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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 – 8:30 a.m.

Session 2A:
Introduction to Day Two

Prof. Sir Robin Jacob
University College London, London

Jürgen Dressel
Head of Global Patent Litigation Strategy, Novartis Pharma, Basel

* * *

MR. CORDERY: Good morning, everybody. Welcome to day two of the conference.

I do have a slight change to the program — nothing too heavy, I promise, and we are not going to finish any later, which is what you need to hear. Professor Mondher Toumi, who was stuck in Paris and could only get here late last night — and indeed his luggage is still not here — has joined us. Obviously, I think it is really important that we hear from Mondher about the marvelous work that he has done. So the plan is to shorten lunch by fifteen minutes and come back fifteen minutes early so that Mondher can be the first presentation this afternoon before we continue with the main program.

Jürgen is going to give a very brief introduction, Robin is going to say a few words after Jürgen, and then we are going to go straight on to the alternative incentives session.

DR. DRESSEL: Good morning, everybody.

I think we had an exciting day yesterday. I found the panels very engaged, very diverse, and I thought the discussions were very stimulating. So I thought maybe I would share a few thoughts on what I learned yesterday, what I took away from yesterday.

We all agree that many great treasures are hidden in these old drugs and they are basically crying to be uncovered. But we also know that is not going to happen without the right incentive.

I still think — and I am happy to be convinced otherwise when we hear about alternative incentives today that there are other solutions to the problem — market segmentation is probably the right way, separating the protected and the unprotected indications. That is probably fair.

But we, of course, also realize that we have a huge acceptance problem when it comes to differential pricing between, for example, cheap generic products and something for which you then find a new indication. Especially in this political climate, that will actually be difficult to resolve. I have to admit I do not have a clear solution for that yet.

So what can be a solution? Should we continue trying to convince the stakeholders that it is actually good for everybody? Maybe the market segmentation I was talking about earlier could become an automatic consequence of the value-based, which must be indication-based, pricing in the future.

We heard also yesterday about other incentives, like transferrable data exclusivity vouchers. I do not know whether that is a solution.

I am very much looking forward to learning solutions today.

Thank you.

PROF. JACOB: As I said yesterday, this is a conference with a purpose. Some people have been coming up and saying, "Where do we go next? Is there some sort of way working parties or something can be done?" As I have said, we are planning to do a book, and maybe we will put something up on a website or something. But what to do next is a really important question.

Now, I have no idea where to go next. I am only a retired judge and a part-time academic in an English university.

But can you put your minds to that? We might debate at some point if we have a moment later day: Where do we go next? How can these treasures be uncovered, as Jürgen puts it? So think about it.

Also think of any questions for the judges' panel this afternoon. We have received a few, but think of any others. They can be frivolous questions because by the end of the day, whatever the questions are going to be, the answers will be frivolous anyway.

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 – 8:40 a.m.

Session 2B:
Alternative Incentives to Patents

Moderator:
Robert Trenchard
Gibson, Dunn & Crutcher LLP, New York

Presenters:
Constance Bagley
Senior Research Scholar, Yale School of Management, New Haven;
CEO & Founder, Bagley Strategic Consulting Group LLC

Prof. David Ridley
Faculty Director, Duke University Health Sector Management Program, Durham

Panelists:
Dr. Bruce Bloom
CEO, Cures within Reach, Chicago

Otto Licks
Licks Attorneys, Rio de Janeiro

* * *

MR. TRENCHARD: Good morning, everybody. In this session we will talk about alternatives to patents for incentivizing exploration of repurposing of existing medications.

My name is Bob Trenchard. I am a litigator from Gibson Dunn who has done a fair amount of patent work in the life sciences space, including on this very topic.

We talked about market failures yesterday, and this really is a market failure. Whenever I hear about failures, my first instinct as a litigator is to sue somebody. That instinct — I do not know if it is right. My esteemed panelists

here as we were preparing for this conference have certainly opened my eyes to alternatives to suing somebody for patent infringement. I personally think there are some patent infringement ideas that have yet to be explored that could help solve this problem, at least in the United States, which is the only jurisdiction I know anything about.

But in talking to Constance, David, Bruce, and Otto, it became clear to me that there is no "one size fits all" answer and that different contexts afford different opportunities. For instance, one we were talking about yesterday at lunch would be in the area of communicable diseases. Addressing the point Jürgen was making, you might actually find political will for public financing of second medical uses that could stop an Ebola epidemic or an influenza epidemic, because those obviously present issues of public importance, almost national defense, that might allow you to marshal the political will to solve the problems.

There are other ideas as well, and Constance, David, Bruce, and Otto will talk about briefly on each of them. We have an eclectic panel, which is consistent with the idea that there is no "one size fits all" answer and that context matters. Constance and David are both from academia, Constance from Yale, David from Duke. They have somewhat different perspectives. David is an economist. Constance is at the Business School but also has a legal perspective. Bruce, whom we heard from yesterday, is out there in the world trying to help solve these problems. Otto is an esteemed Brazilian litigator who litigates patent as well as other issues in Brazil, and he will talk to us about some of the ways that the government in his country has tried to address at least some of these issues.

With that introduction, I am going to turn it over to Constance and then we are going to go straight down the line.

MS. BAGLEY: Thank you. Good morning. It is a real pleasure to be here. Thank you for the kind introduction, Robert, and thank you for giving me this opportunity to share some thoughts with this esteemed group.

I am going to be talking primarily about two things. The first is discovering new uses, so this again would be we know we have the buried treasures; how do we go about finding them?

The side of the equation I would like to focus on a bit more than perhaps we have primarily is the cost side. The question is: To the extent that we can reduce the cost of finding these new uses, it obviously puts less pressure on the patent rights that have to be given the company that indeed does the prospecting and goes ahead and finds the uses.

Public-private partnerships, certainly a concept that I am confident everyone here is familiar with, have been very successful in a range of diseases.

We have seen them first more in the nonprofit space with respect to malaria, tuberculosis, the so-called diseases of poverty, but increasingly they are being used for commercialization of discoveries from the lab.

I am the author with Christina Tvarnø at Copenhagen Business School of an article taking a game theory approach to public-private partnerships,[1] essentially discussing what are some of the terms we need in the contract, what are some of the aspects we need to build structurally into the relationship so we properly align incentives. They range from making sure there is a free flow of information to the fact that research shows that the likelihood of an academic discovery leading to commercialization is very much affected by how actively involved the academic scientist is in the venture.

My undergrad work was at Stanford. I think one of the things that Stanford got right is it made it very easy for professors to take up to a one- or two-year leave, regardless of whether they had tenure, if they wanted to start a new company. It made it therefore possible for people to transmit that past knowledge that really does not come across in other ways.

We see in Europe already with the Innovative Medicines Initiative some stress on open innovation. There is a real opportunity here for having trusted partners, having trusted intermediaries. One program, for example, has a trusted intermediary: you have a consortium of drug companies that have a variety of compounds that they think might be efficacious — or in this case they have one use; we do not know if they have a second — and then we have on the other side a consortium of academics who have a variety of discoveries they have made. Various things are matched against each other with high-throughput technology and the intermediary is the only one that knows until the end whose molecule actually worked with respect to one indication. Then, when that is ascertained, negotiations ensue with respect to how the intellectual property rights get divvied up between the academic organization and the drug company.[2]

There are a variety of mechanisms like that that I think it is appropriate to keep in mind here. Even though it is true that $200−300 million is certainly less than $1.3 billion, again if we were able to enhance the size of our portfolio, diversify it, and do so at a lower cost, it helps us on the back end resolve the problem with respect to pricing.

This also requires the National Institutes of Health (NIH) — and there are people in this room who have written on this topic — to condition grants on limitations on certain rights that historically have been given to the private pharma company involved in such a collaboration. The most onerous would be saying, "We of course not only have a right to what you discover, we have a right

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[1] Christina D. Tvarnø & Constance Bagley, *Pharmaceutical Public-Private Partnerships: Moving From the Bench to the Bedside*. HARV. BUS. L. REV., Vol. 4, Nr. 2, 2014, s. 373−40n, *available at* http://www.hblr.org/wp-content/uploads/2014/10/4.2-4.-Bagley-Pharmaceutical-Public-Private-Partnerships.pdf.

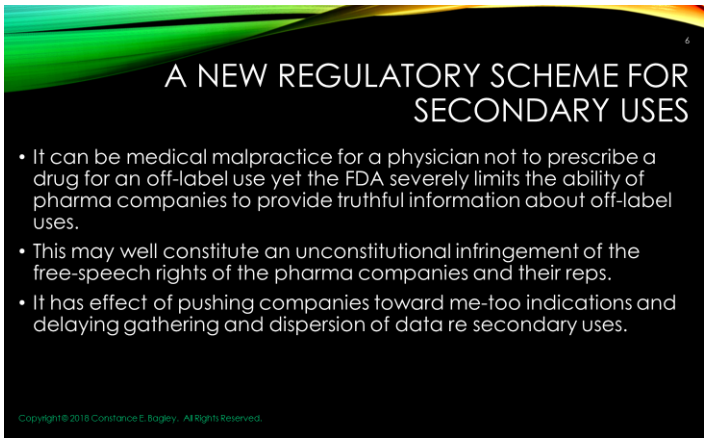
[2] Constance E. Bagley & Christina D. Tvarnø, *Promoting "Academic Entrepreneurship" in Europe and the United States: Creating an Intellectual Property Regime to Facilitate the Efficient Transfer of Knowledge from the Lab to the Patient*, DUKE J. COMP. & INT'L L., Vol. 26, Nr. 1, 2016, s. 1−78, available at https://scholarship.law.duke.edu/cgi/viewcontent.cgi?article=1476&context=djcil.

to all the tools, and we also have a reach-back license so if there is anything else you come up with in the future that relies on anything that you did here, then we are entitled to that as well, with no obligation to be willing to license any of those tools on an any-or-all fair royalty basis."

Again, I think that things like that can clog up innovation. You can end up with the so-called anti-Commons, where you have rights that are given to multiple participants such that at the end of the game you really have no one participant that has all the rights necessary to pursue a particular indication.

When I was a partner at Bingham & McCutchen, we were involved in the Cetus/Amgen Interleukin-2 litigation. That ultimately was the situation there. It took a number of years of litigation. The law firm was very happy to have the clients paying for this litigation. At the end of the day it resulted in a royalty-free cross-license between the two companies.

I think we just want to be open to those structures.



Off-label use: Some people have described to me off-label use as being kind of the dirty little secret with respect to pharma. In areas such as oncology, off-label can be as high as 50–65 percent of the uses of a particular drug.

We have a system whereby a physician is allowed to prescribe a drug for any indication, regardless of whether it has been studied by anybody. Indeed, the American Medical Association has indicated it could be tortious malpractice not to have an off-label use of a particular drug if the physician has reason to believe that it could be more effective than what is currently on the market.

But then we have a system whereby we have the Food and Drug Administration (FDA), as described yesterday, taking the position "but you are not really allowed to talk about it." Now, if the physician specifically asks you about it, you can direct him to your medical advisory group, you can at conferences be present when different physicians may be talking about uses, but as a general proposition it is a scripted dance that has to happen.

Also as indicated yesterday, the Supreme Court has newfound delight in deciding that what historically has been unprotected commercial speech that is subject to regulation and prior restraint should be limited in a fashion almost the same as is afforded the most highly protected range of speech, political speech. This has really been a fundamental constitutional change. When you think about it, if it is extended to all industries, it applies not just to being able to tell people what they cannot say, but also the Court takes the position that the First Amendment protects compelled speech; so it affects what you are required to say.

There have been several cases in this area. The FDA has backed off a bit, realizing that it may be on the losing side of this. It wants to wait until it really has its best case before going to the Supreme Court.

I think industry needs to get ahead of this. Especially as we are aware of the fact that these uses are indeed happening and we know that there is research out there, the logic behind the Supreme Court's approach to this has soundness to it. Why are we preventing people from truthful statements?

Now, we know we have the anti-fraud rules so that in the event that somebody lies post facto you are able to go after them. But the whole idea of the FDA was, "Let's not wait until a bunch of people died from the snake oil; let's go ahead and preapprove things."

But I think we need a mechanism for off-label uses of drugs that have passed the preclinical trial levels for an approved use to be in a different sort of category.

