their eyes to this commercial reality?"

QUESTIONER [Prof. Eisenberg]: Well, they just say they are following the law. You would need to change the statute. This is one of many things that

you would want to change in the statute if you were trying to figure out how to get damages for patent infringement.

PROF. LIETZAN: To be clear, I do not want damages. At the end of the day, if this works properly, they are not going to sell or dispense the drug and then pay.

QUESTIONER [Prof. Eisenberg]: You should want damages, but not necessarily against the generic. I think the real profit incentives problem is the payors. I feel like if the payors want it to happen, the records will reflect —

PROF. LIETZAN: Well, if they have to pay, they are going to want it to happen.

QUESTIONER [Prof. Eisenberg]: That's right. That's the real problem.

And then the other problem, of course, is if there is not a use patent and you are relying on other sources of exclusivity over particular uses, then we could — but don't — have a damage remedy for that. But I think there is a problem with trying to solve this problem at the level of top-down regulations.

PROF. LIETZAN: Compared with the long and painful process of trying to mandate track-and-trace for prescription drugs from the top down, with members of Congress and the state regulators getting into the weeds of the technology and stakeholder discussions of who would have which databases where, this is top-down only in the sense of giving the relevant stakeholders an incentive. But it doesn't micromanage. It says: "You have to fix this. Go off and fix it."

QUESTIONER [Prof. Eisenberg]: But I think you need to go deeper into the micromanagement in order to make it happen.

MS. JUDGE: Well, the pharmacists right now are on Capitol Hill every day complaining about not getting paid enough for the counseling they do, for all the other work that they do right now, and this would be, I think, from their perspective maybe something they would do. But they would need some kind of an incentive or compensation or some kind of recognition.

QUESTIONER [Prof. Eisenberg]: If their payment turned on getting those documents right, they would get the documents right.

MS. JUDGE: Right.

QUESTIONER [Prof. Eisenberg]: But their payment doesn't turn on it unless the insurers want it to happen. So you have to think about the incentives of the insurers and how to change those incentives. That is, I think, really the key to this whole thing.

QUESTION [James Horgan, Head of European Patents, Merck Sharp & Dohme]: Thank you very much for that. I want to draw some analogies with the European situation along the lines that Hans has begun to speak about, and that ties in with comments other speakers have made.

It seems to me that one of the things coming out of this conference is that there are two types of second medical uses: there are those that are patentable and those that are not. The problems and ways of bringing products to market for those two different types of uses may be different.

I just want to think about the patentable uses, which is the area you were looking at. In Europe, as Hans suggested, I think we are a bit further forward than

in the United States. The Dutch *MSD v. Teva* case[2] that I had, and hopefully the UK *Warner-Lambert* case,[3] may well establish that generics do not escape liability, that they are both directly and indirectly inducing infringement in circumstances like this. Neither the originators, the patentees, nor the generics want to be in that situation. There is a meeting of minds there.

As of yesterday, of course, we had a meeting of minds it seemed with some of the physicians' community that they would like to have for good medical reasons indications on prescriptions. The pharmacists also would be very happy with that and they would not have a problem prescribing.

So what we come down to in Europe is the same situation you have in your proposal. The problem is: where is the money coming from?

The issue for us in Europe is, who does that leave us suing? The state. I don't mean one of the fifty U.S. states; I mean the nation-state. It does seem to me that we are moving toward that position. Naturally, we do not want to sue the state, but where the law has ended up is that there needs to be a dialogue with the state on the enforcement of these claims and how income flows to the originator.

I suppose one of the things that concerns me, depending on how the *Warner-Lambert* case is decided, is what might happen if infringement is found; what is the relief that is to be given? I think the problem here is that there has to be a recognition by the courts that the state has awarded a monopoly, but that does not entitle the state to infringe that monopoly, be it indirectly or directly.

Perhaps then the meeting of minds for a conference like this is actually saying to us that we need to put advocacy into our own countries, to say, "Look, the solution to repurposing medicines, to getting these second uses, actually requires you as the payor to recognize there has to be a differentiation in the way you pay and the way you deal with reimbursement, substitutability, all that stuff that fits under your national rules."

Actually, in Europe we find ourselves ultimately in the same place, albeit from the patent side I think we may be a further step forward than you are in the United States.

Sorry. That was more a comment than a question.

MR. HIRSCH: If you are going to go after, from the current standpoint of the way we organize it in the United States, the generic substitutability, you would have to be very careful about making changes along the lines of what Hans was talking about.

At this point there really are not any true generic companies, I think everybody is working on the specialty and innovative side, and people would

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[2] See The IPKat, English translation of Dutch Supreme Court decision in *MSD v Teva* highlights UK Supreme Court's *Actavis* decision (Nov. 30, 2017), http://ipkitten.blogspot.com/search?q=ribavirin.

[3] Warner-Lambert Co. LLC (Appellant) v. Generics (UK) Ltd t/a Mylan and another (Respondents), Case ID: UKSC 2016/0197; UK Supreme Court case details and hearings documents available at https://www.supremecourt.uk/cases/uksc-2016-0197.html. [*Note*: Subsequent to this conference, the UK Supreme Court hearings were held February 12−15, 2018. *See* LifeSciencesIPRReview, Summary from the UK Supreme Court Hearing, *available at* https://www.lifesciencesipreview.com/news/warner-lambert-v-actavis-a-summary-from-the-uk-supreme-court-hearing-2723 (Feb. 21, 2018).]

agree that legitimate innovation, as opposed to things that are less clearly innovation, are worthy of some sort of protection to encourage the sale of the product and the development for the new use to benefit patients.

But if you just go in and start tweaking the law of induced infringement, for instance — which is what I heard Hans talking about, or at least what it sounded like you were suggesting — you have a real risk of creating disincentives for further genericization of the markets, going in and increasing liability, which is what the suggestion seemed to be, for generics when they do not have control over the substitutability is just creating additional liability.

Generics are not foolish. They are going to know that there are multiple uses and that, even if they carve it out, they might be subject to liability, and you will have real questions about whether or not you will continue to see generic launches for products that have multiple indications. You just need to be really careful about how you do it.

QUESTIONER [Mr. Horgan}: I think on that legal front the ship has sailed. The finding of liability for generics in Europe is very much in the line of case law on indirect infringement in the United Kingdom that comes from cases about potato-picking machines and about seating arrangements on Virgin Atlantic aircraft. So this is not a *de novo* legal theory. In a sense, it is applying those rules on indirect infringement to this particular claim type, second medical use claims. This issue of foreseeability arises from that line of case law very clearly.

I think where we come down to, though, is that we want the generics to be able to sell, and the generics want to be able to sell, free of liability. But the way the legal construct has worked is you are running a patent case, when really, as I said yesterday, you need to bring in all these other areas of law. The peculiarity of patent law is that it is essentially harmonized around Europe and it is the same law.

But that is not the case for all the reimbursement and pharmacy substitution stuff. That is fragmented and, therefore, finding the solution to this does require engagement with, and a desire to engage from, the state actors here.

QUESTION [Bob Armitage, IP Strategy and Policy Consultant; Formerly General Counsel, Eli Lilly]: Once water goes over the dam, it takes a tremendous amount of energy to get it back behind the dam. In a similar vein, once IP-protected technology becomes a commodity, it would take a tremendous amount of effort to get it back to an IP-protected status so that the one-time commodity could again be monetized as though it were intellectual property.

It occurred to me that if someone discovered that eating baked beans could be an effective therapy for preventing Alzheimer's Disease, as an individual desiring to take advantage of this prevention therapy I could simply go to my local Walmart store and purchase a four-dollar can of baked beans that I could then consume, say, one every month, and for a nominal cost I might eliminate my risk of ever suffering from Alzheimer's disease. On the other hand, based on recent reports of some nonclinical work with the generic drug metformin, I could decide today to go to the Walmart pharmacy and, for the same four dollars a month, get any one of four FDA-approved strengths of the generic drug metformin, including even the extended-release metformin formulation. All of

these formulations are generic and anyone with a prescription in hand could get Walmart's $4-per-month deal on this medicine.

As a patient myself, I happen —for much less than $4 per month — to actually purchase what was once called "baby aspirin" as a similarly preventative therapy. It the case of aspirin, the preventative is for heart attack and stroke. For about 100 years, this 81-milligram aspirin formulation has been similarly available generically.

I am wondering, if someone had actually not been in this conference for the past two days and were just looking at this issue from the consumer point of view, if they would not have a sense of total disbelief that we were even considering the topic of un-genericizing generic drugs that were being made available to the public at commodity prices—about the price of a can of beans.

If the general public's understanding of our initiatives was that we were suggesting to turn back commodities into some intellectual property-protected property, particularly a commodity that currently is readily available on the market for four dollars but as an IP-protected product might cost $40 or $400 or more, then I submit they might conclude that all of us are just plain crazy. I fear that such a conclusion would not be wholly unjustified.

With all due respect, the potential that we might all be a bit out of touch with such mainstream thinking about the de-commoditization of a medicine once available generically has nothing to do with insurers and payors. Today, if I want to start metformin therapy, given its speculative potential in preventing Alzheimer's disease, the cost to me is four dollars a month, whether or not I actually have insurance. In fact, given the complicated manner in which drugs are priced to consumers in the United States, I might be better off going to Walmart and just asking the pharmacists to hand me the generic drug without handing the pharmacist my insurance card. It could potentially cost more than four dollars with insurance the way the current system works. In the United States, there are patients with no insurance or insurance that might impose co-pays for whom the un-genericized medicine would be accessible only if commodity priced.

I suggest as we are thinking through the possibility for somewhat elaborate changes to patent laws or their enforcement that we need to think how the average Walmart shopper would look at any program designed to limit affordable access to the over 1200 medicines that are listed on a chart on the wall in the Walmart pharmacy that are already being dispensed at four dollars a month (or ten dollars for three months). Seen from their eyes, how do we justify potentially taking away life-saving and life-enhancing medicines that today are cheaper than a can of baked beans?

If the answer is that the cost of the research on the new use of the old drug needs to be funded, we might better serve the aims of this conference by finding the funding though some pay-forward mechanism, not a pay-back mechanism that requires this type of de-genericizing old medicines.

PROF. LIETZAN: Sure. My response is similar to what I said regarding metformin, earlier. I am focusing on encouraging an innovator whose product is still fairly early in its life cycle to study a few more uses. I am not focused on trying to salve a drug that has been around for a while.

QUESTIONER [Mr. Armitage]: If you go down that route, as you eventually must in the United States, you will need to make may trips to Capitol Hill. During this political effort you will have the problem that Hans raised. Today, whether the biopharma industry is being unjustly vilified or not, there are many issues of patent-lifecycle "evergreening" that are — and continue to be — alleged. Rightly or wrongly, the industry has been repeatedly accused of acting to impede full access to generics in ways that are not legitimate, not ethical, or even not legal. Thus, any legislative initiative will face a huge hurdle to get around the "evergreening" allegations — and, in fact, the real-world potential for what any objective observer would call patent-lifecycle "evergreening." Without really compelling answers, these issues I submit are likely to doom those efforts.

PROF. LIETZAN: I would distinguish between new indications, as to which there is an easier story to tell, and other innovations that are attacked for evergreening. And I would submit that going up to the Hill and saying "let's actually let patents be functionally excludable" — in other words, let's focus on enforcing the laws that you, Congress, have already written — might be an easier sell than "Hey, let's make everything fourteen years."

MS. JUDGE: It is harder than you think.

QUESTIONER [Mr. Armitage]: Yesterday I was feeling sorry for Pfizer, given the difficulties it has faced getting respect for its pain use patent right for Lyrica.® That sympathy for the Pfizer Lyrica® story, however, is unlikely to be shared by many outside the biopharmaceutical community.

As an example, I just pulled up the FDA Orange Book to see when Lyrica® was first approved in the United States. It was approved in 2004. It is now 2018, nearly fourteen years later. Is fourteen years enough time for this drug to be IP-protected and for Pfizer to have turned a justifiable profit on Lyrica®, or does Pfizer now need to dominate the entire Lyrica® market — or at least most of it — for several additional years to recoup the cost for a pain medication?

And, if we find a way to partially de-genericize Lyrica® for Pfizer, are we going to do this on a one-off basis and say: "Pfizer, you're right, you spent a lot of money on pain, so you are going to get a little more time when no generic can get access to Lyrica®?" How do we know how much is enough? Does it make sense to have special rules for partially de-genericizing Lyrica® for as long as patent protection on the use lasts?

If the Lyrica® pain use patent expires ten years after all the other Lyrica® patent protection, does that fourteen-year period then become twenty-four years before any generic companies can freely come to market without owing some measure of tribute to Pfizer if the commodity they are selling is used as a pain patient? If Pfizer must allow generic copies of Lyrica® on the market, but somehow get the benefit of innovator-like pricing for pain patients and Walmart-like generic pricing for all other patients, don't we run the risk of creating a regime that is so complex and so graphic in demonstrating the gulf between generic pricing and innovator pricing for the same dosage form of the same molecule that it becomes almost impossible to get public support for this type of regime?

Just consider the Lyrica® patient in the United States, with no insurance or a high insurance co-pay, lamenting that if only she could be diagnosed with Parkinson Disease could she could afford her medicine for diabetic nerve pain.

Rather than take individual examples of enforcement difficulties for use patents, such as the Lyrica® story, in my view we must go way back to the beginning of the process and focus on IP incentives needed to assure the best medicines can be developed, not those with the best patents, which includes IP incentives to develop the best uses for those medicines.

When a scientist comes forward and says, "Can I put this exciting new discovery in the pipeline?" the answer to that question, in part, turns on the foundational question: Do we have IP protection that is sufficient to allow us to make that investment prospectively? If the scientist can be told we will have fourteen years of solid IP protection from generic drug entry, it is overwhelmingly likely that the IP protection will not be a limiting consideration in whether the new discovery can enter the pipeline. My guess is that fourteen years would have sufficed for Pfizer to develop Lyrica® for all the approved uses now on its label.

My concern is that after about fourteen years of protection for a molecule, even if the originator has come to market with new uses, it becomes very, very difficult to make the case for longer protection for that long-protected molecule. Any new regime adding additional protection should not be devised without giving full consideration to the politics of adding yet more IP protection. Critics of the industry should not be given an easy route to arguing that what the innovator industry is seeking is, in effect, a scheme to protect some commercial aspect of its old medicines forever.

MR. AINSWORTH: We are out of time.

Thank you to the panel for a fantastic session. Thank you to the audience.

[Session adjourned: 3:40 p.m.]

**University College London | Georgetown University Law Center**

# CLINICAL INNOVATION:
# Fair and Effective Incentives for New Uses of Established Drugs

*Georgetown University Law Center*
*600 New Jersey Avenue NW*
*Gewirz Student Center*
*Washington, D.C.*
*Friday, February 9, 2018 – 4:00 p.m.*

## Session 2H:
## The Impact of Technology and Large Databases on the Development of New Medicines from Existing Drugs

***Moderator:***
**Dr. Felix Frueh**[1]
*OpusThree, San Diego*

***Panelists:***
**Dr. C. Anthony Altar**
*Chief Scientific Officer and Senior Vice-President, Verge Genomics, Inc., San Francisco*

**Dr. Iris Grossman**
*VP, Head of Earl Stage Development, Global R&D, Teva Pharmaceuticals, Petah Tikva*

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MR. CORDERY: Welcome back, everyone, to the final two mini-sessions of the day, a fun one at the end and a serious one to begin with on the impact of big data. What we are going to do, just so everyone is clear, is this is going to be a forty-five-minute session, then we are going to the Judges' Panel. We are going to finish at 5:25 so that Robin can make some final observations, and we are going finish on the nail at 5:30 — at least that is the plan — so that everyone who needs to get away can get away. That is what we are going to do.

Our moderator is Felix Frueh from OpusThree, and I will allow him to do the introductions.

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* Opus Three is consulting for Teva Pharmaceuticals and was invited to participate in this conference on the request of Teva.

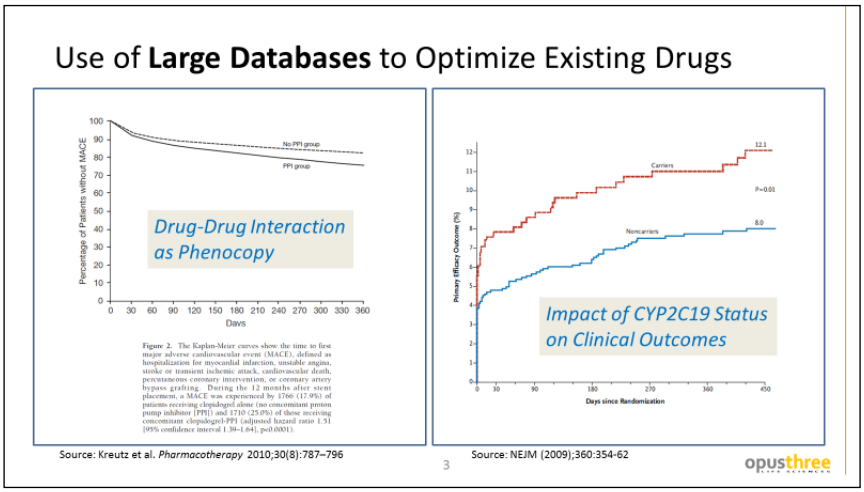
DR. FRUEH: Thanks for the introduction, and thank you to all of you who decided to stay. We are not the "fun" part, so you have to stick around for that. We are the "nerdy" part. I think we are the only panel where there are only scientists up here, so I hope you will stick with us.

We want to introduce some novel ideas and concepts into what you have all been discussing over the last day and a half. What happens on the science side? What are the new developments, the new technologies, that are introduced into drug development approaches that may help to actually make the ideas around patentability and exclusivity for either generics and/or novel uses of compounds that have been around for a while feasible?

I will kick it off with some examples that I have collected over the years, work that I was involved with and work that others have done. It follows really a general theme: that is, if you are looking at what is happening at the bench — and I don't mean you guys' bench but the lab bench — there are opportunities with genetics, genomics, and proteomics, all sorts of novel biomarker-type technologies that over the last couple of decades have helped to introduce a completely new way of thinking about who should be exposed to certain therapies, who should not be exposed, new targets that are being discovered, so that we can fine-tune the drugs in a way that we just could not have done before.

A couple of examples of this: when you think back to the vast majority of drugs and how they have been used over most of the years, it has been sort of "one drug fits all" paradigm for a particular indication. We realized, however, that (1) response rates really are not what they potentially could be, they are significantly lower; and (2) adverse events could perhaps be predictable if one knows a little bit more about the individual who gets exposed to the particular compound.

But how can you find out who is potentially at risk for either an adverse event or for lack of efficacy?




One example is looking at large databases. This is work that was done at the pharmacy benefit management company Medco, where I was involved in research. We hypothesized, based on a suspicion that we had about the way Plavix or clopidogrel is metabolized, that individuals with a genetic variation in

an enzyme that is responsible for the metabolism, the breakdown, and therefore the activation, of the drug may actually not get the benefit. If you cannot activate the drug — Plavix is a prodrug — you do not really derive what the expected benefit would be.

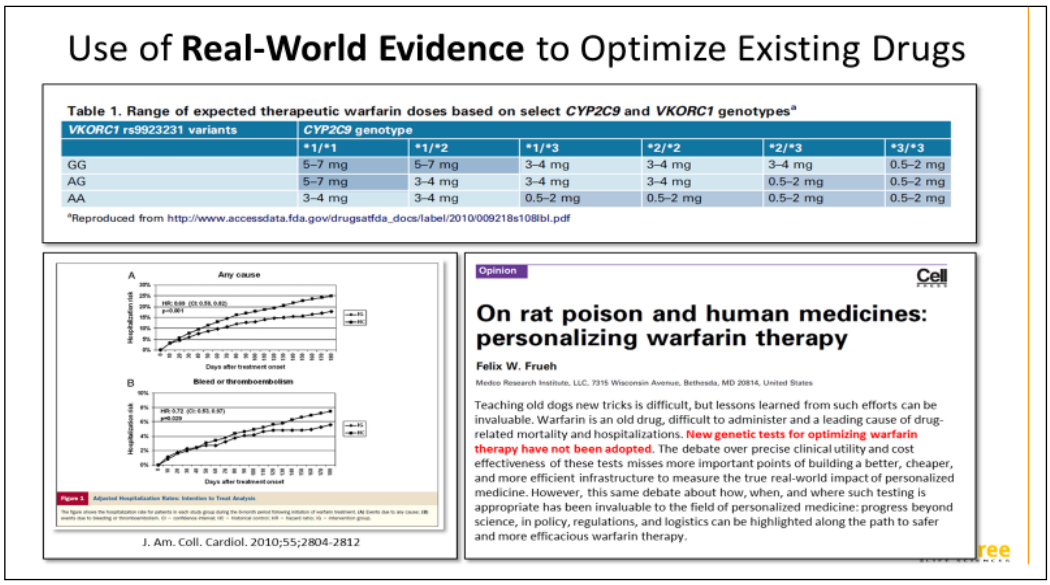
But we did not have any information on genetics. So how do you do that? We thought, *Well, if you have a second drug that blocks that very same pathway, you have a similar circumstance like a genetic variation. You have a so-called "phenocopy" of that.*

So we went into our database of about 65 million belly buttons in the United States and said, "Okay, let's look for outcomes that match the populations of patients that are just on clopidogrel versus patients that are taking Plavix and a proton pump inhibitor that blocks the activation of Plavix."

We found about a twofold increase in cardiovascular events in the population that had the additional drug, the proton pump inhibitor. Therefore, we concluded that most likely by blocking that activation pathway of Plavix you actually may not get the benefit from the drug. We now have the rationale to go back into a genetic study to see whether or not that is actually true.

On the left-hand side there, you see the data that came out of the database that we were looking at; that is, the use of big data or the use of a large database for hypothesis generation. On the right-hand side, you see the outcomes in carriers and non-carriers of this particular genetic variation.

That led us to do two things: (1) because we were operating a large pharmacy, we fired off alerts to pharmacists that they should be very careful in prescribing proton pump inhibitors at the same time as Plavix; and (2) at the same time, inform about potentially performing a genetic test so that if a genetic variation is present, an alternative drug therapy could be chosen.




A second example where real-world evidence really came into play is warfarin. As you may have heard earlier in the conference, warfarin is an

anticoagulant that has a very problematic clinical profile because it has a very narrow therapeutic window. That means that you really have to get the dosage just right. If you overdose, you may end up with bleeds; if you under-dose, you may end up with clots.

I put on the lower right-hand side an article that I wrote a few years ago.[1] Considering that this conference is about drug repositioning, I think warfarin is a pretty interesting example because it was actually sold as a rat poison initially. Rats were bleeding out. Well, it's an anticoagulant. It may also work in humans, which it then did, obviously with the exact same risk profile as also found in rodents. So, not surprisingly, it is difficult-to-administer drug.

But the point of it is that at the same time that alternative therapies came to the market — some of them were presented yesterday — the usability of warfarin did not really get optimized with the use of genetic testing. Genetic testing for two genes, 2C9 and VKORC1, could fine-tune warfarin therapy and make the drug actually a whole lot safer.

We demonstrated that in a clinical trial where we looked at the reduction of hospitalizations in situations where we introduced genetic testing into the marketplace. We found about a 30 percent reduction (in hospitalizations) that was mostly due to the fact that physicians felt more comfortable prescribing higher doses. Physicians were worried that they were putting patients at risk of harm and reduced the dose too much, and the genetic test gave them the confidence to start with a higher dose. Not surprisingly, that was a somewhat controversial finding because the drug has been on the market for a long time and it had never been compared to the newer therapies (i.e., comparing these newer drugs with genetically optimized warfarin therapy).

This is one of those situations where I think an old drug could be significantly enhanced. It is much cheaper to use than the newer competitors.

A completely different way that we are looking at disease is by characterizing it at the molecular level. We have heard in the indication sessions today and yesterday that most of what is written on any drug label is specific to a particular disease or disease-specific organ, e.g., breast cancer or lung cancer: you have a specific type of disease, it affects a certain type of organ, and that is what you are treating.

Until recently, there has been to my knowledge no label out there for the treatment of a molecular characteristic rather than an organ-specific disease. Basically, you are only looking at the presence or an absence of a specific marker and that is what your indication is.