The analogy I would like draw here is to the securities law. In the securities law, in order to foster innovation, in order to foster the building up of capital, there is more freedom given to entrepreneurs, to innovators, to sell securities to so-called "accredited" investors, people who either have enough money or enough savvy that they are supposed to be able to figure out what indeed are the risks, enough power to demand information. So they are regulated with a lighter hand.

However, we have accompanying that the fact that if you are in the business of selling securities, even if they are exempt securities, you have to be licensed by the financial industry regulatory authority; you have to take some exams; you have to have training; you get fingerprinted; you get a background check. In addition, we have a system whereby if an offering is above a certain amount, you have to file something that is a truncated, much cheaper version than what it would cost you to do a prospectus.

So the thought — and this is something that I worked on with a couple coauthors in a *Cornell Journal of Law and Public Policy* article that came out in the winter of 2013[3] — is that if we created something akin to what we have for secondary uses, what we allow in the securities field with respect to young companies, innovative companies, that still are not raising a massive amount of

[3] Constance E. Bagley, Joshua Mitts & Richard J. Tinsley, (2013) *Snake Oil Salesman or Purveyors of Knowledge: Off-Label Promotions and the Commercial Speech Doctrine*, CORNELL J. L. & PUB. POL'Y (JPPL), Vol. 23 : Iss. 2, Article 2, *available at* https://scholarship.law.cornell.edu/cjlpp/vol23/iss2/2 .

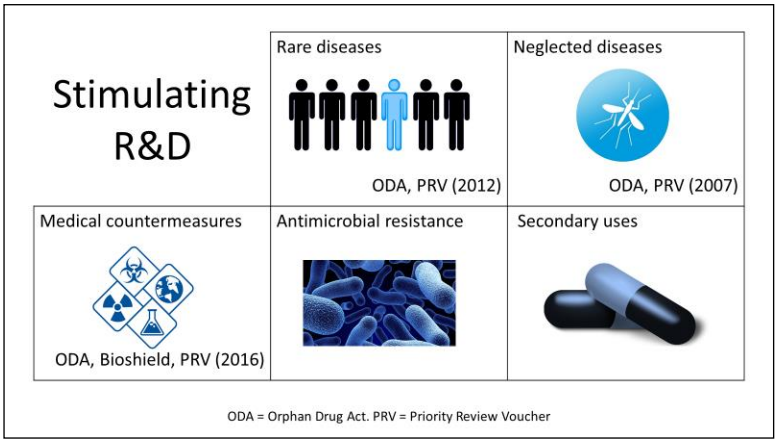
money, we make the tradeoff, as we do with securities, between safety and access.

But if we built an institution so, for example, we limit what the drug companies are allowed to say in the respect that — just as when you have a registered offering you have to give someone a written prospectus before you can talk to them and have sales talks about doing it — there would be a requirement before a sales rep can initiate a discussion with respect to a secondary use, "here are the latest journal articles" — and they cannot be all fancified with the company's logo; they have to be basically the plain vanilla, the way the thing was posted — have a system whereby records were kept of those visits, whereby the sales reps are required to do follow-up visits, go ahead and try to receive from the docs indications as to how in fact these indications have worked, and this is getting reported to the FDA. If the volume of off-label use goes above a certain percentage, at that point you would be required to go ahead and, if you want protection and you want broader distribution, file an application for a new use.

Just some thoughts there with respect to really the ability to try to both get new molecules from the bench to the bedsides but at the same time start to build a regulatory infrastructure that makes it possible to, as Arti Rai mentioned yesterday, crowdfund, crowdsource, both some of the data gathering and some of the fundraising by looking by analogy to how we have promoted innovation, not just in the United States but other countries, by having an intermediate category for a drug that at least we know has a safe indication in one use.

And one could certainly imagine a preclearance whereby the FDA says, "Look, the fact is we cleared that one because the use was so compelling — it was a children's disease and there was absolutely no alternative — we are going to have kind of blacklist (no, these ones we are not going to let you do); but for a very broad range of things — the aspirins, heparins, and the like — we are going to."

PROF. RIDLEY: In his opening remarks, Jürgen talked about the importance of market segmentation. I think he is absolutely right, and Ben Roin has argued persuasively on this as well.



But I want to explore a few alternative mechanisms. The problem of market failure is not unique to second medical use. We see this in other settings as well.

• For example, with rare diseases, especially ultra-rare diseases, we worry that there are not enough patients to constitute a big enough market, even if the developer can charge a high price.

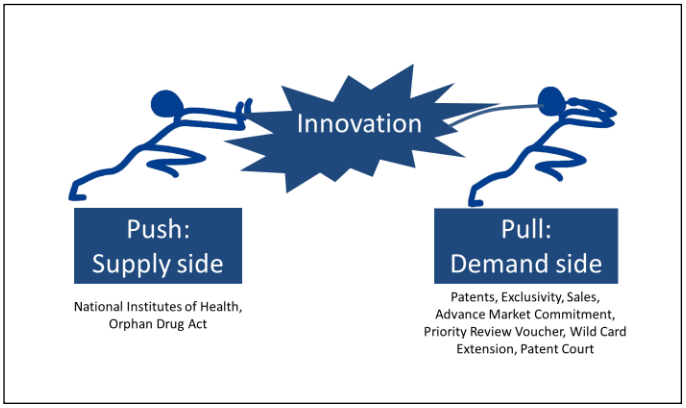
• With neglected diseases it is the opposite problem: a lot of people suffer from the diseases but they are unable to pay.

• With medical countermeasures — for example, treatments for anthrax or smallpox — we hope there will never be a market for the treatments; however, there might be, and so we want to encourage development of such products.

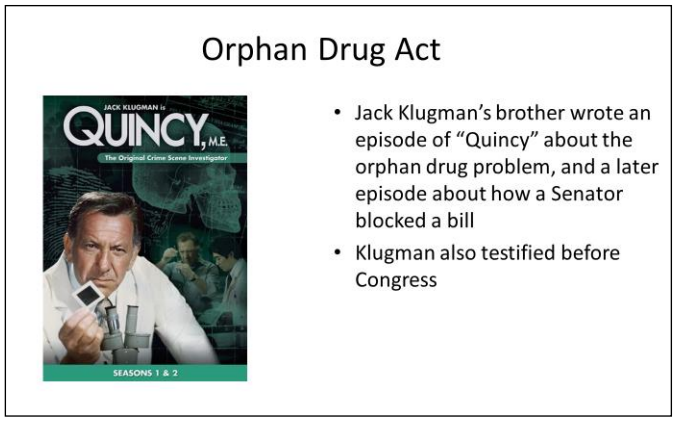
• Antimicrobial resistance: if someone develops a great new antibiotic, the best response by society is to put it on the shelf and use it as a backup. Well, that is not much of a market for a product developer.

For many of these problems, governments have created market mechanisms to address them. For the first three market failures — rare diseases, neglected diseases, and medical countermeasures — we use the Orphan Drug Act. As you know, the U.S. Orphan Drug Act came first, followed by Japan and Europe. We also use the priority review voucher for those first three. For antimicrobial resistance we have the Generating Antibiotic Incentives Now (GAIN) Act.

So the question is whether there is some other mechanism we can use. Again, I think market segmentation, differential pricing, and data exclusivity are especially valuable, but I think it is worth looking at these other cases and seeing if we can learn anything.



Connie spoke persuasively about the need for lowering cost. We can think of that as being on the push side. Much of what I am describing is on the pull side. So Connie spoke about lowering cost; I am talking about increasing revenue, although the Orphan Drug Act does a bit of both.



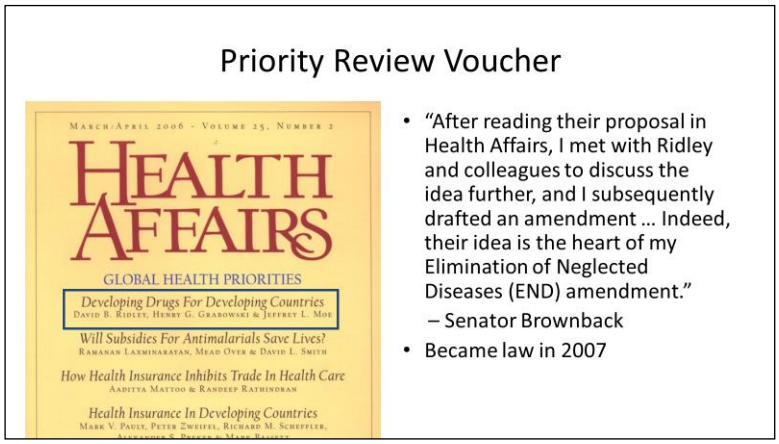
Was anyone watching American TV in the 1970s? Do you know *Quincy*?

DR. BLOOM: Sure.

PROF. RIDLEY: That's fabulous, because my students never know who the heck Quincy is. In my classroom I am the only one who was watching American TV in the 1970s.

Do you know the story about Jack Klugman and the Orphan Drug Act? One of the episodes of *Quincy* was about the need for drugs for rare diseases and a push for Congress to act. A later episode was about a member of Congress who

was slow to act, which was truly the case. Then Jack Klugman testified before Congress. So Quincy (Jack Klugman) was partially responsible for the Orphan Drug Act. So I say to you gentlemen you need a Jack Klugman. Brad Pitt may be available.



This was not a case of Brad Pitt, although Henry Grabowski and I are often mistaken for Brad Pitt. Henry Grabowski (in the back of the room), Jeff Moe, and I wrote a 2006 paper[4] that became law in 2007 thanks to a progressive member of the Senate, Sherrod Brown, and a conservative member of the Senate, Sam Brownback. Here is a case where we were able to take a paper from publication to law in just about eighteen months, thanks to in part the fact that we were able to argue that this was free, at least off-balance sheet. That is always helpful. We will talk more about politics in the noon session.

My intent is to highlight other cases where there are market failures, and creative solutions to address them.

Prizes can work well. But a challenge of prizes is coming up with the money.

Henry, Jeff, and I found the money by finding an inefficiency. The inefficiency is that the cost of faster FDA review is low relative to the value of faster FDA review. So we grabbed that inefficiency, closed it, and used the value to encourage treatments for neglected diseases.

We suggest thinking about other prizes to address the need for second medical use. Our argument is not that prizes will solve the problem, but that they might be one tool of many in the toolbox.

DR. BLOOM: Good morning. I am pleased to be here. I am amazed at all of you taking such time out of your lives to be here for two days.

This is something near and dear to our hearts. I have been doing repurposing in the nonprofit sector since 2002. We are out there in the daily grind trying to move these things forward. When I got the invitation to come and participate, I thought this was a really great opportunity.

I am going to talk twice this morning, but right now I am going to talk about some things that we can do. I am going to talk quickly about five realistic things that could be done, three of which you can do right now to deal with this market issue and two which are potential things that could be done

[4] David B. Ridley, Henry G. Grabowski & Jeffrey L. Moe, *Developing Drugs for Developing Countries*, HEALTH AFF. (Millwood), 2006 Mar-Apr;25(2), at 313-24, *available at* https://www.ncbi.nlm.nih.gov/pubmed/16522573.

One thing we are doing right now is jurisdictional or indication arbitrage. In discussing this, I am going to primarily talk about repurposing very inexpensive and widely available generic drugs, not proprietary drugs or pipeline compounds or anything in the rescue area.

If I am interested in commercial drug repurposing and I know a category of drugs that might be repurposed for a new indication off-label, if I repurpose a drug in my own jurisdiction, then I suffer from the same problem we talked about yesterday, which is generic substitution. So, if I have a higher-priced branded drug with market approval, I am going to have a difficult time earning money, as physicians and payors will substitute the cheaper generic that is available. But if I instead test an analogue from that same class of drugs that is available in a different jurisdiction but has never been approved for any use in my own jurisdiction, then I can have some exclusivity because I am the only one in my jurisdiction that can market this drug for sale.

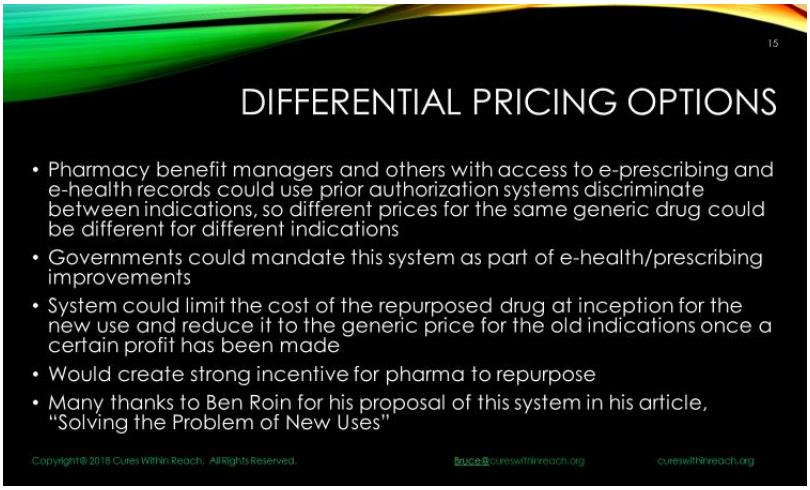
Cures Within Reach is doing this in several situations where there are drugs that have been approved in Japan that were approved after similar drugs were already approved and established in the United States but they never were brought to the United States because they could not get a decent market share. If we can find a repurposed use for them in the United States, they can be commercially repurposed.

This jurisdictional arbitrage can incentivize companies to pay for the the jurisdictional arbitrage market approval work that needs to get done in the United States because there is a chance for market exclusivity. It also works outside the United States as U.S. drugs typically are approved in most other jurisdictions. So this is a way of creating some market opportunity for corporations in the repurposing world that can really make an impact right away.

The second opportunity in this category is differential pricing, which Ben Roin spoke about yesterday [see Session 1F]. We at Cures Within Reach had not really thought of the idea of differential pricing until we read Ben's 2014 paper,[5] which took me three years to read because it is so long. It is

[5] Benjamin N. Roin, *The Case for Tailoring Patent Awards Based on the Time-to-Market of Inventions*, UCLA L. REV. (2014), *available at* https://poseidon01.ssrn.com/delivery.php?ID=
402119071098093000118112106008121117098000022029012082094008081086110085087000110101049058006100016121016066080113075124076092104032069065006076012071065085093108007081053072023114082114078100005113091127095094011070101016023023015112122

amazing! If you have not read his paper on solving the market problem of repurposed drugs, it is an amazing bit of work — and, Ben, we are glad to have you here.



One of the things that we think about concerning differential pricing is to treat these situations almost like we treat utilities. We give utilities monopolies for a particular time and at a particular cost because of the development costs they incur to deliver power to users. We do not give them unlimited ability to charge because, since they have a monopoly in the marketplace, they would charge whatever they could, so we give them the ability to make a reasonable profit.

I wonder if we could do the same thing for companies that repurpose generic drugs. For example, Metformin right now costs the average person somewhere between $2 and $7 a month for their type 2 diabetes. But if a company could prove that it worked for an unsolved disease, say a disease such as lupus, it might require payors to pay $300 a month for the lupus Metformin until the company that brought this to the marketplace had received perhaps 150 or 200 percent of its investment, and then you could bring the cost down to the level of the generic cost for the other uses.

This differential pricing would require a change in regulations, so that the company that brings the repurposed drug to market can have the exclusivity necessary to make a profit, but not unlimited pricing autonomy. As Ben Roin said yesterday and in his article, there are already processes in place that can help us know for which diagnosis a drug is prescribed, so this is something that could conceivably be implemented in the United States quickly. Differential pricing can provide sufficient market incentive without stripping away the cost-benefit of repurposing these inexpensive and widely available and remarkably safe drugs.

A third thing that is happening right now — it happens in clinical practices every day — depending on what statistics you believe, somewhere between 15 and 23 percent of all prescriptions in the United States are written off-label, which is just market drug repurposing that physicians are doing, many without any kind of scientific validation or substantiation. Nonetheless it happens all the time.

However, there are treatment facilities that are starting to pop up specifically around the idea of using off-label drugs that have good scientific, and often clinical observation, data to support their use. There is a group in the United Kingdom, which has now opened a treatment facility here in the United States, looking at this, and there are lots of small pockets of other clinical practices doing this kind of work.

It seems like a market incentive way to take advantage of generic drug repurposing to provide access for patients which they often do not have right now. One of the benefits of at least some of these treatment facilities is that they collect the data from each patient, so they are in essence doing sort of an on-the-ground, real-world-evidence clinical trial of generic drug repurposing so that they can continue to move this kind of repurposing forward.

As we do more personalized and precision medicine, I think we will see that more and more clinical practices are going to look for generic drugs and nutraceuticals and other things that are already approved for human use that could be reused in a particular patient situation that would help with adding to the standard of care, even sometimes replacing the standard of care.

I want to talk about two other potential market incentives for the repurposing of generic drugs.

One we are pioneering in England now is to use social finance. The idea is that if we could repurpose inexpensive drugs to improve patient outcomes and, at the same time, reduce healthcare cost, we would receive a percentage of that healthcare cost reduction to repay the private investment that paid for the repurposing research. We are working with NHS in England to try to create a ten-project portfolio of repurposing research in rare diseases using generic drugs. Impact investors would fund the research and the NHS or Public Health England or some other government entity would be the success payor. And, if there was excess payment back to the social impact bond, it would be used to create another portfolio.

There are literally hundreds, if not thousands, of ideas. On our CureAccelerator platform right now we have over 180 fundable clinical trials, all repurposing some kind of generic drug, device, or nutraceutical.

We think that this is an opportunity to one day create a global social impact bond. One of the benefits of repurposing is if it works in one location, it works in every other location where the patient has that disease and the drug is

available. So repurposing has the ability to spread throughout the global marketplace even if the research only takes place in a limited location.

The last thing I want to throw out as an idea is: What if there was a one-penny tax on every prescription that was sold? Last year in the United States alone there were 4.6 billion prescriptions, which would provide $45 million to fund the kind of generic drug repurposing research that Cures Within Reach does right now. If we could globalize this, there would be even more funds available for repurposing research.

The costs of repurposing research are very low, especially in relation to *de novo* research. When the results of repurposing research clinical trials are robust, physicians and patients could decide whether to use these repurposing therapies off-label. It still would have a huge impact on patients and promote the repurposing and the validation of these kinds of ideas.

Those are five things that we could either do right now or are doing right now. I will turn it over to Otto to cover other information.

MR. LICKS: Thank you, Bruce.

Before I start, I would like to thank Prof. Jay Thomas and Sir Robin Jacob for the opportunity to be here and share some of the views of a developing country.

I will touch briefly on some of the suggestions that we heard today from Bruce, but I will try to focus on one and be specific on what David mentioned regarding rare and neglected diseases, a big problem in a developing country. I tackle that through a means that Constance mentioned at the beginning, through the public-private partnerships.

But before I do that I have to make sure that if you only have time for one piece of information out of my talk, I would like to share with you that Buenos Aires is not in Brazil. [Laughter]

What about drugs in Brazil? It is a big country. If you do not count Alaska, Brazil is bigger than the contiguous United States. We do not have a lot of people; we only have about 200 million. It is the sixth largest pharmaceutical market.

We have a public healthcare system called Sistema Único de Saúde (SUS) that caters to 90 percent of those 200 million people. You do not have to be a Brazilian, you do not have to be a taxpayer, you do not have to be a resident. You arrive in Brazil and you are entitled to all expensive monoclonal antibodies; you are allowed to obtain every single pharmaceutical drug, not only those approved in Brazil but approved elsewhere in the world; if it is approved by European Medicines Evaluation Agency (EMEA) or it is approved by FDA, the Brazilian government will bring on a name-based system until the product is approved in the country.

That is expensive. That is why we pay a lot of taxes. But, unfortunately, that does not solve the problems of neglected diseases and some of the rare diseases that affect our specific population down in the tropics.

Non-patent incentives

Tech-transfer with the Brazilian government

Partnerships for Productive Development are **long-term government contracts** (5 to 10 years) signed between a **government-owned pharmaceutical industry** (public institutions) and private companies, alone or in consortium (private entity), with the **MoH's approval**, involving the (i) **transfer of the manufacturing technology**; (ii) the **supply of a product** considered strategic for SUS, usually with exclusivity; and (iii) the **nationalization of the API** by one of the private companies

That is where the public-private partnerships help in trying to bring to patients much needed medicine.

First, I would like to make sure that when focusing on alternative incentives to patents in Brazil I do not give you the impression that patents are not available in the country. We do have patents. We have patents for second use. We have patents for second use of known compounds. We have patents for new indications of products already in the drugstores.

Further, we do not have skinny labels. We do not have skinny labels because of our food and drug regulatory system. Brazil in the last twenty-five years has been known to be the paradise of substandard drugs. We do not have a very strong regulatory system and, at the same time, we have a lot of money to buy drugs. So, unfortunately, a lot of people show up there selling junk.

At this point in time we have tough regulations on what generics can sell in Brazil to try to curb the problem of substandard drugs. By the time we get our regulatory system fixed we might have to revisit what the patent system is all about.

Brazil has just joined the The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH). We are in the process — it is a long process, a five-year transition period — but I hope that when we get our market as well regulated as in the United States and Europe we will be able to look again into the prohibitions for skinny label when we look into access and pricing. But as of now skinny label is not a possibility.

With that brief introduction, I will now get into the non-patent incentives to bring drugs to Brazil. And what kind of drugs? Drugs for malaria, Leish-maniasis, tuberculosis, hepatitis A, influenza, chicken pox, mumps, rubella.

We have those well-known diseases that we call neglected, but at the same time we have new diseases, such as Zika. You might recall that when Brazil hosted the Olympic Games many female athletes looked into whether or not they should go because we had the Zika virus problem in 2015 and 2016. With the Zika virus we had a potentially very serious condition of microcephaly for woman who contracted the Zika virus while pregnant or before being pregnant.

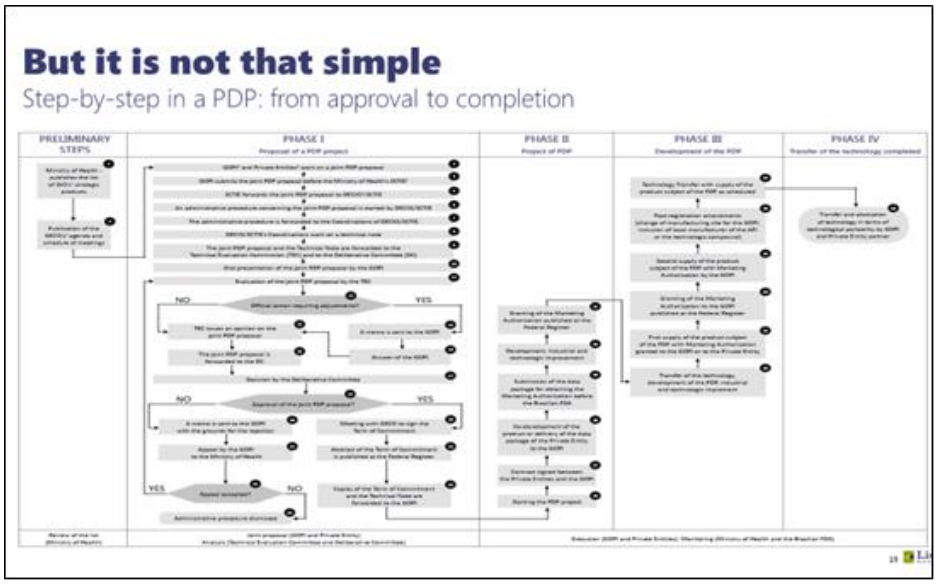
In an eighteen-month period of time, we had over 200,000 notifications, about 15,000 cases of babies with microcephaly. In Brazil trying to deal with that has cost us close to $1 billion. We did not do a good job, and the kids that ended up with microcephaly have really not a good treatment.

Just last year researchers from California together with researchers from Brazil started to look into a second use of Sovaldi from Gilead, approved for

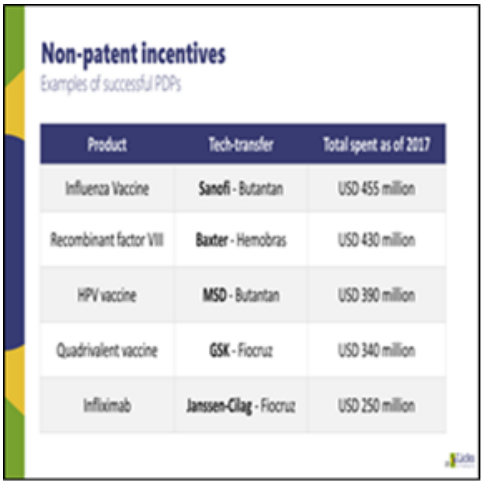
hepatitis C, for the Zika virus, and the ability that Sovaldi has to make sure that babies born to women who were positive for Zika would not have microcephaly.