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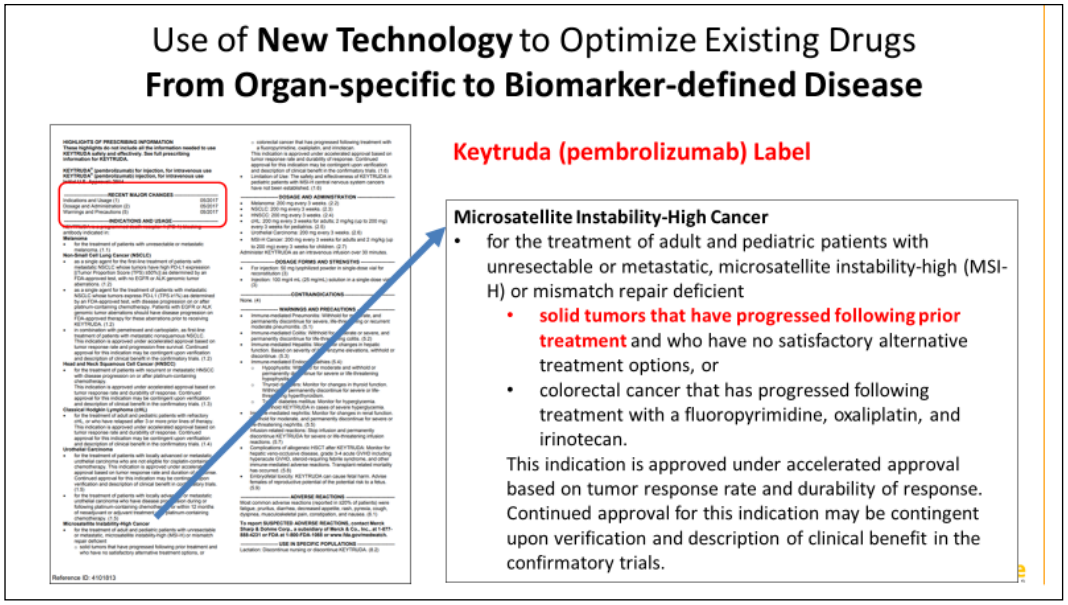
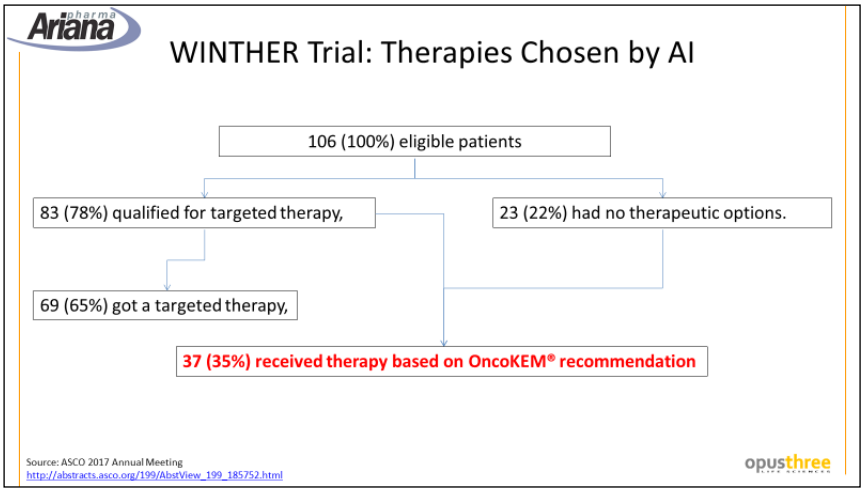
[1] Felix W. Frueh, On Rat Poison and Human Medicines: Personalizing Warfarin Therapy, Trends in Molecular Medicine 18(4):201−05 (February 2012), available at https://www.researchgate.net/publication/221880802_On_rat_poison_and_human_medicines_Personalizing_warfarin_therapy.




The first time this approach was taken was with the introduction of the notion of microsatellite instability for a drug called Keytruda (pembrolizumab) where it was shown that in the presence of microsatellite instability the drug actually works pan-cancer. Irrespective of the organ which is affected by the cancer, this drug has efficacy.

I think that for the first time we are looking at how these new markers can demonstrate clinical utility. We came to the conclusion that perhaps the way we are looking at the characterization of disease may be something that we have to rethink as well.

I am not a lawyer, I do not know what kind of consequences this has on patents or exclusivity or any of those things, but I do think that they could be wide-ranging and that it may require some rethinking about the use of older drugs. I see it as an incredible opportunity,



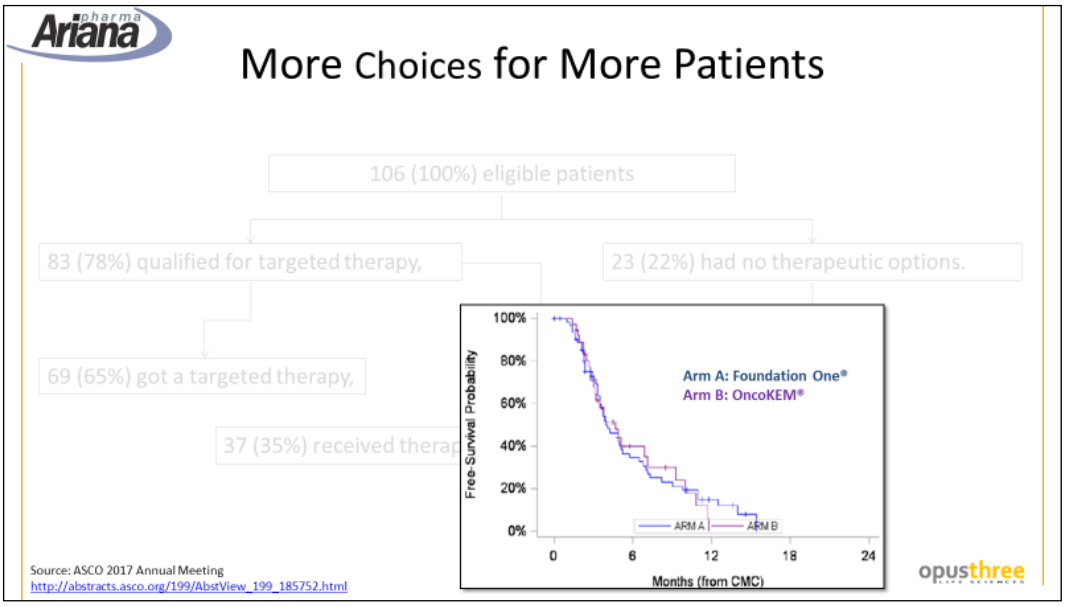

The last example I want to talk about is one where artificial intelligence (AI) has been used to identify therapies that otherwise would remain hidden from clinical use. This is a trial where a company called Ariana Pharma was asked to

participate in an effort called the WINTHER trial through the Worldwide Innovative Network (WIN) consortium, where the identification of targeted therapies through a resource from FoundationOne, basically genetic testing for the identification for appropriate targeted therapy, was compared to a completely different approach.

This different approach is based on an AI algorithm that includes such things as the mechanism of action of a great variety of drugs that have not necessarily anything to do with oncology but are related to the pathophysiology, the biochemical pathways, and patient characteristics, such as in this case gene expression profiling. In other words, it is a simulation and modeling approach to identify one or more drugs that may result in similar efficacious effects as "targeted therapies."

The trial found that if you are taking the proscriptive approach where you have a "companion" diagnostic-like identification of genetic variations upon which you then select the appropriate targeted therapy, because that is the way those drugs have been developed and the targets have been identified, you lack information for a certain percentage of patients, in this case 22 percent, that had no therapeutic option based on their molecular profile.

So what are you going to do with these patients? You want to treat them anyway. That is where the alternative AI approach came in. The results of this approach (called OncoKEM) were also used in additional cases where physicians were uncomfortable with the use of the targeted therapy for whatever reason, including, for example, cost. These therapies cost up to $100,000 a year, and if there is a much cheaper alternative with the same predicted efficacy profile, that might be a really nice thing to consider




The outcome is shown here as progression-free survival. You see that there is really no difference between the targeted therapy arm and the arm that was found for the drugs that were selected through that AI approach. The point here is that the drugs that were used in that second arm, the OncoKEM or AI arm,

are not oncology drugs. They are sometimes two or three drugs that were identified as blocking relevant pathways associated with the type of cancer based on the molecular characteristics that were identified by gene expression profiling.

There is absolutely no way that you can *a priori* predict these findings. So how do you generate patents for these situations? Every patient in this case had a different drug regimen. What is now the patentability for drugs in this type of situation where the "off-label use" is something that is completely unknown? You have a repertoire of different compounds on your shelf that do things that you know about based on your molecular understanding of the pathway, for example, that the drug interacts with, and you select them based on how you characterize the disease.

If you think about the example that I was using before with Keytruda and you are now thinking about this last example, what we are looking at is the future of where drug therapy is going to go. It is, in some ways, a complete departure from the one-to-one relationship of a compound and a particular indication.

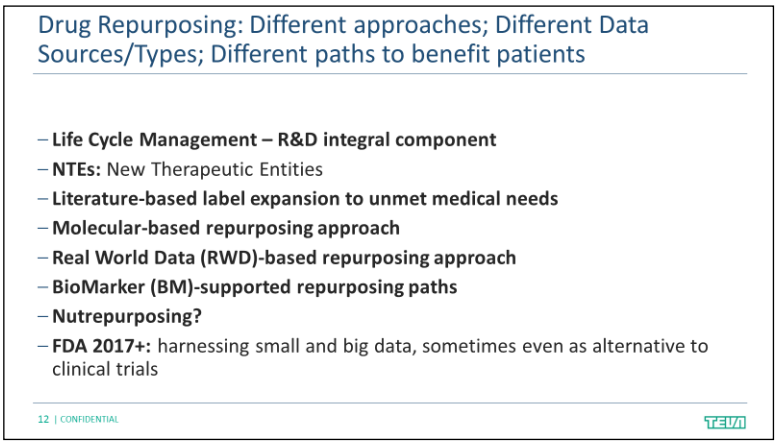
I want to challenge you to think about how one can encourage this kind of approach, where you are having likely the most benefit from an IP perspective in the algorithms that go into the identification and the characterization of disease rather than the molecule itself.

I want to leave you with that.

First up is Iris, and then Tony.

DR. GROSSMAN: Hello. Thank you for the invitation. A really fascinating conference.

I want to share with you some perspectives from a systematic approach to repurposing. I am at Teva on the specialty R&D side, but working very closely with my Generics colleagues, really coming out of this belief that we have the unique ability to look at the intersection between generics and specialty. The strength stems from the fact that we have internally very massive high expertise in formulations and other ways to deal with generics, as well as the world's largest cabinet of medicines; and then specialty capabilities, particularly focusing on diseases of the central nervous system (CNS), pain, headache, and respiratory disease. I will share with you the strategy that I built around this.




These are the different points I want to touch on. I will not go into a lot of detail on all of them, but this is kind of the sphere as I am thinking about what we have been doing, as an industry, around the concept of developing existing compounds for different indications.

Let's start with the most common approach to repurposing, which literally every specialty pharma company uses, which is "life cycle management" (LCM). We *always* look for additional indications, usually in adjacency indications. We start these LCM activities very early on in discovery, development, and onward along the pipeline.

I just received a report this morning stating that Keytruda (Merck) has 700 — at least that is what it says there — different clinical trials ongoing, so apparently quite a bit of life cycle management.

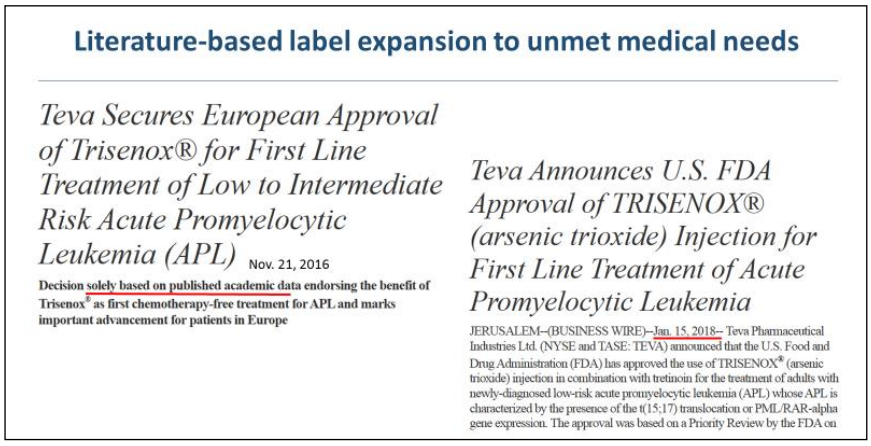
We at Teva have Austedo™, which in itself is a repurposed drug. It is deuterated tetrabenazine. It was approved last year for symptomatic relief of chorea associated with Huntington disease, and is already approved for Tardive Dyskinesia as well. In addition, we are in trials for treating Tourette's syndrome — all very important unmet medical needs. Thus, again, life cycle management at a very broad perspective.