If Brazil did not have a patent system, Brazilian researchers would not have had access to Sovaldi. Sovaldi is patented in Brazil. Sovaldi is available and paid for by the Brazilian government. That is how physicians know how to use it, researchers have access to it, and, by using it in the population, you get to talk about the possibility of second use. If patents were not available in Brazil, if Sovaldi was not available, Brazil would not have the first use and would probably not have the possibility of this important second use for the Zika virus.

Further, the Brazilian government is trying to establish Partnerships for Productive Development (PDP) with companies and is willing to use SUS's market power on purchasing drugs to develop and bring into wide use new cures.



Prof. Thomas told me that at the end of my talk I can give a test and people who will fail it will not be allowed to get out for lunch. So you do have to pay attention to each of those five columns boxes on Slide 16. Unfortunately, we do not have time for that, but I will be glad to answer any specific questions.



Product	Tech-transfer	Total spent as of 2017
Influenza Vaccine	**Sanofi** - Butantan	USD 455 million
Recombinant factor VIII	**Baxter** - Hemobras	USD 430 million
HPV vaccine	**MSD** - Butantan	USD 390 million
Quadrivalent vaccine	**GSK** - Fiocruz	USD 340 million
Infliximab	**Janssen-Cilag** - Fiocruz	USD 250 million

I would like to show you some of the good results when the steps and procedures of a PDP, as laid out in Slide 16, are implemented. In a program that is not even ten years old, we already have access to products that were difficult to obtain in Brazil, that were obtained in Brazil in limited quantities, and for which we are looking into developing additional indications.

When an off-label indication is established in Brazil by SUS and/or the Ministry of Health, that is a quasi-system of making that a formal indication. The

Brazilian government establishes that the SUS healthcare system is allowed to purchase in quantities needed for the off-label/second use and that the physicians are allowed to prescribe that drug for this off-label use. So, with the PDPs, the Brazilian government seeks a system by which drugs can be developed, produced, purchased and prescribed (by physicians) in large quantities. It does not work for all cases, but it is making a difference.

Of course, it is fairly recent — it is not even ten years old — but we hope that this will be changed and improved. It does not solve all the problems, but it helps in many of them. It is one of the best alternatives to develop new uses that we have had in basically thirty years with the public healthcare system of trying to support rare and neglected diseases.

With that, I thank you all again for the opportunity and look forward to questions.

MR. TRENCHARD: We are happy to take any questions from the audience, but I have one first, so I am going to use that prerogative. This is really for Bruce and Constance together. You both talked about the value of allowing and then capturing data about off-label uses as a way of exploring second or third medical uses or getting drugs repurposed for new uses. Effectively, Bruce, you said this is the way the market is actually doing it — or Constance may have said that; one of you said that.

Do either of you find — Bruce especially, since you are on the ground actually trying to implement these projects; but Constance, if you have researched it — that in those sorts of projects, which effectively require patients to agree to be guinea pigs, there are certain clinical areas where that strategy is more effective than others? I ask because I could see in oncology when someone has run out of options they would be willing and I could see in multiple sclerosis where it is a lifelong condition that is not fatal they would not. Do you find those ideas being more useful in some clinical areas than others?

DR. BLOOM: I think yes, although our experience is that these ideas pop up in every area of medicine.

There was an interesting paper five or six years ago from Eric von Hippel and others at MIT that said that as soon as a drug hits the market 59 percent of the potential new uses are discovered by clinicians that are using the drug within the first five years of the drug being out on the market.[6] So, physicians start using the drug, and because some patients have co-morbidities, these patients take the drug for Disease A and they see an impact on Disease B, and that is what gets things started. Or the drugs are used in academic medical centers where there is a lot more academic thought into the repurposing of drugs.

At Cures Within Reach we have had great success in the area of rare diseases, where so many of those patients have literally no hope that somebody else is going to find a cure. We do not know the genetic origin for most of the

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[6] Harold J. DeMonaco, Ayfer Ali & Eric Von Hippel, *The Major Role of Clinicians in the Discovery of Off-Label Drug Therapies*, Final version published in PHARMACOTHERAPY (2006) Vol 26, No. 3, pp 323−332, *available at* https://pdfs.semanticscholar.org/4b2d/22090c4ff34a75bf2edf1778af01f7ee06c2.pdf.

7000 rare diseases and it is just really hard to think of how you might handle them. Many of them are multifactorial.

So if I had to say where drug repurposing is most useful, I agree with you that it could be oncology. In oncology, patients often run out of therapies that work, so they look to their physicians for another alternative, almost always because of acquired resistance to the current therapy. Often, these oncologists will utilize non-oncology drugs to help in those situations.

Cures Within Reach is co-funding a trial in Germany right now in which the research team is using nine different non-oncology drugs in association with the standard-of-care drug, because preclinical data indicates that acquired resistance to the standard-of-care drug can be stopped by this combination of non-oncology drugs. Thinking of ten drugs in the same clinical trial is kind of mind-boggling — I guess that is a bad pun for brain cancer.

I would ask Connie to respond to that same question.

MS. BAGLEY: Sure. I think that one always is going to be looking at cost-benefit analysis — certainly the physician is — and if it is an ailment that is not life-threatening and there seems to be a good enough drug out there, then, absent undue pressure from marketing folks or other extraneous factors that could go into the decision, one would expect much less in the way of off-label.

I would say, though, that what we have now is even worse. You are now a guinea pig, but you are not told you are a guinea pig, you are not told what the risks are of what you are being given, what the alternatives are.

I was unaware of what Brazil is already doing in this area, but I think that is where we need to go. We need to either change the standard of care and say to physicians — and they are a good lobby group; the American Medical Association is not going to let you win on this one — "Either change the rules and say you can use drugs only for on-label, or I think we do need to have a supplemental system" — you probably have a good fancy name for yours — a system whereby when it is a second purpose drug — and again I am drawing a sharp distinction between that and a drug that has never gone through trials at all — I think those should continue to be off-limits in terms of promotion.

At least this way you are providing information to the patient, at a minimum that it is an off-label use. And if we are able to incorporate into this obligations on the pharmaceutical company selling the drug to do follow-up — again kind of this crowdsourcing — to get some information with respect to side effects and efficacy and that sort of thing, I think we get two benefits from that and not just one.

MR. TRENCHARD: Jürgen?

QUESTION [Jürgen Dressel, Novartis Pharma]: My question is to Constance: Don't you see a devaluation of the regulatory approval process when you make these sorts of judgments of having something in between, of having easier access without the formal regulatory approval? Wouldn't I as a patient prefer to have an approved use versus something where there might be scientific evidence? What is actually the incentive for the originator to do expensive and risky trials which finally lead to the formal approval? Why should he do that when he can get away with just having it prescribed off-label?

MS. BAGLEY: One aspect of my proposal I failed to mention is that the limitations would be based on the qualification of the listener. In terms of the promotion of the off-label use, it would have to be a communication directly with a licensed physician. That would knock out physician assistants, nurse practitioners, and others. Also, if you are in this quasi area, no public advertising. I think that mechanisms like that — you are right — certainly do change the calculus for some drugs as to whether it is worth it to go the gold standard.

But my proposal also says that if more than *X* percent of the use is off-label, you do then have to go ahead and do the trials. That again is akin to in the securities law: even if you have never done a registered offering of securities, if you grow a company beyond a certain revenue number and a certain number of shareholders, you are required to register under the Securities Exchange Act and provide periodic information so people know more about this company in which they are now invested.

The idea is to have it initially available to a limited set of accredited listeners and to force you to go for the full Monty, if that is appropriate in this context. I probably should not do this in a room with a number of Brits because I am sure I do not know all the connotations.

DR. BLOOM: We have seen the movie. [Laughter]

MS. BAGLEY: But require you to go the full bore if it is more than, say, 10 percent or whatever of the usage.

Excellent question.

MR. TRENCHARD: A lot of the discussion here has been exactly about the issue of dancing around the question of how do you fund Phase III trials. So far the patent system seems to be the most efficient system to consistently fund those trials, which are, as Prof. Grabowski was talking about yesterday, in the neighborhood of a couple hundred million dollars a pop. Any given drug company, a really big one, can have a hundred or more running at one time over the course of years.

Bruce, you had mentioned having utility-type regulation, where you would effectively guarantee that there would be a return on investment for somebody running the required trials. Are you aware of any instances in which that has been implemented and actually worked?

Otto, does that sort of thing happen in Brazil with the off-label uses of drugs that are approved outside the country? Do people come in and actually do Phase III trials in Brazil because they think they are going to get enough of a return from the Brazilian market alone?

David, most economists when they hear “regulation” go “ugh,” and I am curious to hear whether you do.

MR. LICKS: In terms of assuring some type of return, unfortunately, what we have seen in Brazil is that you just allocate the risk to someone else.

I will give you an example. The Brazilians on the public partnership project started one to produce pegylated interferon and years ago started actually to build a factory in Brazil. Well, now the factory is almost completed, maybe a few years from today, after having massive investment, but physicians no longer want to use the product.

What are you going to do with that pegylated interferon? Clinical development moves fast. You cannot tell the Brazilian population, those almost 200 million people, that they are getting a drug that someone invested in, or that the government invested in, for the last five-to-ten years, and not the best drug that has been just approved last year.

What we have seen is that the physicians and the public institutions do not look into the investment, they do not look into the policies. The physicians have only one thing in their mind, the patient. If for that particular patient the best drug is the one that got to the market just yesterday, they just do not care about the PDP; they want the best drug available for the patient.

DR. BLOOM: I do not know any instances where a government or other payor currently provides a guaranteed rate of return for the market approval of a drug. But there are some incentives that provide a similar kind of support for market approval of drugs that might not make a profit. The Orphan Drug Act in the United States provides orphan drug designation for any drug, regardless of whether it is for a rare disease, if it is unlikely to return a profit if brought to market.[7] The idea is that the orphan drug designation might be valuable enough to offset the lack of market profit. Orphan Drug Designation incentives include grants, tax incentives, and extension of exclusive marketing rights to a drug for seven years.

Pharmaceutical companies that are represented here have assets on their shelves that are no longer patentable that could help patients. If there was some way for government or other payors to guarantee that if the company moves them through the pipeline to market and the drugs benefit patients and the company could get reimbursed for their costs plus some profit, we believe there are people at the pharma companies who would be motivated to do that. But right now these pharma companies have no way of getting these patent-expired assets to market, even when they have strong evidence that they could benefit patients.

The same thing with generic drugs. Cures Within Reach has received a huge number of ideas for repurposing generic drugs that we know could help patients, but there is no market incentive for anybody to take them through a market-approval process, even an abbreviated 505(b)(2) process. This makes it tough.

PROF. RIDLEY: So the question is you successfully bring a product to market and you get reimbursed for your costs plus a small rate of return?

MR. TRENCHARD: Yes. What is the feasibility in your mind of a system like that?

PROF. RIDLEY: It is tough. I think you would want to be certain that you are going to make it to market, because what do you do with the companies

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[7] FDA, Orphan Drug Act—Relevant Excerpts: "affects more than 200,000 in the United States and for which there is no reasonable expectation that the cost of developing and making available in the United States a drug for such disease or condition will recovered from sales in the United States of such drug. Determinations under the preceding sentence with respect to any drug shall be made on the basis of the facts and circumstances as of the date the request for designation of the drug under this subsection is made." https://www.fda.gov/ForIndustry/DevelopingProductsforRareDiseasesConditions/HowtoapplyforOrphanProductDesignation/ucm364750.htm.

that do not make it to market? There are a lot of really small companies doing fabulous work. So I think you would want to be 100 percent certain that you are going to get to market if you do that. I think instead I would rather see push funding, which is funding up front, tax credits and NIH funding for example, or a prize at the end.

DR. BLOOM: Can I make a comment on that? I agree. I would love to have push funding. But, as obvious as it seems that there are generic drugs that are widely available and inexpensive with good preclinical and clinical observation evidence that would help in unsolved medical needs, no government anywhere in the world is funding that with push funding. It seems like the most obvious place for a government to spend taxpayer money, because not only does it improve patient outcomes, but in almost every situation when you have an unsolved medical need there are huge medical costs being paid to just provide palliative care.