Now we will go through some of the more complex types of repurposing or repositioning out there.

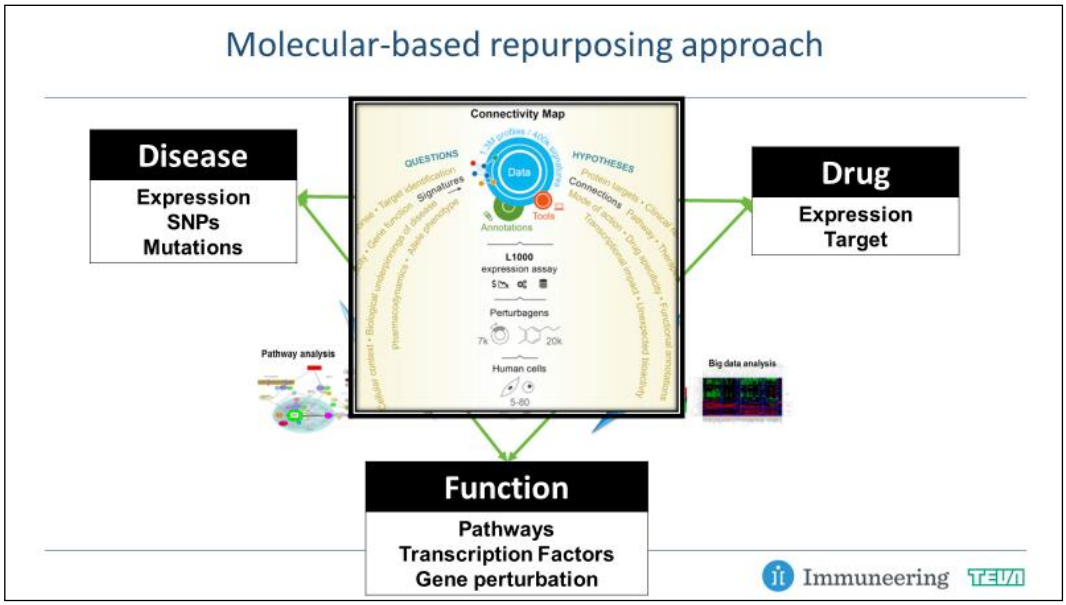

One that we won a prize for is what we call novel therapeutic entities (NTEs). It is the idea that with the exact same entities — we do not change the chemical itself but change the way the drug is formulated or delivered — we can introduce a very profound benefit for patients and physicians. For instance, we are going into late-stage development in just a couple of months for a once-in-two-months or once-in-three-months risperidone injection for schizophrenia, which is an amazing potential quality-of-life solution for a population in whom the adherence challenge today is very high, needing to inject every other day or take a pill every day. And there are many other examples in this category.

Let's go to the other ways where we are really repositioning in the sense that we discussed today and yesterday.

The next approach I am going to discuss is a pretty interesting one. We did not even know it would be successful, given the strict regulations around prospective data submissions in general. We are very grateful to the regulators for realizing that a literature-based approach can also enable expansion of the label.

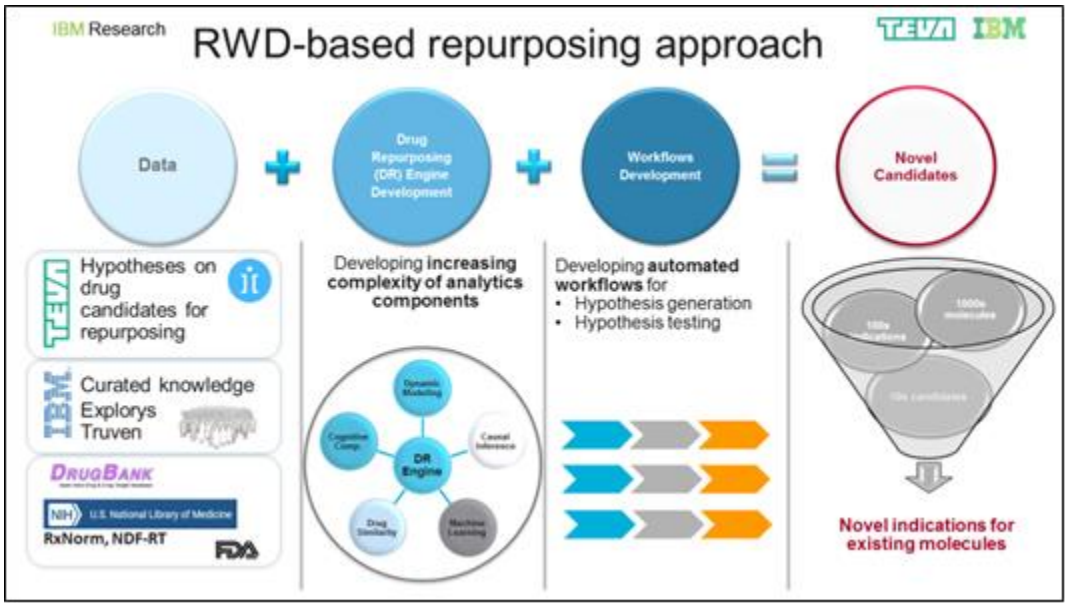



This is Trisenox®, which was launched in 2002 for acute pro-myelocytic leukemia. As you can see, in 2016, solely based on published academic data, we were able to expand the label in Europe. Then, shortly thereafter, a year and a half later, we got the same approval by the FDA, which is really remarkable because it is the first time that a regimen can be given to patients without the need for chemotherapy in this otherwise life-threatening disease.




Now the area where I spend most of my time. I am a geneticist with a background in medical sciences. Where my team has been focusing its approach is a very systematic screening of what we understand about systems biology, anything from sequence genetics to RNA expression, proteomics, electronic medical records (EMR) — and the list goes on and on — and looking also at social media as a marker.

From my perspective, any type of data that I can collect in a reliable, cohesive manner is a source of understanding the disease, the drug's mode of action, or the patient needs in totality. I think about those parameters, sometimes in integration or at other times as orthogonal ways, that in the end I require. We have very strict criteria that help us filter through what is a real reliable signal and what is unlikely to be useful.

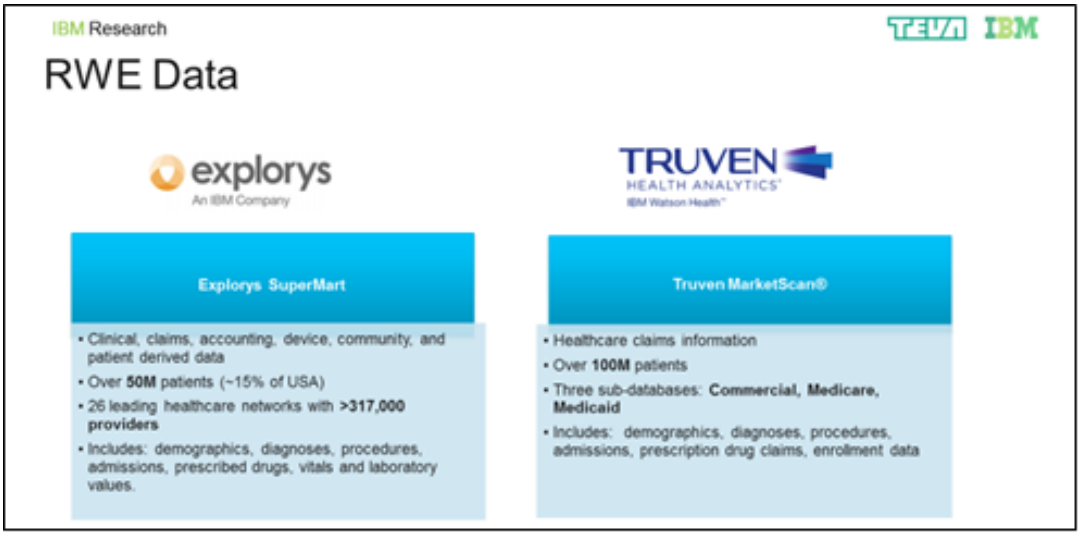



There are many databases out there. The Connectivity Map (CMap) from the Broad Institute, just one example, has now almost 1.5 million profiles. They take cell lines and they treat those cell lines with 20,000 different drugs at several different doses with several different regimens. This is a very systematic approach. There are other databases like that. These are amazing. Really, truly amazing.

But a lot of caveats. For instance, I am interested in the CNS diseases. The profiles that I can infer from a transformed cell line are, let's say, limited. There are many different phases of confirmation that we are doing: *in silico* confirmation and then experimental confirmation, first in the expression level, then we go into preclinical models, and then we do the animal model confirmation. So it is quite a rigorous approach, undoubtedly shorter than starting from scratch, from discovery of a new chemical entity.

However, this is by no means color-by-number . . . having more data did not make it easier; it actually made it a little bit more complex. There are much more controversial outcomes, and it is difficult to tease out a true signal when you go into these massive data sets and analysis.

Another approach is shown on the next slide: In this conference, we talked a lot about real-world data. In this slide I describe another collaboration, this one is with IBM Research. We looked at different databases here. These are all either internal information that we have gathered, internally created or acquired, and then publicly available data. There are many, many databases that allow you to go through useful parameters on the disease, therapeutics and patients' characterization. You do not need to be big pharma or have large funding to start such initiatives.

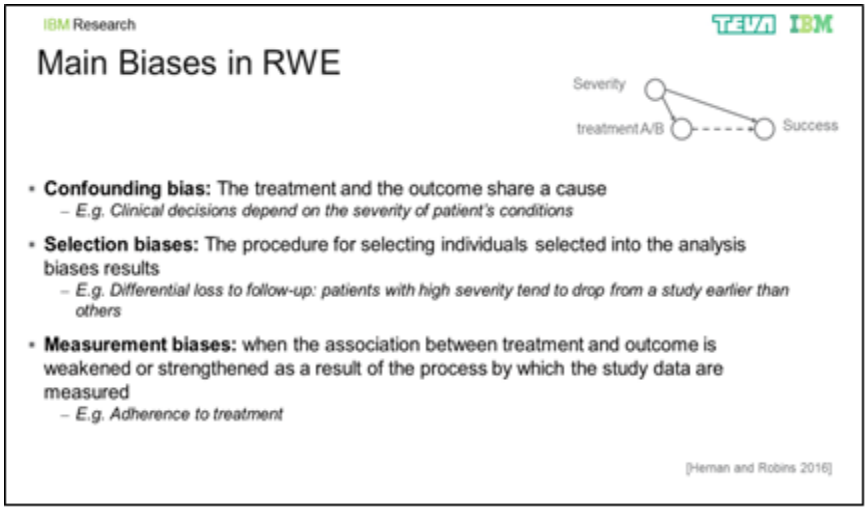



Then we apply many different types of artificial intelligent (AI) or machine learning, and other simple statistics can work quite well for certain indications. Then you go through looking at different types of inferences, as long as you really know how to define your scientific questions. So what are the endpoints? You really need to go through this very carefully, not to fall for biases or for what would seem like a positive signal, but actually is not informative.

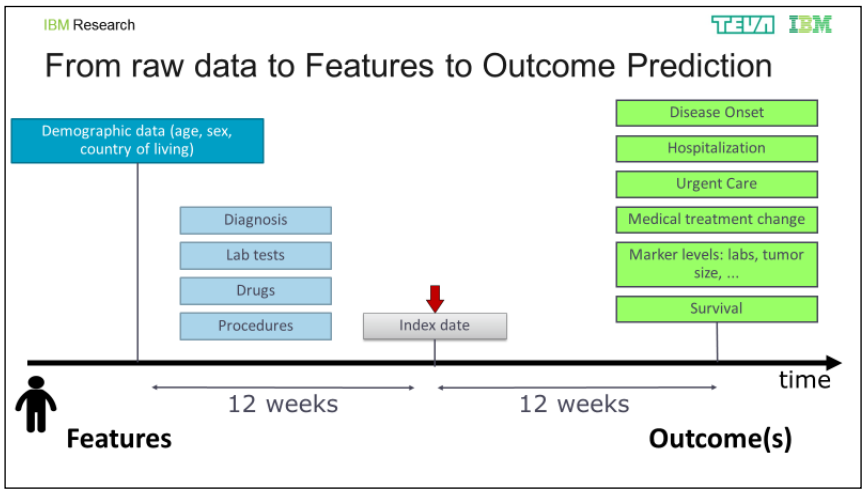
Then you create these flows: how do you generate hypothesis, test hypothesis retrospectively, then test prospectively, and so on. You go through this, as is shown in this funnel. At the end of the day, you end up with very few candidates that you take forward.