By funding these kinds of relatively inexpensive and rapid Phase II/Phase III repurposing research trials, government could really help patients and reduce your overall healthcare spend on those patients. But, for whatever reason, it does not seem to be an initiative that the governments are interested in pursuing

Pursuing market pull at least provides the ability for private capital or some other funder to get involved where the governments just do not seem to be doing it.

There are some very large private philanthropic investors who could do this, but the idea of putting together a portfolio and doing Phase II and Phase III trials is such a large pot of money that the Gates Foundation or some other significant funder would have to be involved to move it forward.

MS. BAGLEY: With respect to looking at the cost and what the government is and is not doing, I was struck yesterday when I was told that the tradeable vouchers could be worth as much as $100-200 million. You could probably hire a lot of people at the FDA, a lot of scientists at government labs, academic labs, and the like for that kind of money.

I do not know to what extent the FDA has any plans to really do a kind of top-down operations research analysis of the approval process, but if we look at the numbers we were shown yesterday about how the prices are going up, it does seem to me that there have to be gross inefficiencies, and it probably means you have a class of scientists that are not subject to the normal pay scale for the government and that sort of thing.

But we have done this with other things, and I think that if we were to, in particular, have a couple moonshot-type projects for superbugs, Ebola and that sort of thing, bringing in the private sector and maybe some of my colleagues from business school just operationally, clearly that speed is worth a tremendous amount of money. My guess is we could add capacity at a rate that is cheaper than the trading, where it seems like the windfall is mainly going to the company that does the first testing and gets the voucher.

MR. TRENCHARD: Yes, sir?

QUESTION: I want to ask David a question. We talked about drugs that are up on a shelf and how do we deal with that issue. One model that industry has

played with sometimes more heavily than others is trying to out-license those things. You look at a spinout, you look at trying to get investors, you try to bring together somebody who might have some expertise in that area, and then you let the market decide which of those things it makes sense to advance. They do that by saying, "We are going to reward you if it is successful and not if it is not successful." What is your view of that from an economist's point of view?

PROF. RIDLEY: I think this might be a recent example. Pfizer had moxidectin for river blindness and left it on a shelf. Medicines Development, a nonprofit in Australia, took it off the shelf and they are hoping for approval this year. The reason they took it off the shelf to move it forward — and they show that it is better than ivermectin, and Merck has been giving away ivermectin for a while, which is a good drug — is it turns out moxidectin is even better, but nobody wanted to develop moxidectin and compete against free.

But because of the priority review voucher, Medicines Development has taken it off the shelf, gotten some money from the Global Health Investment Fund, and they expect to win a voucher and maybe sell that voucher for $100 million, pay back some of the investors, the Global Health Investment Fund, and use some of the money for access to the drug, to give it away for free. The hope is that now they will be able to eradicate river blindness thanks to these two drugs together.

That is a case where a drug was on a shelf and someone else picked it up and there was an incentive for someone else to pick it up. It never would have gotten off the shelf if there wasn't some possible return because you are not going to spend money bringing it to market when there is no possible return.

MR. TRENCHARD: Dr. Banerjee?

QUESTION [Dr. Amitava Banerjee,] UCL Farr Institute of Health Informatics]: Are we focusing on the right diseases and the right drugs? This term "neglected diseases" is maybe not fit for purpose now.

The Institute for Health Metrics and Evaluation (IHME) at the University of Washington Global Burden of Disease Study has shown that actually the same diseases are the big causes of burden of disease whichever country you are in, whether it is heart disease, cancers, COPD. We are still in this "diseases of the West and diseases of the East" paradigm, which is defunct.

The reason I say this is that for secondary use medications maybe where we should be putting our money is where we can have most impact, which is in the causes of greatest burden of disease, whereas we keep focusing on the neglected tropical diseases, which are not necessarily the big burden of disease in the poorest countries of the world. I wonder if the panel have any comments on that.

PROF. RIDLEY: I think you raise an important point. There are many of us, myself included, who are very focused on the traditional neglected diseases.

What a wonderful world we are in that we say that they are not neglected anymore, that we can move on! I think that is fabulous. I think we are getting there. My guess is we are not quite there yet, but I think you are right that that is the future and that is a wonderful future.

But it is still very much the case that we are developing a lot of drugs for

cardiovascular disease and cancer. It is not like we are awash in drugs for neglected diseases. Since the voucher was launched, we've gotten five, which is great, but we have had a lot more cancer drugs.

So I think your point is well taken, that is the future, but I do not think it is time to ignore the neglected diseases just yet.

MR. TRENCHARD: With that, the "iPad of death" has said it is time to go.

[Session adjourned: 9:44 a.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 – 9:47 a.m.

Session 2C:
The Current Patent System Doesn't Do It! – A Case Study
What Would an Ideal System of Incentives Look Like?

Moderator:
David Barr
Arnold & Porter, New York

Presenters:
Bob Armitage
IP Strategy and Policy Consultant, Marco Island;
Formerly General Counsel, Eli Lilly

Mark Stewart
Assistant General Patent Counsel, Eli Lilly, Indianapolis

Panelists:
David Korn
Vice President IP & Law, Pharmaceutical Research and
Manufacturers of America (PhRMA), Washington D.C.

Toni Santamaria
Head of IP (Europe), Accord Healthcare, Barcelona

Prof. Ben Roin
Fred Kayne (1960) Career Development Professor of Entrepreneurship,
MIT Sloan School of Management, Cambridge

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MR. BARR: Hi, everyone. This panel has been assigned the rather daunting task of proposing an "ideal system." When Brian Cordery sent me the topic for our panel, I said, "Well, let me find out what is the 'ideal system.'" I looked up the definition of "ideal": first definition, "satisfying one's conception of what is perfect"; second definition, "existing only in the imagination, desirable or perfect but not likely to become a reality."

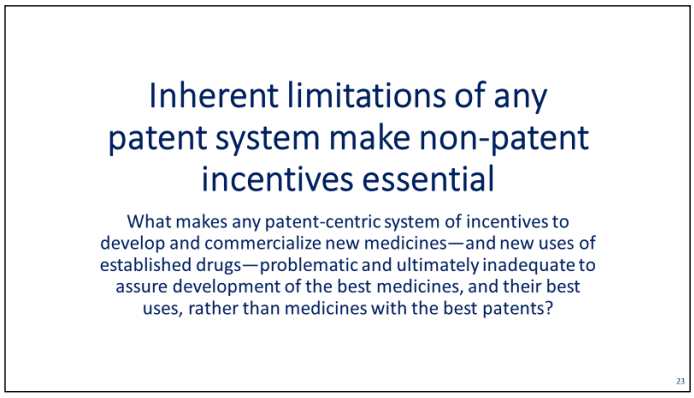
It is our task to propose a system, and, hopefully, it is not just going to be aspirational but we will propose something concrete and, with your help, it will become a reality, or at least parts of it will become a reality.

My name is David Barr. I am a biotech and pharmaceutical patent litigator from Arnold & Porter in the New York Office. I have been doing litigation for a long time. Most people think of litigation as a zero-sum game, but for a lot of my career I have also done transactional work deals. Maybe we have to borrow from deal-making ideas, where it is not a zero-sum game, where all parties to the transaction or to the proposed system can gain from it.

We have a great panel here today to discuss the ideal system. We will start with presentations from Bob Armitage and Mark Stewart, both of whom have a big-pharma perspective. Bob retired from Lilly and is now a consultant. Mark is still at Lilly and is Director of Patent Litigation. Toni Santamaria from Accord Healthcare is here to give us a generic's perspective on the ideal system. David Korn, Vice President for Intellectual Property and Law for the Pharmaceutical Research and Manufacturers of America (PhRMA), focuses on all aspects of IP law that are affecting legislation in Congress, in the courts, in the Supreme Court, and in the FDA. Finally, as Sir Robin pointed out, we have a superhero here who has been traveling at the speed of light back and forth: Ben Roin is back from MIT, and he has large S underneath his shirt so he can give us the superheroic aspects of the ideal system.

With that, I will turn it over to Mark.

MR. STEWART: Thanks for the opportunity to be here.



We heard a lot yesterday about problems with patent systems all over the world in terms of providing the proper incentives for pharmaceutical companies to develop additional indications for approved drugs.

Incentives for developing the best medicines/uses, rather than medicines with the best patents?

- A most promising NME[1] drug or its most promising use may be ***unpatentable***; have patent protection that is of ***uncertain validity***; or be protected through a strong patent position that, even with patent extension opportunities, may have a ***too-short, post-approval patent term***.
- A most promising new use of an approved drug may similarly be unpatentable; have patent protection that is similarly equivocal; or be protected through a strong patent position may have a too-short, post-approval term of protection against generic drug entry.
- ***Even the strongest patent position carries with it a significant potential for an anomalous, unexpected litigation outcome.***

[1]NME is a reference to a "new molecular entity," producing a drug based on a novel molecule.

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Rather than rehash all of that, I want to instead give you a real-life example, a case study, that I think illustrates many of these problems, plus a few more. That will take us into a discussion that Bob Armitage will lead related to an incentive system that moves away from being patent-centric. The system that Bob will discuss provides incentives to develop the best medicines and uses rather than incentives to develop only medicines with the best patents.

An optimal IP regime protecting NME drugs/new uses from generic drug entry should not be patent-centric

- Relying on patent-centric protection from generic drug entry entails too much risk/uncertainty—*sitting atop research and market risks—exacerbating the need for rewards to match such aggregate risks*.
- The more innovative and unprecedented the drug, the more likely it is that unforeseeable development challenges may produce an unexpectedly long time to reach the market—rendering the post-marketing patent life shorter for the most innovative drugs.
- ***Patent protection for new medicines tends to be perverse—the least innovative drugs can be projected to have longer post-marketing patent life than the most innovative drugs.***

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I think the third bullet point of this slide is just worth mentioning briefly. • Patent protection for new medicines tends to be perverse — the least innovative drugs can be projected to have longer post-marketing patent life than the most innovative drugs.

Atomoxetine (Strattera): A case study in why isn't the current patent system adequate?

1. Delays in the initial approval of a NME drug may preclude the development of additional indications given the timing of compound patent expiration.
2. Method of treatment patents are more vulnerable to attack once the compound and its mechanism of action are prior art.
3. Method of treatment patents are more vulnerable to attack if they encompass discoveries that are made during clinical trials.
4. Method of treatment patents can be difficult to enforce such that approval of additional indications even if they are patented can actually open the door to generic competition sooner rather than later.

Oftentimes, drugs that are not as innovative — such as drugs that have a routine formulation development path, drugs without significant side effects, drugs with predictable pharmacokinetic properties, and drugs that sail through clinical trials and get approval — will have a much longer post-approval exclusivity period than potentially more innovative drugs that may have to overcome substantial development hurdles. For example, the drug may be useful to treat a disease that has few treatments or is otherwise not well developed or the clinical trials may be lengthy and complex. Those types of drugs, which are arguably more innovative, are going to have a much shorter

exclusivity period post-approval. That seems to be a bit perverse. The case study I am going to discuss illustrates this point well.

Case Study Timeline

The development of atomoxetine (Strattera) for the treatment of ADHD

- Early 1970s atomoxetine discovered.
- Jan. 10, 1974 - atomoxetine compound patent filed.
- Feb. 2, 1982 - US atomoxetine compound patent issued.
- 1980s - 1992 - atomoxetine studied for urinary incontinence through phase II and studied for depression through phase III.
  - Atomoxetine failed to show adequate efficacy for either indication.
- 1994 - Dr. John Heilgenstein convinced Lilly management to conduct a proof of concept (POC) study for ADHD before material expired following the depression studies.

This case study relates to development of the drug atomoxetine for the treatment of attention deficit hyperactivity disorder (ADHD). The brand name of the drug is Strattera™. It is approved for ADHD in adults and children. Given its history, it is actually quite surprising that this drug was developed at all for any indication, especially for ADHD.

In the early 1970s atomoxetine was discovered. The compound is a small molecule. The compound patent was filed in 1974 and then issued eight years later in the United States. At that point, U.S. law was such that the patent term was calculated as seventeen years from the date of issuance rather than twenty years from the date of filing, as it is now. Therefore, the atomoxetine compound patent had a February 1999 expiration date.

In the 1980s and early 1990s atomoxetine was studied for two different disorders based on its discovered mechanism of action, which involved norepinephrine reuptake inhibition. The drug acted by increasing levels of norepinephrine in the synaptic clefts in the brain.

First, it was studied for the treatment of urinary incontinence and studies were completed through Phase II. But the drug failed to show adequate efficacy.