My colleagues in other companies or academia confirm our own experience, which is that when you start from a gene expression type of screening these public datasets, about one in ten would be confirmed at the first stage: did the genes that you expect to modify actually turn out to be modified when you did the test by yourself, as compared to what you inferred *in silico*? This is just to give you a sense of the attrition there.

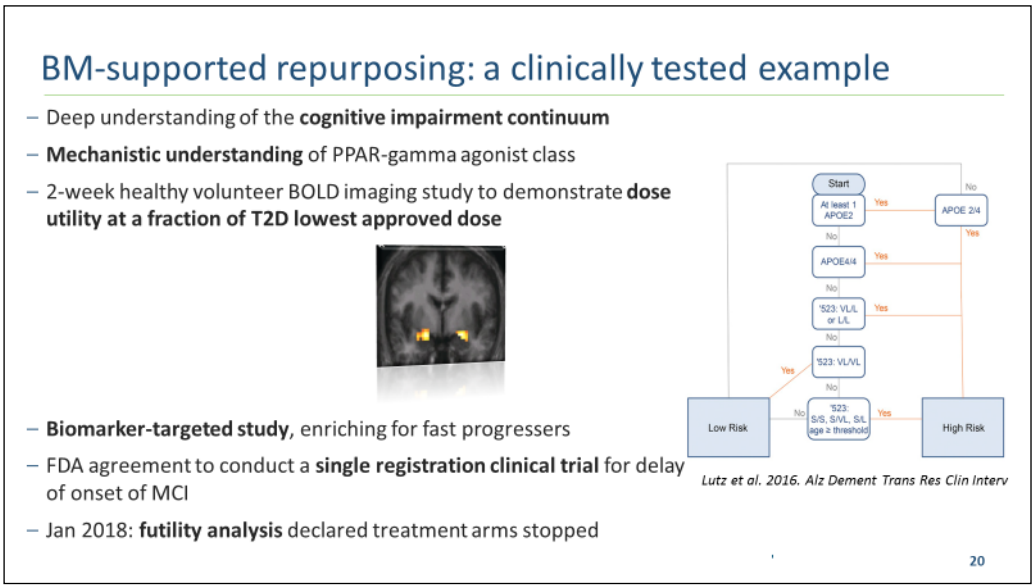
To give you a sense of this endeavor, IBM research has a massive data set. This includes in totality more than 150 million patient records, pf which ~100 million are electronic medical records. You can look at the general characteristics here. Truven (comprising the remaining ~50M records) is a claims database. So a lot of data. They have for the United States relatively long follow-up, so a great resource for us to do this massive screen.




I cannot emphasize enough how many biases are included in a data set like that. It took us about a year to sift through the database for a single disease and look within that disease for candidates. On this slide are just a few examples of the biases that we see. It is not always obvious how to tease them out, how to find proxies, and how to really clean your data as you go through this analysis.




Once you do, you have to go through all these processes of defining what is the pre-index state, prospectively what you are looking at, how you are going to define your population, what are the outcomes. Usually, the outcomes that you get out of an EMR are very different than the outcomes that I design in my clinical trials. How do you reconcile what at the end of the day is meaningful? How do you define all these parallel secondary endpoints that would help you decide if the signal is true or false?




This is an example of a repurposed drug that I had been privileged to be part of before joining Teva, when I was with Zinfandel Pharmaceuticals, headed by the late Allen Roses.

This was a very interesting approach in the context of this conference because the idea came out of a deep understanding of mechanisms of disease. We were interested in cognitive decline and ultimately Alzheimer's disease. It was key to understand back then that to tackle the disease you need to go into earlier stages of the disease. We all know now that it is literally too late to start treating, definitely in the context of clinical trials, at mild or moderate post-symptomatic stages. Accordingly everybody now is going into the mild cognitive impairment (MCI), the stage before Alzheimer's.

We had a good understanding of the PPAR-gamma agonist class. We were all ex-employees of Glaxo. There we studied rosiglitazone in the context of Alzheimer's as well.

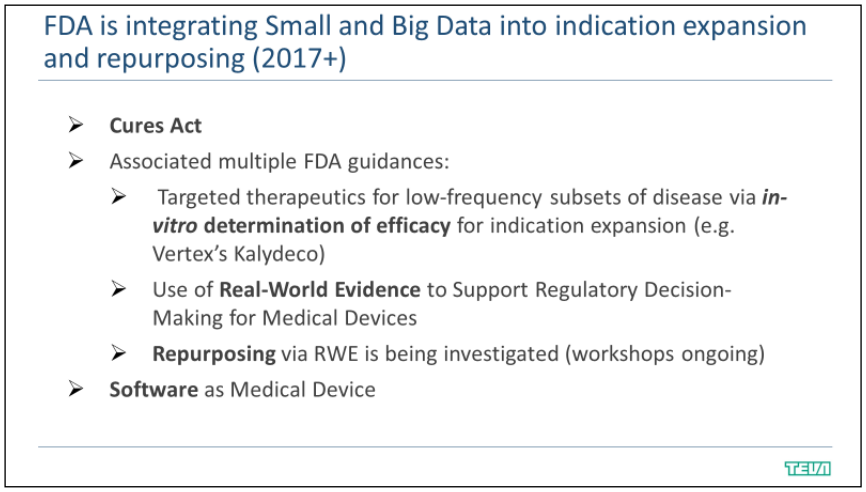
Then we decided to go after pioglitazone, which is a cleaner or a safer PPAR-gamma agonist. However, we knew it was highly used in the market and was going to be genericized by the time we finished our clinical trials. And we knew we were going for literally a prevention indication. So you want to make sure you are giving people the lowest dose possible, exposing them to minimal risk, for decades of chronic therapy. You do not want to introduce risks, which are associated with any pharmaceutical, to patients before they are really patients. They are pre-symptomatic people, like any of us.

We ran a very short two-week healthy volunteer brain blood oxygenation level dependent (BOLD) imaging study. We showed that the area in the brain, the hippocampus, which is first affected in Alzheimer's, is the area where we can increase the oxygen utilization of the neurons and supportive tissue. That was the basis for dose selection. It was just about a tenth of the minimal dose that was used in the market at the time, and I think still today. So, clearly, a barrier for generic competition from that perspective.

Then we got approval, or at least a verbal statement, from the Agency that we would be able to run a single Phase III clinical trial, given the indication and the length of a trial like this. We ran the study in biomarker-preselected populations. The idea was that we selected individuals we knew would be relatively quick progressers because then the length of the study would be something we can look at. Otherwise, it would be presumably fifteen years — clearly not feasible.

All these in totality created a very unique package. We partnered with Takeda for the TOMMORROW study. Unfortunately, literally three weeks ago the futility analysis was announced to have been met, so the treatment did not work. But that was a very valiant effort toward repurposing, and the biomarker arm of the study is still ongoing.

Just to finish up, repurposing can be all kinds of things. I do not know if you saw this article. A meta-analysis recently published on caffeine and coffee compared to decaffeinated drinks finds all kinds of very good things about drinking a lot of coffee — not too much, but relatively a lot.[2] I think this puts everything in perspective. Literally, for every trait that was tested there, including neurological diseases and cancers, it had benefits. This is amazing. I am not advocating anything here, but it is an interesting publication.




I think the FDA has been particularly innovative in the last year and, with the Cures Act[3] and the commitment to enact it, we are seeing dramatic changes that would be particularly relevant in the area of repurposing. It opens the gate for a lot more innovators to go into this field because now we can use in certain circumstances *in vitro* data, real-world data, and software as a medical device. All these enable me as a scientist to innovate more, to come up with more candidates.

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[2] Grosso et al., *Coffee, Caffeine, and Health Outcomes: An Umbrella Review*, ANNUAL REV. NUTR. (2017) Aug 21;37:131-56. doi: 10.1146/annurev-nutr-071816-064941, *available at* https://www.ncbi.nlm.nih.gov/pubmed/28826374.

[3] 21st Century Cures Act of 2016, Pub. L. No. 114-235, __ Stat. __, codified at 21 U.S. Code § 355g (Cures Act), *available at* https://www.gpo.gov/fdsys/pkg/PLAW-114publ255/pdf/PLAW-114publ255.pdf.

My plea to you is to create the right incentives to bring to patients more efficacious and safe solutions of this type. Thank you.

DR. ALTAR: Hi. I am Tony Altar. I am the Chief Science Officer at a company called Verge Genomics. As you might tell by the name, we are focused on genomic-based drug discovery.

When Felix asked me to talk about the application of new technologies to repurposing drugs, at first I didn't think I had much to say. Then, as I thought about it, I realized in fact that my own research experiences touch on this.

I am only going to show you one slide. It is late, and I don't want to be the speaker who is between you and your coffee, after what you have just heard from Iris Grossman about the benefits of caffeine. I want to talk about these four topics because I think they are each interesting examples of drug repurposing.

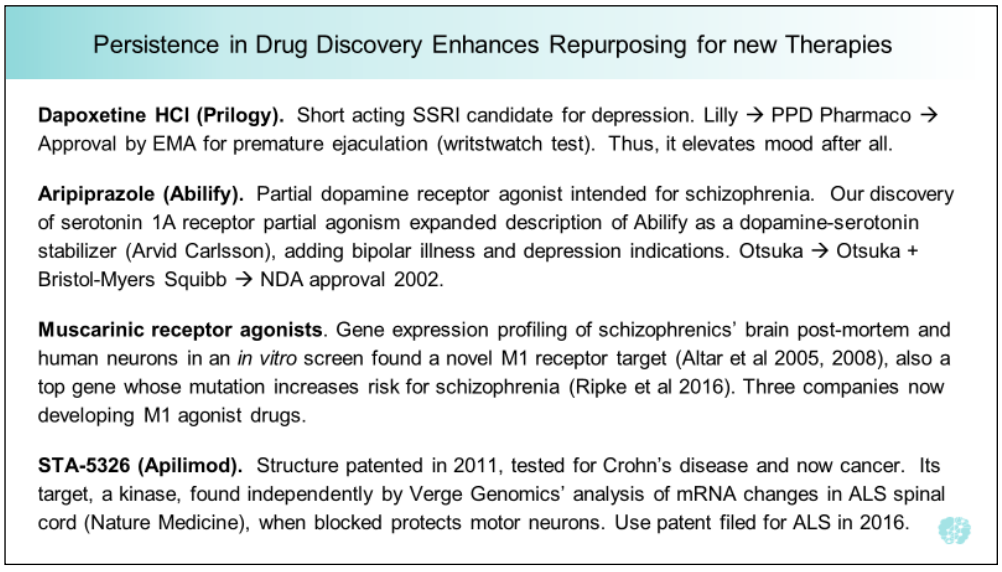
The first question we have to ask is: Why is there drug repurposing? Why do we have this opportunity?

The answer is fairly straightforward, and that is because nature itself is biologically conservative. There is a finite number of biochemical pathways that all organ systems — in fact, all cells within the brain — use to metabolize, to signal, to communicate, to do a variety of their functions.

The reason we have side effects from drugs is because a drug target in the brain also is a target in the liver, or maybe a target in the adrenal gland, and so we get wanted effects but we also get unwanted effects. So, right off the bat, you know there is a basis for repurposing drugs because drugs activate redundant systems in different tissues. What is good for one tissue may be good for another, especially in disease.

When we run a clinical study, we are only looking for the action of that drug on one particular patient population because we are running after one particular biochemical mechanism for one disease. But the side effects tell us there are other mechanisms that are in play by the same drug.

So, as scientists, we are in a sense constantly repurposing the drugs we study. It is a very natural process of what we do. As I thought about my own work, I realized that was the case.



Let's look at the first example, and we are going in increasing order of technical complexity. The first one is dapoxetine hydrochloride. This was a Lilly drug designed to treat depression. It is a selective serotonin reuptake inhibitor (SSRI).

The problem with dapoxetine is it very short-acting. You give it to the patient, it is chewed up by liver enzymes, the kind that we have already heard about, and the drug is gone in several hours. Interestingly, if you want to treat depression with an SSRI, it takes four-to-six weeks of chronic delivery to get an antidepressant effect.

We realized when we were evaluating a variety of drugs that were coming out of Lilly that wanted to get rid of these useless, short-acting SSRIs. Interestingly, one of the side effects of this drug is it delays ejaculation; it decreases sexual interest in women; it increases the ejaculation latency in men. Ah! Maybe there is a repurposing of this drug for men who have the problem of premature ejaculation.

So for the men in this study we used this incredibly technical test with a stopwatch and measured the duration of time until ejaculation occurred. [Laughter] Dapoxetine was fantastic; it lengthened time to ejaculation. Not only that, it would wear off in a few hours. As a result, I think we ended up with an effective antidepressant mechanism after all.

Fortunately, the regulators in Europe agreed. Prilogy was approved by the EMA for premature ejaculation and is a drug that is now on the market.

I thought that was a great end-of-conference example to lighten up your afternoon a little bit. That story is completely true. [More Laughter]

The second example: I was lucky enough to be the Global Director for Otsuka Neuroscience. I managed the team that discovered Abilify. Abilify is another drug that we as scientists were focused on as being effective for schizophrenia. Abilify is what is known as a partial agonist at the dopamine D2 autoreceptor. You probably know that blocking dopamine receptors is the mechanism for treating schizophrenia. In fact, every drug to date does it that way.

We in the lab were working on other receptors and discovered that Abilify was also a partial agonist at a serotonin receptor, an action which we understood from the large literature. Iris talked about literature-based discovery as a mode for repurposing drugs. We learned about partial agonists at this same serotonin receptor as being good for depression and anxiety.

As I recall, we rewrote some of the invention claims for Abilify, not only to be used for schizophrenia but for the twofold-to-threefold more common problem of bipolar disease, known as manic-depressive illness; and also for depression itself, which is ten times more prevalent than is schizophrenia in the general population.

As a result, we were able to work, very kindly, with Dr. Arvid Carlsson. Arvid discovered dopamine and received the Nobel Prize in 2000. I worked closely with Arvid, and had myself started some of the same work back in the mid-1980s, which underscores my theme of persistence as the key in drug discovery. Arvid came up with the concept that Abilify would be a "dopamine-serotonin stabilizer"; it would keep the levels of both of these neurotransmitters at

a lower but a fixed, intermediate level. That is how you could treat schizophrenia and how you could help with the depression and anxiety syndromes of bipolar disorder and depression itself.

As a result, we did a partnership with Bristol-Myers Squibb. We developed Abilify and filed the NDA. It was approved in 2002. Abilify went on to become the world's biggest-grossing drug in 2014. Amazingly, in 2015 it sold almost $10 billion. I think some other drug snuck up ahead of that, probably Lipitor.

That was a very gratifying example because we were able to essentially repurpose this drug for even more prevalent indications. Some of the high points of my career have been getting hugs from people who have been treated effectively by Abilify.

The third example is discovering a novel use for muscarinic receptor agonists. This comes from work that we did at a company called Psychiatric Genomics that I ran in the early 2000s after leaving Otsuka.

We profiled the brains of patients who had died with schizophrenia and we asked the simple question: what are the genes whose expression is changed because these patients had schizophrenia?

As we did this, we looked in the areas of the brain that are associated with schizophrenia, particularly the hippocampus. We found that cells in this brain region looked like they were suffering from diabetes. They had a profile of gene expression which looked exactly like diabetes.[4]

This gets back to my earlier point that different tissues can express the same biochemical deficit and produce wildly different symptoms. You can get diabetes if gene expression changes in the pancreas and the muscle; you can get schizophrenia if you have this diabetes-like biochemical change in the brain.

That is exactly what turned out to be the case. We replicated this diabetes profile of gene changes in another cohort of patients. By doing *in vitro* screening, we were able to identify that the only class of drugs that could reverse this diabetes-like profile in neurons were muscarinic acetylcholine receptor agonists.[5] These are drugs that had never been purposed for treating schizophrenia before and this was a brand-new way of treating this disease. In fact, as I mentioned, to date the only drugs, including Abilify, that treat schizophrenia are drugs that lower dopamine signaling by essentially blocking the D2 receptor.

We also found, through Stephan Ripke's work in 2016, that the very same muscarinic 1 receptor is one of the top genes whose variation is a risk factor for schizophrenia disease.[6] That is an important finding.

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[4] C. Anthony Altar, et al., *Deficient expression of proteasome, ubiquitin, and mitochondrial genes in hippocampal neurons of multiple schizophrenia cohorts*, BIOL. PSYCHIATRY 58: 85−96 (2005).

[5] Altar, C. et al, *Insulin, IGF-1, and muscarinic agonists modulate schizophrenia-associated genes in human neuroblastoma cells*, BIOL. PSYCHIATRY 64: 1077−087 (2008).

[6] *See* A. Sekar, S. Ripke, et al., *Schizophrenia Risk from complex Variation of Complement Component 4*, NATURE 11;530(7589):177−83 (Feb. 11, 2016), *available at* https://www.ncbi.nlm.nih.gov/pubmed/26814963; T.H. Pers, P. Timshel, S. Ripke, et al., *Comprehensive Analysis of Schizophrenia-associated Loci Highlights Ion Channel Pathways and Biologically Plausible Candidate Causal Genes*, HUM. MOL. GENET., 15;25(6):1247−54 (Mar. 16,

So we have a confluence of data from genomic work and genetic work which points to this one receptor as likely being involved in the cause of schizophrenia. Now three companies are working on developing a very interesting class of muscarinic agonists, just as we predicted, to treat schizophrenia. Those compounds are getting a lot of attention now in terms of development.

Finally, I would like to end up with work we are doing now at Verge Genomics. There is a compound called apilimod, which, interestingly, we pulled out with similar methods employed at Psychiatric Genomics — so here I am, fifteen years later, now working for a company that is a genomics company, and we are now using gene expression profiling in patient brain tissue as a basis for curing neurodegenerative disease.

We are focusing on amyotrophic lateral sclerosis (ALS) and Parkinson's disease (PD). We did a very similar thing. We got all the publicly available data from ALS patients where the motor neurons that die in the disease were profiled for how their gene expression patterns differ from those patients who did not have ALS but are age-matched. We found a very impressive, consistent signature of about 200 genes out of the 10,000 that exist in neuronal tissue that had a characteristic change in their expression in ALS patients' tissue. Among those genes were genes that are known to be targets of this drug apilimod.

We took apilimod and exposed it to motor neurons in culture. Interestingly you can grow motor neurons from stem cells. If they came from ALS patients, they die faster in culture compared to the motor neurons that are derived from stem cells that came from normal healthy people. With this nice *in vitro* model, we put apilimod in there to block this enzyme and we actually protected against the loss of the motor neurons. We also went on to produce *in vivo* data showing that we could protect against an ALS model in the animal model as well.

A patent was filed — another example of repurposing — for the use of apilimod in treating ALS, and apilimod, as I mentioned, was patented as a structure in 2011. It has been tested by other companies for Crohn's disease — it failed — and now it is being tested in cancer patients.

We are not sure that apilimod would be the actual drug to go with because there are predicted limitations of its blood-brain barrier penetration, but analogues that can get into the brain are much more likely to be candidates that we are likely to go after. This work was just published this week in *Nature Medicine*. It came out on Monday.[7]

This is another example of where you can use some pretty high-level innovative approaches and come up with a very traditional approach, a single drug which now has to go through the standard kind of development pathways. That is in our plan for our ALS and our PD programs.

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2016), *available at* https://www.ncbi.nlm.nih.gov/pubmed/26755824.

[7] Yingxiao Shi et al (2018) *Haploinsufficiency Leads to Neurodegeneration in C9ORF72 ALS/FTD Human Induced Motor Neurons*, NATURE MED., published online (Feb. 5, 2018) https://www.nature.com/articles/nm.4490.

These four examples come from my own personal experiences. As I look back, these are some of my favorite career highlights. They are all examples of repurposing drugs for new indications. By looking at similar biochemical changes, like for diabetes now, maybe you can repurpose the mechanism for a new indication, which is something we have done for schizophrenia.

We have learned a lot from listening to you today about patent strategy and the legal aspects of this, and I really appreciate it.

The message I would like to leave you with is the thought that all of us scientists are essentially repurposing when we are studying drugs because most approved drugs have almost always been studied for something else. We are finding new uses either for old drugs or for known mechanisms. If it were not for that, I am not sure where we would start from, but that is another chapter.

Thank you.

DR. FRUEH: Thank you both very much.

I notice we are almost out of time. I have a lot of questions prepared. We will skip all of that. I want to open it up to the audience for questions.

QUESTION: Dr. Tony, it has always been a mystery to understand the interaction of the releasing neurotransmitter in the synaptic cleft with the receptors present at both pre- as well as post-synaptic levels.

Dapoxetine, just like all of the SSRIs, like fluoxetine and paroxetine, was initially very successful and popular for treating depression. Some of the side effects we know also are because of the binding of the drug basically with subtypes of receptors leading to a side effect like delayed ejaculation and are turning out to be a positive case in another way.

A contrasting scenario is there is a class of drugs known as selective serotonin reuptake enhancers. The classic case is tianeptine. What is your experience, because you have been doing a lot of research in CNS disease? A pharmacologist gets confused. What is happening exactly at the synaptic cleft?

DR. ALTAR: What is happening with drugs like that — and this is getting pretty technical, guys, and really nerdy science — is you have a target of the neuron and then you have the nerve that innervates it. This innervating nerve releases the neurotransmitter. That neurotransmitter binds to a receptor on the target neuron. That is called the post-synaptic receptor.

But these systems are very clever. They have the same receptor on the terminal as a sensing organ. The neuron says: "Oh, I see how much neurotransmitter is in that cleft; there is a lot of it, so I am going to slow down my rate of firing." What some antidepressant drugs can do is block that sensitive presynaptic sensor receptor so the neuron goes: "Oh, I don't have any neurotransmitter out; I better start releasing a lot more." So they are fooling the negative feedback system to release more neurotransmitter.

QUESTIONER: Right. But one of the major limitations there is we do not quantify at the molecular level exactly how much neurotransmitter is required.

DR. ALTAR: Yes.

DR. FRUEH: I am sorry to interrupt the question, but I believe we are getting very much into the technical weeds here that very few people understand. We can maybe take that offline afterward.

QUESTIONER: That's fine. Thanks.

DR. FRUEH: We probably want to move on, unless there is one quick last nontechnical question at that level that anybody has to get off their chest.

QUESTION [Dr. Amitava Banerjee, UCL Farr Institute of Health Informatics, London ]: Thanks very much. All three really great presentations.

I am very interested in the field of informatics. One area I find where that is coming up is an over-hyping of proteomics and artificial intelligence. One of the areas that I have had to get into by chance in the United Kingdom is making sure that doctors are trained in evidence-based practice in these new areas of data science.

I was very interested in Iris's example where it ended up with a futility study, because in the United Kingdom at the moment it is being seen that every bit of research has to have proteomics and genomics, thinking that is going to be a panacea. I wondered if you could speak to how you manage to show that there is really amazing progress going on, but a handle on the hype as well.

DR. GROSSMAN: So welcome to my world. I always find, particularly after a study fails, that everybody wants to talk with me. Maybe you fix it with some genomic profile.

In my perspective, it is about education, as you say, really curbing enthusiasm *a priori*, explaining what to expect and how to go very systematically about it to ensure there is *a priori* a very clear definition. So, even in your exploratory endpoint section, it needs to be prespecified pretty clearly what you are going to do. You want to do some exploration, but you do not want to shoot in every direction, and then obviously you are going to have lots of random positives. So it is all about being very methodological, really understanding the science and the mechanisms as related to specific diseases, as related to specific tissues, and so on, and then being very critical when you do the interpretation.