Following that failure, Lilly went back to the drawing board and decided to look at this drug and mechanism in depression. Lilly took the drug all the way through the end of Phase III, yet the trials failed to show an adequate statistical improvement in the treatment group.

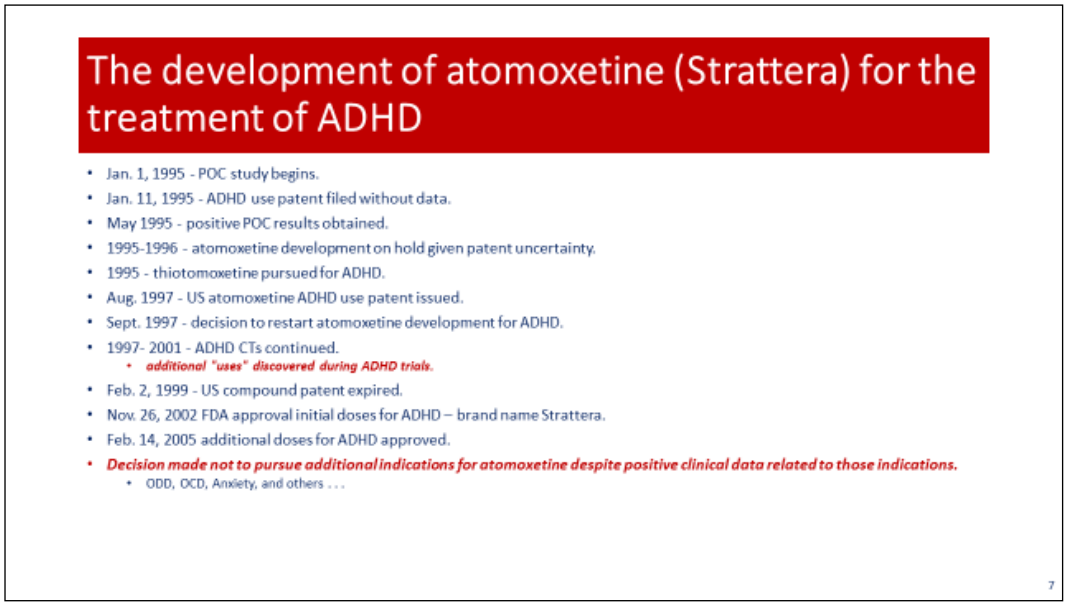
At that point the drug was put on the shelf. It was only four or five years away from compound patent expiration, and it seemed clear that even if the drug continued to be studied it could never be approved and launched with patent protection that would allow Lilly to recoup the enormous investment required to get the drug to the market.

Dr. Heilgenstein, a Lilly scientist, felt strongly, however, that this drug should continue to be studied, and that it had additional uses, one of those being attention deficit hyperactivity disorder (ADHD). Dr. Heilgenstein hypothesized that atomoxetine could be the first non-stimulant medication to treat ADHD in children.

It was known that the stimulants (such as Ritalin™) which were on the market at this time to treat ADHD, worked through both a dopamine and a norepinephrine mechanism. There were and still are, however, a number of problems with stimulants: They are controlled substances; there is the potential

for abuse; parents do not like to put their children on controlled substances; and there are numerous side effects.

A non-stimulant ADHD medication would be an important breakthrough therapy. Dr. Heilgenstein thought that manipulating only the norepinephrine pathway might give you efficacy in ADHD while avoiding all the negative attributes associated with stimulants and the dopamine pathway.



He convinced Lilly management to fund a proof-of-concept (POC) study using material left over from the depression studies that had still adequate stability to be used in clinical studies. Lilly agreed to fund those studies, and a group at Harvard Medical School did the initial POC study that began in early 1995.

At the same time we started those studies we filed an ADHD method-of-use patent for atomoxetine. Note that the use patent was filed without data because the trial was going on in parallel.

In the summer of 1995 we got positive POC results.

In 1995−1996 atomoxetine development was put on hold, given the patent uncertainty. Now you are only three years away from compound patent expiration and you do not have any use patents that have issued yet. So basically no patent protection.

Instead, Lilly focused on a different drug, thiotomoxetine, which had a similar mechanism of action, norepinephrine reuptake inhibition, but it was a different compound having a longer patent life for the compound. However, that drug failed pretty quickly because of some pharmacology issues.

But then, in 1997, at about the time that drug failed, the U.S. atomoxetine ADHD use patent issued, so the company decided to take a gamble and restart atomoxetine development for ADHD.

From 1997 through 2001 clinical trials continued for ADHD. We had some anecdotal evidence from physicians that maybe there were some other uses that could be explored. ADHD is co-morbid with a lot of other disorders, like anxiety and excessive compulsive disorder, and there were some initial signals

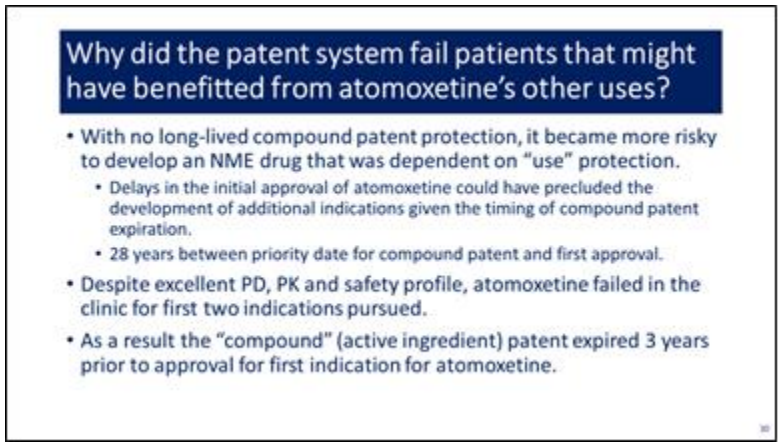
that maybe symptoms in those disease areas were improving as well; but it was not clear whether that was an ADHD improvement or whether you actually had something separate there.

In 1999 the U.S. compound patent expired.

Then, three years after that, the FDA approved some initial doses of atomoxetine for ADHD.

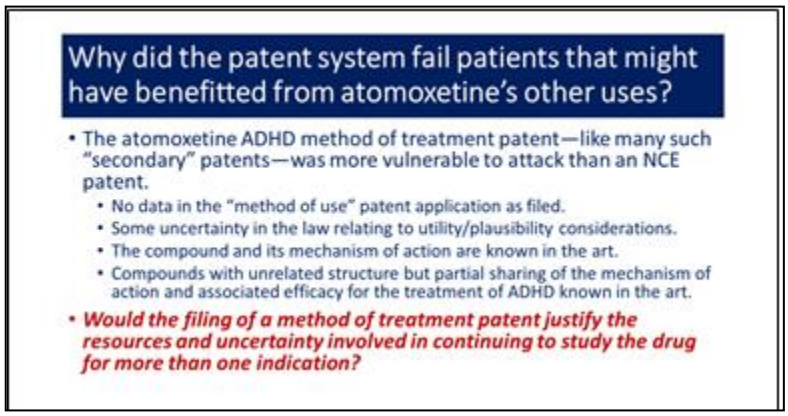
In 2005 additional doses for ADHD were approved and put on the label.

The decision after that was not to pursue any additional indications even though we had some positive signals in some clinical trials.



Lilly took a significant gamble developing atomoxetine with only a single use patent in place to provide exclusivity. This strategy was particularly risky. Twenty-eight years had lapsed from the priority date of the compound patent to the first approval for the drug. Taking the risk here, however, actually did pay off.

Atomoxetine, now known as Strattera™, is an important drug. It was a breakthrough product in the ADHD field because it was the first non-stimulant medication approved. But it very easily might not have been developed. Many other companies might have made a different decision and permanently halted development after the first two failed attempts at developing the compound especially given the timing of compound patent expiration.



Even though there were a number of concerns with the ADHD use patent, Lilly has successfully asserted and defended the patent against generics around the world. For example, there was no data of any kind in the patent, and so that created a hurdle. Lilly actually lost the district court litigation in the Hatch-Waxman case against ten generics because of that issue, but the Federal Circuit overturned that.[1]

[1] *See* Eli Lilly and Company v. Actavis Elizabeth, https://cases.justia.com/federal/

There was also some uncertainty related to the fact that both the compound and its mechanism of action were known in the art prior to the filing of the ADHD use patent which created additional concerns related to obviousness. But Lilly has prevailed in litigating that issue as well.

There were also problems related to pursuing additional indications for Strattera™. Lilly had concerns about some of the preliminary and promising signals coming from clinical trials which could have acted as a disclosure impacting patentability. And even if additional uses could have been patented, they would not have extended exclusivity for the molecule.

Once the ADHD use patent expired, any additional use patents that Lilly might have would be ineffective because the compound would be generic at that point due to cross-labeling and generic substitution issues. And without a compound patent in force certainly, even with all uses covered by issued patents, the loss of any particular use patent would have opened the compound up to generic competition. That scenario is particularly concerning today given the new inter partes review procedures in the Patent Office under the America Invents Act (AIA). It would indeed be very risky for any company to continue to attempt to develop a drug that failed to show efficacy for two different indications studied over a fifteen-year period, that lacked compound protection, and that was protected by a single use patent filed without data when the compound, its mechanism of action, and the clinical trials associated with the failed indications were in the art.

The Strattera™ case study clearly illustrates why the current patent system does not provide the proper incentives to develop the best medicines and instead provides incentives to develop only medicines with the best patent protection. Delays in the initial approval of a new compound may preclude the development of additional indications (or perhaps any indication) given the timing of compound patent expiration.

Method of treatment patents are more vulnerable to attack once the compound and its mechanism are prior art. Method of treatment patents are more vulnerable to attack if they encompass discoveries that are made during clinical trials. Method of treatment patents can be difficult to enforce such that approval of additional indications even if they are patented can actually open the door to generic competition sooner rather than later.

How many drugs are sitting on the shelf because they either have no patent protection or because there is a concern that patents, if filed, might not be strong enough to provide exclusivity enabling the sponsor to at least recoup its investment? Many of these are drugs are safe and could be pursued for diseases where there is an unmet medical need so what is the solution?

I will leave it there and Bob can tell us what the perfect solution is.

MR. ARMITAGE: Good morning. In picking up where Mark Stewart left off, I am going to outline in a few slides an entirely new type of IP incentive

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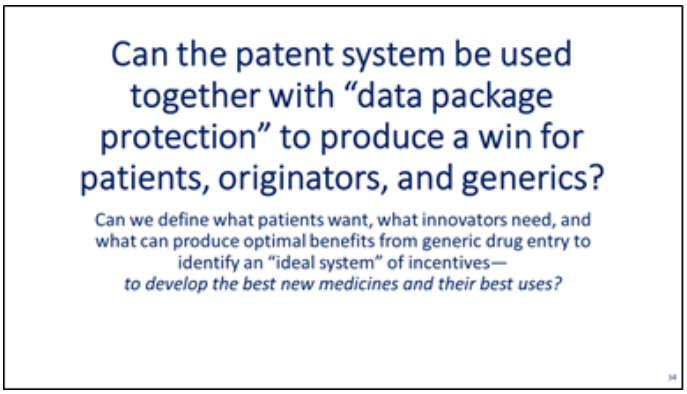
appellate-courts/cafc/10-1500/10-1500-2011-07-29.pdf?ts=1411156320. We also successfully litigated that issue in the United Kingdom. http://eplaw.org/document/uk-actavis-v-eli-lilly/

system. It is a system designed specifically for new molecular entity medicines. It would apply equally to both traditional drugs and the biologic medicines.



The gist of this incentive system lies in aligning data package protection with whatever patent protection is available for these new molecular entity medicines, thereby creating a fixed and common period of combined IP protection. By appropriately setting the length of this fixed and common period of IP protection, it would almost entirely eliminate the patent centricity that now bedevils the U.S. Hatch-Waxman system.

The atomoxetine tale related by Mark is a good case study for what can go wrong with the current U.S. system of incentives to develop new medicines. The atomoxetine story — and others like it — provide an imperative for finding a less patent-centric replacement, such as the fixed IP protection period that I will be discussing today.

We will never know what the best clinical uses for atomoxetine might have been. While its single approved use in ADHD represented an important contribution to human medicine, now that atomoxetine is available as a generic drug, there is today no incentive for Lilly (or anyone else) to investigate possible new uses for atomoxetine.