There are many futility analyses or now there are many other mechanisms where you do the adoptive design to really ensure you know who is looking at data, bringing in some experts who are independent and are going to tell you what you do not want to hear, and have the accountability to say no to a program you really liked and nurtured for years but is telling you it is not going to work.

DR. ALTAR: I will just add two quick things.

One is the quality of the data that comes in. I am not necessarily a big believer in big data, but I sure am a believer in really good-quality data. I will take a small amount of great-quality data any day over big, big noisy data. But sometimes that is all we have to work with.

The second thing is to use tools in the laboratory to then validate the genes that look like they are really important players or the pathways that you identify from the big data. So the *in vitro* cell model I described — *in vivo* animal models can play a big role there, too — can be used to take these gene candidates that come out of the initial genomic analysis, and now systematically test each one and see which ones really do continue to validate the hypothesis that you got initially. That is the second half that is just as critical as the first half.

DR. FRUEH: Thank you very much. Thanks everyone.

[Session adjourned: 4:55 p.m.]

# University College London | Georgetown University Law Center

# CLINICAL INNOVATION:
# Fair and Effective Incentives for New Uses of Established Drugs

*Georgetown University Law Center*
*600 New Jersey Avenue NW*
*Gewirz Student Center*
*Washington, D.C.*
*Friday, February 9, 2018 – 4:55 p.m.*

## Session 2I:
## Judges' Panel

***Moderator:***
**Karl-Heinz Metten**
*Boehmert & Boehmert, Frankfurt am Main*

***Panelists:***
**The Hon. Arthur Gajarsa**
*Former Judge of the Court of Appeals for the Federal Circuit, Washington D.C.; Distinguished Jurist-in-Residence, Franklin Pierce Center for Intellectual Property, University of New Hampshire, Concord*

**The Hon. Roger T. Hughes QC**
*Former Judge of the Federal Court of Canada*

**Prof. Robin Jacob**
*Sir Hugh Laddie Chair in Intellectual Property, University College London; Former Judge of the High Court and the Court of Appeal of England and Wales,*

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*Senior Judge, Court of Appeal, The Hague*

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MR. METTEN: Now we are nearly at the end of this wonderful conference. This is the judges' panel. It will be mainly a Q&A session. And, there will be brief reports and updates.

Let me briefly start by introducing the panelists.

You know pretty well Prof. Sir Robin Jacob. He is the Sir Hugh Laddie Chair in Intellectual Property and Director of the Institute of Brand and Innovation Law at University College London. He was a High Court judge and a Lord Justice of Appeal in the Court of Appeal. He is the Chairman of the Advisory Panel on the Appointment and Training of Judges of the Unified Patent Court, I think quite important. He also acts as an arbitrator and mediator. And, as we already have heard, he has written extensively on IP matters.

Rian Kalden is a Senior Judge in the Court of Appeal of The Hague. In

2002 she became a judge at the District Court of the Hague. She heads the division of the Court of Appeal that covers IP cases. She has also written on IP matters, for example, about supplementary protection certificates (SPCs) for second medical use.

The Hon. Mr. Arthur Gajarsa was a former United States Circuit Judge of the United States Court of Appeals of the Federal Circuit 1997−2012. In 2012 he joined the University of New Hampshire School of Law and was appointed Jurist-in-Residence.

The Hon. Roger Hughes is a former Judge of the Federal Court of Canada, which he joined in 2005. He also worked as a partner in a Toronto-based law firm before that and served as a past president of the Patent and Trademark Institute of Canada and as director of the Advocates Society. He is now practicing as an arbitrator and a mediator.

Let me give a brief summary of the two days just as a starting point for the Q&A session.

We have learned that generic repurposing is rare and it must be the goal to increase the amount of second medical uses. Here the judges, also, come into play and have their responsibility. We heard the plea that patents must be in the focus, that is very important. And there must be a reward for those activities to provide for second medical use. We also learned it must be a system where we have legal security which is sought by industry. We had a very impressive talk by Barry Schindler about the importance of patents for, in particular, the startups [see Session 2D].

As I said, we prepared some questions. It will be a Q&A session and you are heartily invited to present your questions.

Maybe it is best to start, Rian, with your brief overview or update on the latest development in the Netherlands.

JUDGE KALDEN: Since I was in Seattle two years ago, I thought I owe you a little update on the legal position in the Netherlands and maybe broadly in Europe.

The situation at the time was there was a major discussion going on about the scope of protection of second medical use claims, and there were certain decisions in Europe, especially in the United Kingdom, which was unfortunately followed by our District Court, limiting the enforcement possibility of second medical use claims considerably. Now I am quite happy to say — and James has already touched upon it — that our Supreme Court has actually dealt with that quite thoroughly in a very recent decision in, I must say, a very sensible way.[1]

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[1] On Nov. 3, 2017, the Dutch Supreme Court (*Hoge Raad*) handed down a landmark decision on the infringement of second medical use patents in the *Merck Sharp & Dohme Corp. ("MSD") v. Teva Pharma B.V. and Pharmachemie B.V.* ("*Teva*") case relating to MSD's Swiss-type second medical use patent protecting a combination therapy of ribavirin and interferon alpha for a specific group of hepatitis C patients. Decision of the Supreme Court of the Netherlands (Hoge Raad), 3 Nov. 2017, IEF 17300; LS&R 1539, English translation of IEF 17241 *available at* http://www.ie-forum.nl/artikelen/supreme-court-of-the-netherlands-msd-teva-pharma-english-translation.

The Supreme Court held that a manufacturer or seller of a generic product directly and indirectly infringes a Swiss-type second medical use claim if it is reasonably foreseeable that the

In the Netherlands it has now been decided quite clearly that there can be direct infringement and indirect infringement of second medical use claims. I will not set it out in more detail, but I think there are a few things to be noted about this decision in addition to that.

What has been decided also is it is not only the manufacturer but also the seller that can be held liable for patent infringement of a second medical use claim. That is quite important because at every step down the chain of distribution you can actually enforce your patent. To get to infringement it is not just the subjective knowledge but it is objective knowledge that has to be established. Therefore, every time a manufacturer or a seller foresees that its product is going to be used for the protected indication, that is sufficient to establish infringement.

There are a few open issues that still have to be dealt with.

One issue is that a generic company can escape from liability by taking the appropriate measures as much as possible to prevent its product from being used for the patented indication. Now it is entirely unclear what measures it should take because everybody also agrees that the generic cannot entirely prevent its product from being used because of the substitution problem.

Our Supreme Court in another decision upholding mine was very pragmatic in that sense.[2] One of the objections to our decision where we granted an injunction against a generic company was that the generic was then injuncted from also entering the market with its generic products for the allowed use. But the Supreme Court said: "Well, you have not done enough to prevent infringing use, and you must decide whatever you have to do; it is not the court who should tell you what measures you should take." So that is the responsibility of the generic company.

Another issue still open is the remedies. We gave an injunction. I must also say that the protected use was almost 95 percent while the open use for the generic was just 5 percent or something. So the injunction was merited under this situation, but there might be other situations where the allowed use and the protected use are more equal, and then you get into all sorts of troubles.

I would suggest there are three things to be done.

First of all, in situations where a patent is not possible because it is obvious or not novel and there might be something like a market protection system in place — now, I am just a judge, I am applying the law, so I am not there to make the law — I think it is very important that some thoughts will be given about that alternative system for second medical use systems.

The second one that is extremely important, and I think should be the major concern at the moment, is the substitution system that is going on all over

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generic product will be used intentionally for the patented use. The Court further held that second medical use claims relating to a "new" patient subgroup convey the same protection as second medical claims relating to a "new" indication. The Court also held that a reasonable protection for the patentee justifies that indirect infringement of Swiss-type claims is possible in the same way as an EPC 2000 claim, as there is no real difference between the two. One can at the same time directly and indirectly infringe a Swiss-type claim, according to the Supreme Court.

[2] Sun Pharmaceutical Industries (Europe) B.V. v. Novartis AG, Supreme Court of the Netherlands, 14 April 2017, Case No. ECLI:NL:HR:2017:692.

the world. If an indication is mentioned upon prescribing any medicament, that solves so many problems. It solves the problem I just mentioned, for a generic to be required to take measures to prevent any infringing use. But if the indication is mentioned, the pharmacist will know which product to dispense, and then a carve-out is sufficient. So it benefits the generic company as much as the innovator company if that is done by indication.

It also solves the problem of our Medicinal Board having to publish in their opinion the full label online to protect patients' interests. Patients get confused if they get a product which does not mention its indication. So that is also solved.

I think that it should be a primary interest that the politicians understand that substitution, while there is no indication of what it is used for, is of primary interest to solve all these issues.

Along with that, another concern is that there is a very unfavorable environment towards the pharmaceutical interest. I think it will be a task for both innovators and generic companies to join together and make some political efforts — or lobby, or however you want to call it — and bring this to the attention of the politicians to solve this problem.

We had a great vibe, we had a fantastic conference, and maybe from this there could be joint efforts to convince them that at least this is a major step forward.

Thank you.

MR. METTEN: I think we can go ahead with the questions.

One question has been posed to us by Janis Shute is: Should the patient's voice be playing a greater role in prioritizing research and incentives for repurposing medicines? I think she had in her mind the *Dallas Buyers Club* movie about the HIV-positive man who tried to somehow acquire a set of medicines to cure himself and also others.

PROF. JACOB: Roger, you can talk about the patient voice.

JUDGE HUGHES: I think that is really a question of policy. Judges are not there to make policy; judges are there to decide cases.

But let me give you a different impression entirely. Judges are the end of the road — if all else has failed, you sue somebody. What you've got to sue them with is largely a patent.

For many companies that have a patent the patent sort of develops a mythological characteristic about it — it is "the Lyrica™ patent" or it is the whatever else patent — and the companies do not look at it anymore as just a functional document. They look at it as a Holy Grail and think that anybody who attacks it or questions it is somehow impugning their whole corporate ethic.

Well, from a judge's point of view, our job is to dissect that patent and see if it is good. Often the person or the company that sues under that patent really has not done that job for a long time. We see patents that were perhaps filed a little too early, with not enough data in them and not well expressed; we have seen patents that do not even claim the actual pharmaceutical that is being sold anymore; and they really have not been exposed to scrutiny for a very, very long time. Then, there is resentment that grows by some companies that have asserted

their patents because they find that their patent is held invalid.

JUDGE GAJARSA: First of all, I am glad to hear that some supreme court understands patents much better than our U.S. Supreme Court. Thank you for pointing that out. [Laughter]

In the United States we have a different landscape that was changed by the introduction of the America Invents Act (AIA) in 2011. As you heard during the conference, it took almost fourteen years to amend the patent statute that was originally enacted in 1952.

The landscape has changed because of a procedure which is taking place now before the Patent Office. In 1984 there was the introduction of the Hatch-Waxman Act, which created the opportunity for generic companies to challenge patents, and there was an incentive built into that statute to provide for the challenges by the generics to obtain exclusive sales marketing for a number of months, 180 days usually, if you were first in line to challenge the patent.

That has changed since 2011. There is a procedure in the Patent Office called inter partes review,[3] which at the beginning very few pharma companies even took advantage of. Just to give you some statistics, last year there were 211 petitions filed with the Patent Trial and Appeal Board (PTAB), which is part of the U.S. Patent and Trademark Office, seeking the review of patents. Any time a patent is issued it can be challenged in an inter partes review.

If the patent is challenged at the same time that the patent is also challenged in an Abbreviated New Drug Application (ANDA) action before the federal district court, usually the district court will accept a motion to hold that litigation in abeyance while the Patent Office reviews the patent. There is an incentive there also because the Patent Office must act at least within eighteen months of the issuance of the filing.

You might have heard that some people feel that the inter partes review is a "death squad" for patents. A number of patents have been held invalid during that process. It has now been attenuated somewhat because as the process becomes more mature, I think the judges at the PTAB have matured along with the process in making sure that the aspects of patentability are respected.

What is happening, I think, is the beginning of the process where even the incentive to regenerate new drugs could be a change because a new drug use is not necessarily patented — or patentable for that matter — because a new method

[3] Inter partes review is a trial proceeding conducted at the Patent Trial and Appeal Board to review the patentability of one or more claims in a patent only on a ground that could be raised under §§ 102 or 103, and only on the basis of prior art consisting of patents or printed publications. For first-inventor-to-file patents, inter partes review process begins with a third party (a person who is not the owner of the patent) filing a petition after the later of either: (1) 9 months after the grant of the patent or issuance of a reissue patent; or (2) if a post-grant review is instituted, the termination of the post-grant review. These deadlines do not apply to first-to-invent patents. The patent owner may file a preliminary response to the petition. An inter partes review may be instituted upon a showing that there is a reasonable likelihood that the petitioner would prevail with respect to at least one claim challenged. If the proceeding is instituted and not dismissed, a final determination by the Board will be issued within 1 year (extendable for good cause by 6 months). The procedure for conducting inter partes review took effect on Sept. 16, 2012, and applies to any patent issued before, on, or after Sept. 16, 2012. https://www.uspto.gov/patents-application-process/appealing-patent-decisions/trials/inter-partes-review.

is not necessarily not obvious from the previous use.

So where are we with respect to regeneration? I have come to the conclusion after the two days of this conference that we need to have some new legislation at least to recognize that the new uses of drugs from old drugs that have been in existence for a while might need to have some incentive for the market to be provided so that the patent and the new use can be protected. Without that, I think it is going to be very difficult.

It is not like the warfarin drug that has now been used as a blood thinner, or Avastin which is used in a number of different areas. It is the kind of a situation where you need to incentivize the marketplace for the development of new uses.

I do not know whether or not you would be able to get that legislation in front of this Congress, or any future Congress, without really evergreening not only the new use methods but also other elements that might come into play. This is why it took so long for the AIA to be adopted by the Congress, because every-one dipped their oar into the water and everyone's interest had to be satisfied.

So I am beginning to wonder whether or not regeneration as required can really be recognized by the Congress to give the protective aspects of the incentives that we need to generate the new methods for use of old drugs.

MR. METTEN: May I ask another question? Is it really necessary — and this is my impression — to put so much emphasis on the plausibility/credibility test? Can't it be considered kind of a hindrance to second medical uses?

PROF. JACOB: I agree. I think that it is complete nonsense. The word "plausible" is not in any statute.

JUDGE GAJARSA: That's right.

PROF. JACOB: And what's more, the inventor does not have to be a person skilled in the art. He can be a wild and woolly-haired inventor who says, "I will tell you that this compound will cure such-and-such and I claim it." And if it is right, supposing it is true, what then? He has the incentive now to work out that what he said was actually carried out and prove it. And if it is not true, who the hell cares? The patent is not worth anything.

This plausibility thing is a very dangerous problem. And it causes a problem in another way. If you have to have plausible evidence — they say, "You can have *in vitro*," but this is fudging it really — if you want something plausible, you really need at least animal model experiments.

But you may need in the second medical use cases actual patients, and now you have a huge problem about disclosure. You disclose to the patients — you have to apparently — what you are treating them with, and apparently they do not have to sign nondisclosure agreements. That is called ethics. It is a funny kind of ethics that stops the patentability and, therefore, decreases the incentive for new methods of treating people.

I think this is a very dangerous doctrine indeed that you shouldn't be able to patent it because it is speculative. Of course it is speculative. Every pharma patent is speculative.

All you ever get in a pharma patent of the kind I grew up with is a tiny twitch in a mouse because you have given it something or other, or it didn't twitch

when it otherwise would have twitched. That was the very first big pharma case I was involved with. Actually, it had a ridiculous experiment. It was for a tranquilizer. What you did is you put two mice on a little electric grid. If you hadn't give them the drug, when you gave an electric shock each one thought the other one was doing it and they started fighting. If you gave them the tranquilizer, they didn't fight. It was called the "mouse rage test."

Is this going to be anything useful in people? You are miles away. You have not made an invention in any real sense yet, but you are allowed to have a patent for it. So I think we should get rid of plausibility.

MR. METTEN: Thank you.

JUDGE HUGHES: The one most useful thing that I heard in the last two days that I think can be done without legislative intervention is the European system of flipping the onus. In other words, put the onus on the generic to say that they have taken every reasonable step to ensure that their drug is not being sold for the repurpose claimed in the patent.

PROF. JACOB: It hasn't worked. We tried it in England. The judge ordered the National Health Service (NHS) to do things. You cannot do it. What are they supposed to do, stand at the pharmacy and say, "Don't do that?"

JUDGE HUGHES: No, every reasonable step.

JUDGE GAJARSA: How much off-label use is there for generic drugs in England? Is that a common occurrence?

PROF. JACOB: As far as I know, yes.

PARTICIPANT: Eighty percent.

JUDGE GAJARSA: Eighty percent? No liability attaches, and that is part of the problem, isn't it?

JUDGE KALDEN: That whole issue does not arise if you prescribe by indication, because then, by nature, the pharmacist would be able to check whether to dispense the generic product or the originator product. That is why I think that solution, making sure that is in the system, does away with a lot of problems.

PROF. JACOB: We heard the Danish story [see Session 1C].[4] They have it there and it works.

JUDGE KALDEN: Absolutely. And they sued the pharmacists and they were injuncted for substituting a generic product for what should have been an innovator product. Of course, they were obliged to substitute, so it sounded a bit

[4] On June 25 2015, the Danish specialty court for intellectual property rights, the Maritime and Commercial Court in Copenhagen, rendered a 50-page decision in a preliminary injunction action filed by Warner-Lambert and Pfizer against Krka and the Danish Association of Pharmacies. The Danish Health Agency intervened in support of the Danish Association of Pharmacies. The decision of the court balanced the Danish rules on substitution against the protection of second medical use patents and decided in favor of the second medical use patent (no infringement by Actavis, but by pharmacies). In Denmark any prescription must include information about the indication. The Danish Medicines Agency decides which medicinal products can be substituted with each other— in substitution groups. Patent rights were not taken into consideration. The pharmacies are under an obligation to dispense the cheapest medicinal product in the same substitution group, unless the doctor has stated "No substitution" on the prescription, or the price difference is below certain limits. *See* Session 1C, full decision at Appendix A.

unreasonable, but it made the government immediately implement new legislation to make sure that prescription was by indication. So the solution is readily available.

JUDGE GAJARSA: Here in the States, though, a doctor can prescribe a generic versus a patented product and it is up to the insurance company at that point. Some insurance companies will not pay for a patented product if a generic is available.

JUDGE KALDEN: I would call that patent infringement. [Laughter and applause]

MR. METTEN: I think we should turn to the audience now.

QUESTION: This is perhaps more of a comment than a question. You mentioned incentives for the repurposing of existing drugs. I would like to encourage you to think about the same kind of incentives for compounds that may not have made it actually to the market. They may have failed in Phase III because of efficacy for the indications that they were investigated in.

But there are probably many more compounds that sit in libraries where patents are expired but you cannot really do anything with them anymore because there is no way that you are going to get funding to do research that looks for the same molecules in different indications.

PROF. JACOB: If the product is not on the market, if there is not a generic version on the market, everything changes. You can have a known product which is not patented.

QUESTIONER: Very often you see academic publications that suggest a mechanism of action.

PROF. JACOB: That is a different question.

QUESTIONER: Then you are stuck because it is prior art and there is no manner-of-use patent.

PROF. JACOB: That is a different question. It is just not patentable at all.

QUESTIONER: Yes. So my point is I think it is a very similar situation to an existing drug except that the molecule has not made it to the market yet. But there is knowledge and prior art that prevents creating an incentive at the moment for someone to take that and go out and basically raise money to run a clinical trial to show it does.

PROF. JACOB: Well, it depends. It is case by case. But if it is just something that did not make it to market for Condition A, there is nothing to stop somebody taking it to the market and investigating it for Condition B and getting a use patent on the basis of Condition B, unless it is obvious in some way or other from what somebody did that is written.

JUDGE KALDEN: Maybe there you could have some mechanism for market protection. But that, of course, has to be well thought out. You cannot have evergreening because the patent system prevents evergreening. But, on the other hand, there is still investment necessary to bring a second medical use product to the market.

I am not saying I have the solution, but I think there is definitely merit in investigating whether an alternative form of protection could be available. But that is not up to me.

JUDGE GAJARSA: But how do you incentivize the person to do the research and to go through the testing process without having some protection for the market that is established? You cannot do it without some kind of protection.

QUESTION [Dr. David Cavalla, Numedicus]: Exactly. I think that last point is the important one, how to incentivize. If I may, I think the metric of how much off-label use there is is not the right metric because, in a way, the whole system is set up to disincentivize off-label use. It does exist, but there are things to control it. I think there would be a lot more off-label use and a lot more development of off-label uses if there were a commercial incentive in place to allow the development to occur.

JUDGE GAJARSA: There are present incentives for a generic to challenge a patented drug today through the Hatch-Waxman procedure. But the problem there is the fact that the system has now become a little bit more complicated because of the IPRs that have started to be established. You can have more than just one IPR filed against a patent and it just continues on.

The question arises under the Hatch-Waxman Act: if a generic is successful in challenging a patent, there is an incentive there for a 180-day exclusive for the generic company in the marketplace. That does not arise under an IPR challenge. So that incentive has been eliminated or diminished.

QUESTIONER [Dr. Cavalla]: Yes.

The other comment I would like to make, if I may, relates to Sir Robin's comment about the wild and woolly man. That is, absent the plausibility question, I think that it is open to said wild and woolly man to produce a great long list of potential indications for a drug without any substantiating data at all, and effectively close out the opportunity for successor patentees.

PROF. JACOB: If he's got it all wrong, he loses his patent.

QUESTIONER [Dr. Cavalla]: It is still written.

PROF. JACOB: And that's not bad. Just because it is written down, that is not enough for novelty in any practical sense — at least not in my court, not that I've got a court anymore.

JUDGE HUGHES: I am going to challenge some patent drafters because I think that they do overwrite a lot of these patents. I think there has to be a reexamination by those patent agents and others drafting patents about tightening that process up. There is a lot of just throwing garbage in there and hoping that it will fly.

QUESTIONER [Dr. Cavalla]: Yes. But it is not just that they think it will stick, but also that it would discourage the other entrants later on.

JUDGE HUGHES: A patent is not a peer-reviewed document. That is a problem. It is just the wild and woolly man gone amok.

PROF. JACOB: I was reversed by the Supreme Court, and I was very cross with them at the time, but it is one of the few times when I have been reversed when I thought they were right.[5]

[5] Human Genome Sciences v. Eli Lilly, UKSC 2010/0047 (Nov. 2, 2011), *available at*

That HGS patent was a wild and woolly patent. They said, "This stuff will cure all these things," and there were several pages of stuff listing what it would cure. It was all speculative, very thin. They said, "Oh no, you can narrow it down to the thing it does work on." I think that was a bit wild and woolly. If it hadn't worked on anything, the patent wouldn't have mattered at all.

But I have had second thoughts about it. It is not of course good law, but there is something to be said for saying, "You have this patent, it is pretty wild and woolly, and you conduct the research and it turns out to be good. You would not have done the research but for the patent."

That is actually how all pharma patents are developed. That is why it takes years and years and years to get drugs to market. It is not like a mechanical invention where you get the patent, there it is, you can see how to make it, and you go out and make it. Pharma patents do not really fit the model of patents that was invented in the nineteenth century for machines, but they pretend they do.

JUDGE GAJARSA: There was some discussion at one time of changing the time periods for patents, where you could have a stratified time period: you could have a software patent for five years, a mechanical patent for ten years, and a drug patent for twenty years.

PROF. JACOB: Twenty-five.

JUDGE GAJARSA: Right, but that was never accepted by the Congress.

JUDGE HUGHES: I like Bob Armitage's idea of maybe extending it. But I am going to give you the incentive for that. If you want to extend it to the fifteenth year, then you pay 10 percent of the revenue derived from that product into some fund for research. If you want to extend it for a second year, that is 20 percent; for a third year it is 30 percent, and so on. At some point it is not going to be economic to pay that kind of money. Nonetheless, you get a bit of an extension and there is some funding for some of these altruistic societies.

PROF. JACOB: You are doing that now, Roger. Twenty percent of the cost of a new medicine is spent on research. It just happens to be done by the pharma company that is selling the product. That is the model.

PARTICIPANT [Bob Armitage, IP Strategy and Policy Consultant]: The industry accepts your offer, by the way. [Laughter]

PROF. HUGHES: You've got a deal.

JUDGE GAJARSA: Robert, you have always been on the cutting edge.

[Session adjourned: 5:27 p.m.]

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https://www.supremecourt.uk/cases/uksc-2010-0047.html.