One objective of the fixed IP protection period is to avoid the atomoxetine-like stories in the future with a system where strong incentives are in place such that all of a medicine's important medical uses are clinically investigated before the IP protection period has ended and generic drug entry takes place.

How might such a simple concept as setting a fixed IP protection period accomplish such an ambitious goal?

First, most new uses for a new molecular entity medicine are discovered early on. As Dr. Bloom mentioned earlier, for many medicines, about 60 percent of their best clinical uses are known quite early in the development and commercialization process, typically within five years after a new medicine first gets to market.[2] As Mark discussed, atomoxetine's development timeline certainly validates this observation.

Dr. Bloom's data on the timing of the discovery of new medicine's second and subsequent uses underscores the importance of a continuing incentive that

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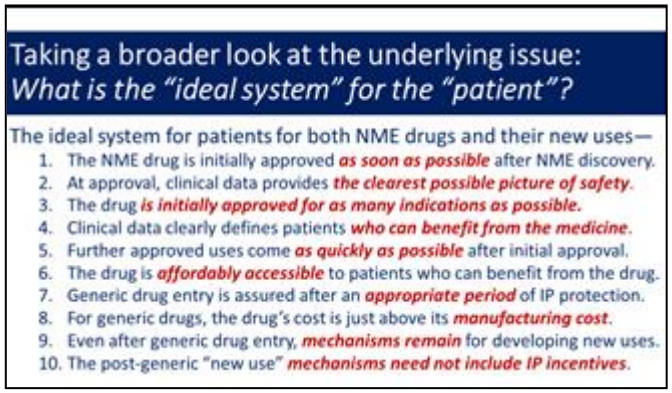
[2] *See* Dr. Bloom's presentation in Session 2B, citing Harold J. DeMonaco, Ayfer Ali & Eric Von Hippel, *The Major Role of Clinicians in the Discovery of Off-Label Drug Therapies*, final version published in PHARMACOTHERAPY (2006) Vol 26, No. 3, pp 323−32, *available at* https://pdfs.semanticscholar.org/4b2d/22090c4ff34a75bf 2edf1778af01f7ee06c2.pdf.

motivates undertaking further clinical investigation once a new medicine receives its initial regulatory approval. Ideally, a continuing incentive would operate effectively during the decade after the new molecular entity initially received regulatory approval. If this could be done, the Bloom data suggest that the vast majority of potential uses for a new medicine would be clinically developed before the time of generic drug entry.

Thus, the fixed IP protection period, as detailed in the slides that follow, was specifically designed as an incentive that would work equally well to encourage the development both of new molecular entity medicines and of new uses for those new medicines during the decade following regulatory approval — and thereby mitigate the need for developing new incentives once generic drug entry for the medicine had taken place. In other words, it is the type of IP incentive system ideally crafted to turn the unfortunate atomoxetine story on its head.

With this overview of where this presentation will be heading, I think it would be useful to now go back and discuss the most important factor motivating its development. That motive comes from asking a simple question: From whose perspective should we look to develop the ideal system for developing new medicines?

I suggest we answer this question by looking from the perspective of the patients that new medicines and their new uses are designed to serve. If nothing else, a patient focus seems to me to be the indispensable perspective from which to define the problem and craft the ideal solution because it may well be the patient perspective will set the political environment in which the merits of the "ideal system" will be debated and its fate determined by policymakers and legislators.



Let's begin by asking the seemingly trite question: "What do patients want?" Specifically, what do they want from their next-generation medicines? I have set out ten bullet points that I would like for us to consider, at least as the starting point for a discussion of such a patient "wish list."

In composing the ten points I did not undertake a patient survey of the type needed to validate this list. Instead, the listing represents a bit of a thought experiment on my part, but one based on my own experiences both personal and professional.

In composing this list, I asked myself what priorities might emerge if I took a group of patients and educated them at a high level on how the drug development process works. The intent of this educational process would be that the surveyed patients would know something about the limitations arising from the science of discovering and developing new medicines and the arduousness of

the regulatory review systems under which new medicines are initially approved for marketing.

In addition, this hypothetical group of patients would then need to be introduced to the notion that developing additional medical uses for established drugs might require special incentives in order for such medicines to be approved and promoted for such additional uses. They would come to understand that those incentives might come with a price tag.

With this type of background, what might these patients come back with as a patient "wish list," given this type of informed view of the scientific, regulatory, and commercial realities as they relate to discovering and developing new drugs?

I can imagine patients explaining that they want new molecular entity drugs approved as soon as possible and with as many approved indications as possible coming to the medicine's label as soon as possible. I envision patients explaining that, when new drugs are approved, they want their prescribing physicians to have the best possible information available with respect to the safety of the new medicine. In this regard, I expect that both physicians and patients will want to know which individuals can and cannot benefit from the drug and why.

If additional uses are to be investigated after drug's initial approval, I believe that patients will want those uses to come through the regulatory approval process as soon as possible, but, at the same time, patients will additionally underscore the importance that medicines must be made affordably accessible.

I believe patients who come to understand how the generic drug industry works will want to make certain that there is a long enough period of protection from generic drug entry for new medicines in order to earn back the investment made to create them. At the same time, once the generic drug era begins, patients will want these generic drugs available at the lowest possible cost.

I believe that patients who come to understand that there are no high-risk, low-reward businesses that can sustain themselves over the long term would be very interested in fostering a generic drug business model that is dramatically de-risked. If the risks and costs associated with generic drug entry can be minimized for generic manufacturers — including patent and other IP-related risks — this de-risking can foster the ability for generic drugs to be profitably sold at just about their cost of manufacture.

In my view, patients are unlikely to be obsessed with assuring that any incentives to develop additional uses for established drugs would be IP-based incentives, as opposed to other types of incentives. At the end of the day, if new uses are to be developed for generic drugs, I suspect that most patients would be concerned if IP-based incentives resulted in a loss of access to low-cost generic copies.

While I believe elements of the patient "wish list" could be empirically verified as generally accurate, the problem with a patient "wish list" is that it eventually needs to account for — and be adjusted to reflect — competing interests. An ideal system for patients cannot be problematic for payors, originators, or generic copiers and end up as politically viable.

Taking a broader look at the underlying issue:
Can patient "wants" and industry "needs" align?

- There are potential conflicts between the 10 patient "wants" and the industry "needs" that must be taken into account and resolved in defining any "ideal" system and establishing its political viability, *e.g.,*
  - The higher the safety/efficacy hurdles before the initial NME drug approval or approval of new uses, the greater the cost and time to regulatory approval.
  - Substantial clinical experience with a drug is sometimes needed before undertaking new clinical work directed to additional indications for use can be justified.
  - No consensus exists on the "appropriate" IP protection for an NME drug.
  - Assuring that drugs are "affordably accessible" to all patients might impair the ability of innovators to charge fair and reasonable prices for a drug.
  - No consensus exists on what might be a fair and reasonable price for a drug.

As one example, there is no consensus manner in which to determine what a reasonable price for an IP-protected drug might be. More importantly, there is no consensus on what a reasonable period of IP protection for a new medicine should be. These are but a few of the areas where an "ideal system" that might work in an ideal world would need to contend with the nitty-gritty conflicts of competing interests found in the real world.

Taking a broader look at the underlying issue:
Is there a consensus hierarchy for IP incentives?

- The primary focus for incentives: ***encourage the development of the best medicines, not the medicines that may qualify for the best patent or other IP protection***.
- The secondary focus for incentives: ***the best medicinal uses for a new medicine are developed and approved at the earliest possible point in time after initial regulatory approval***.
- The tertiary focus for incentives: ***identify additional means for developing new uses only if the primary and secondary incentives are no longer effective to elicit investments in the continuing development and commercialization of such new uses.***

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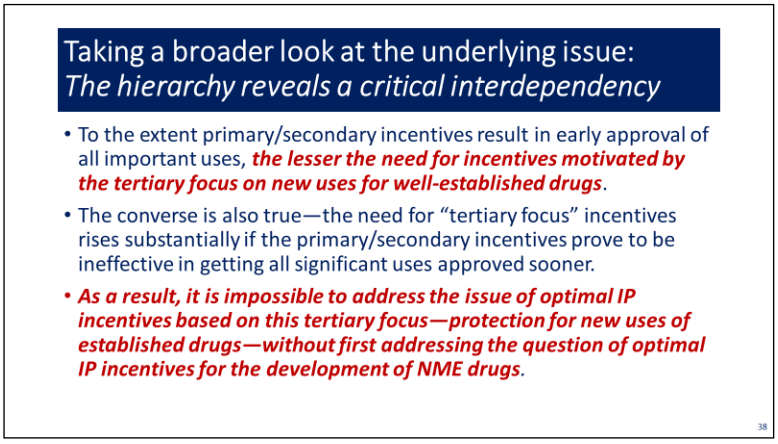
Any accounting for patient perspectives would result in policymakers defining the "ideal system" through a hierarchy of possible objectives for incentives needed to attract investment to develop new medicines and their new uses.

• At the top of the hierarchy would be the type of incentive that Mark alluded to in his talk. The top-tier incentives would be looking primarily to encourage the development of the best medicines, whether or not they had the best patents. Strattera®, as Mark described in his presentation, was a breakthrough in the treatment of ADHD — a first-in-class medicine that provided patients an effective treatment option that was not a CNS stimulant. This is the type of "best medicine" that came painfully close to never making it to patients because it did not have the best in patent protection.

• To the extent we focus on new uses for medicines already on the market, the second tier of the incentives hierarchy would look to assuring development of the best new uses, again at the earliest time after regulatory approval of the NCE drug. As with the new molecular entity incentives, these second-tier incentives would seek to have development decisions made to initiate clinical trials for the best uses, not just uses with the prospect of having the best patents. Too often — again with Strattera® in mind — potentially important uses for an already-approved drug may not be developed because the lack of patent or other IP protection becomes a fatal impediment to broadening the label for the medicine.

• This brings us to the tertiary class of incentives. These incentives would need to operate only to the extent that the primary and secondary incentives do not work to bring all important new uses to the label of a new medicine.



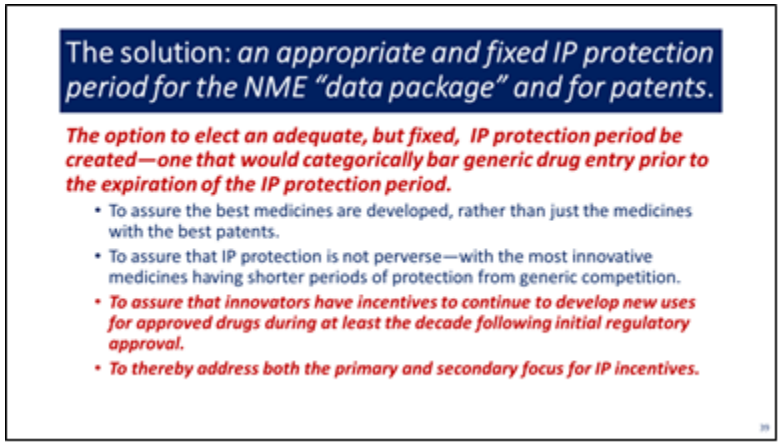
Depending on the effectiveness of the primary and secondary incentives, tertiary incentives may be not be needed at all. If they are needed, the need may be limited. Quite clearly, the need for the tertiary incentives declines dramatically the more effective the primary and secondary incentives are in pushing through the clinical development process all the potential new uses for a new molecular entity medicine.

This interdependency suggests that the predicate for determining what new incentives might be needed or justified to encourage development of new uses for established drugs requires first optimizing the system of incentives for the development of new molecular entity drugs — and the incentives for the potential uses for those medicines that are typically discovered by the time these new medicines have been on the market only a few years.

The independency of this hierarchy of incentives further suggests that this conference on new uses for established drugs may better serve its purpose by reformulating its stated objective in broader terms. Instead of the conference title, "Fair and Effective Incentives for New Uses of Established Drugs," let me suggest a broader, and bit more cumbersome, title: "Fair and Effective Incentives for Developing Both the Best New Molecular Entity Drugs and Their Best and Most Complete Set of Uses and, Once The New Drug Is Inexpensively Available as a Generic Copy, Assessing the Need for Any Additional Incentives to Develop Potentially Important, But As Yet Unexplored, Uses."

In taking this expanded conference program title to heart, I believe that the "ideal system," is the one that I mentioned at the opening of this presentation. It consists of a fixed IP protection period consisting of both patent and data package protection during which generic drug and biosimilar market entry would be barred.

As applied to the United States, this ideal system would require that the current patent-centric incentive system created under the 1984 Hatch-Waxman Act must be superseded — or at least augmented — by this quite different regime. The patent-centric Hatch-Waxman rules would be superseded by an incentive that is virtually patent-agnostic. Biopharmaceutical pipelines could be filled with the best new medicines and studied for their best uses, even when not protected with the best patents.



How would this timewise-aligning of patent and data package protection for a fixed period work in practice? The answer is quite simple. For a new molecular entity medicine, any patent protection for the medicine would be reset to expire on the date the data package protection would be set to expire. This resetting the term of all the relevant patents for the new medicine would produce the common and fixed period of IP protection following the date of regulatory approval.

The fixed IP protection period would be set so that it is long enough to assure the effectiveness of the incentives is adequate to invest both in the development of the initial uses for the new molecular entity medicine and then to continue those development efforts after the new medicine is approved. Specifically, for the nearly 60 percent of new uses known within five years months after initial regulatory approval, the fixed IP protection period would extend long enough to justify the investment in clinical studies needed to validate the safety and effectiveness of those uses.

The fixed period of IP protection would be no longer than necessary to meet the primary and secondary objectives in the hierarchy of incentives. In this way, the establishment of a fixed period would be consistent with assuring medicines are affordably accessible by patients because it essentially eliminates the patent risks associated with today's patent-centric system for determining the date of generic drug entry.

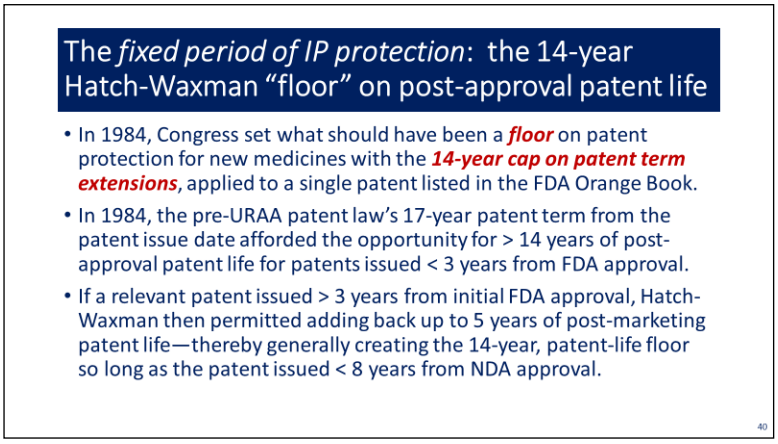
In essence, the originator of the new medicine would face a zero-percent risk of generic drug entry before the fixed and adequate period of IP protection ends. This would be the case even if the patent protection were weak or essentially nonexistent. Reducing industry risks — including IP-related risks — operates to reduce investors' expectations for industry rewards. In this way, the fixed IP protection period is key to establishing the type of lower-risk, innovation-focused business model necessary to making new medicines more affordably accessible to patients.

As previously discussed, this fixed period of combined patent and data package protection must persist long enough to provide the key second-tier incentive in the hierarchy. It is essential that innovators during that fixed period of IP protection have the ability, with complete assurance, to continue to invest in those additional new and "best" uses that may be discovered during the first decade — not just the first few years — after the new molecular entity medicine first comes to market. It is possible that this relatively simple system of fixing a combined patent and data package protection period will all but obviate the need

to establish an elaborate and expensive regime of tertiary incentives because of the relatively few instances in which important potential uses will not be captured through the fixed IP protection period incentive.

Let me again underscore the primary virtue of resetting patent terms to align the patent protection with the fixed period of data package protection is that it should assure that a patent-agnostic decision can be made as to which new molecules may be placed into the development pipeline and subsequent patent-agnostic decisions can be made as to which new uses have sufficient scientific merit to pursue clinical studies to establish safety and effectiveness.

In this way, we assure that the best medicines get into industry pipelines and are developed for their best uses. Molecules that today cannot be developed or whose continued development cannot be justified on patent grounds will look as good from an IP perspective as the medicines with the best patents, because all medicines basically end up with equivalent IP protection.



The unavoidable issue in implementing a single and fixed IP protection period is determining the length of the fixed protection period. In the United States there is a simple and precedented answer to the question of how long. The combined patent and data package protection period should run for fourteen years from the date of the initial FDA approval of the new molecular entity medicine.

When the U.S. Congress looked at this issue in 1984 in the context of patent protection for new molecular entity medicines, it determined that a fourteen-year protection period was a reasonable floor on how long a new medicine should be protected under the patent laws. The Hatch-Waxman Act established this fourteen-year period as the expected patent protection period for a new medicine by establishing a fourteen-year ceiling on patent term extensions.

The fourteen-year cap on Hatch-Waxman patent extensions translates into the expectation for at least a fourteen-year patent life based on the manner in which the U.S. patent law formerly determined the U.S. patent term. Prior to 1995, the U.S. patent term was measured from the date of issuance of the patent and then lasted for seventeen years. If a patent issued less than three years from the date of regulatory approval by the FDA for a new medicine, the originator would, thus, end up with a patent life of at least fourteen years.

After Hatch-Waxman was enacted into law, this three-year window was effectively expanded to an eight-year window because Hatch-Waxman allowed one of the originator's patents to be extended for up to five years. A new medicine protected by a Hatch-Waxman extended patent that had issued within

eight years from regulatory approval by the FDA could enjoy a fourteen-year patent life from the date of FDA approval.

Thus, what was in 1984 effectively a fourteen-year floor on patent life for a new molecular entity medicine provides a viable benchmark for what a reasonable period of fixed IP protection should be before new molecular entity medicines are opened to competition from either generic drugs or biosimilar medicines. During the three-plus decades since Hatch-Waxman became law, the benchmark of fourteen-plus years of post-approval patent life has characterized medicines with the best patents.

Key aspects of an option *to elect* a 14-year fixed period of IP protection for newly approved drugs

1. If the innovator elects the 14-year fixed period, the NME drug will receive ***a 14-year data package protection period***.
2. If the 14-year election is made, ***all Orange Book-listed patents*** will be set ***to expire at 14 years*** from the date of NME drug approval.
3. All OB-listed patents with < 14 years of post-approval patent life would be extended to expire at the 14-year mark; ***all OB-listed patents with > 14 years of post-approval patent life would required to be terminally disclaimed to 14 years*** by the patent owner in order for the innovator to qualify for the 14-year election.
4. ***Patent term extension would no longer be available for any NME drug absent such election for the 14-year fixed IP protection.***

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How would a fourteen-year, fixed IP protection period for new molecular entity medicines be implemented? Part of the implementation would simply leverage provisions of law already in place in the United States under the Hatch-Waxman Act. Under Hatch-Waxman, the originator of a new molecular entity medicine is required to list in the U.S. FDA's so-called Orange Book all of the relevant patents relating to the medicine, including patents relating to the medicine's active ingredient, physical form, formulation, and use. In the implementation of the fourteen-year fixed IP protection period, the law would provide that every patent listed in the Orange Book that would otherwise expire in less than fourteen years from the date of FDA regulatory approval of the new molecular entity medicine would automatically be extended to expire at the end of the fourteen-year period.

On the other hand, because this fourteen-year period would be designed as a fixed period of IP protection, meaning that at the end of the fourteen-year period there would be the certainty of immediate generic drug entry, the patent owners of Orange Book-listed patents expiring beyond the end of the fourteen-year protection period would need to disclaim the right to enforce any Orange Book patent protection that could bar generic drug entry after the end of the fourteen-year period.

While there are some technical complications to implementing a required disclaimer of this type, the biggest of the substantive complications is that this type of IP regime would need to be elective. The fourteen-year fixed IP protection period would represent an optional regime. This new protection would only pertain if all the Orange Book patents could be disclaimed, such that no Orange Book patent owner would have the residual ability to ever bring a lawsuit against a generic company to block generic drug entry after this fourteen-year period had ended. In effect, therefore, the fourteen-year fixed IP protection period would

produce a clear and unequivocal demarcation between a new medicine's IP protection period and the medicine's post-protection "generic" period.

To help companies decide which system to elect, either by continuing with today's patent-centric Hatch-Waxman (or Biologics Price Competition and Innovation Act (BPCIA)) system or by electing the new fourteen-year fixed IP protection period system, Congress would need to further amend the Hatch-Waxman law to specify that the sole means for securing a patent term extension for both drugs and biologics would be to elect the new fourteen-year fixed IP protection period.

The 14-year period of combined patent and data package protection is economically justified

- The 14-year period is adequate, but not excessive, in terms of affording innovators the opportunity to recoup the investment needed to discover, develop, and commercialize an NME medicine.
- The most recent analysis describing the payback period applicable to NME biologic products was published in 2008. "***The break-even lifetimes for the mean product were found to be between 12.9 and 16.2 years*** at alternative discount rates of 11.5% and 12.5%, respectively." Henry Grabowski, "Follow-on biologics: data exclusivity and the balance between innovation and competition," *Nature Reviews Drug Discovery*, published online 12 May 2008; available at http://fds.duke.edu/db?attachment-25--1301-view-503, at p. 486-487.

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A fourteen-year IP protection period can be justified on grounds other than it is the minimum period of protection currently enjoyed by new medicines with the best patent protection. A fourteen-year IP protection period is also a period that can be readily justified by the best academic research that currently exists on the subject of adequate incentives. We heard from Henry Grabowski yesterday about some aspects of his seminal research on this topic, but his landmark work on the cost of drug development determined that, for a biopharma company to actually earn back the investment in research needed to create a new medicine, the "payback" period was between thirteen years and sixteen years post-approval. Thus, the data most recently published by Henry in 2008 demonstrate the reasonableness of the proposed fourteen-year protection period.[3]

The *14-year election option* is a win-win-win regime for patients, innovators, and generic companies

- Assures innovators can develop the best medicines, rather than medicines with the best patents.
- Affords generic companies complete risk-free, cost-free certainty as to the date of generic drug entry.
- Affords strong incentives to develop new indications for use during the decade after initial regulatory approval for marketing.
- Minimizes the need for incentives with a tertiary focus to achieve the objective of assuring that the highest, best, and most complete indications for use are developed and approved for marketing.

As I said earlier, I believe a new incentive system, based upon a fourteen-year fixed IP protection period, not only affords an adequate period of protection for developing the best new medicines

[3] Henry Grabowski, *Follow-on Biologics: Data Exclusivity and the Balance Between Innovation and Competition*, *in* 7 NATURE REVIEWS: DRUG DISCOVERY 479, 487 (2008), *available at* https://www.nature.com/articles/nrd2532: "The break-even lifetimes for the mean [biologic] product were found to be between 12.9 and 16.2 years at alternative discount rates of 11.5% and 12.5%, respectively."

and their best new uses during the decade following regulatory approval, but should minimize the need for any new tertiary IP-based incentives for medicines that have become fully genericized. The fourteen-year, fixed IP protection period will operate in the current highly competitive environment in the biopharma industry in which branded medicines in the same therapeutic class vigorously compete against one another. The ability to successfully market a new drug against a competitor's medicine in the same therapeutic class can often be enhanced by having a comprehensive label with a full complement of approved uses for the medicine.

Where would the foregoing leave the issue of incentives specifically focused on new uses?

- The 14-year election option, together with the ancillary labeling reform (see appendix), should produce a bright line between the 14-year period of IP protection and the time at which generic drug entry would produce immediate access to low-cost versions of the drug.
- At the same time, the 14-year election option effectively precludes any traditional notion of data package protection or patent-like protection from serving as an incentive to develop further uses.
- ***The 14-year election option dictates finding non-IP-based incentives to develop new uses for drugs that have reached the point where low-cost generic versions of the drug dominate the market.***

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Thus, the fourteen-year fixed IP protection period should result in the best medicines being developed for all their best uses, not just the medicines with the best patent protection, leaving little need for further incentives to develop additional uses once generic drug entry or biosimilar market entry has begun. Indeed, for medicines for which the fourteen-year fixed IP protection period applies, there would be little room for IP-based incentives for medicines that had become fully generic at the end of the fourteen-year protection period. This suggests that the look for incentives to develop new uses of established generic drugs take a broad approach that would need to include non-IP-related incentives.

Considerations relating to the development of new uses once generic drug entry commences

- At the date of generic drug entry, an innovator will already have spent between 20 and 30 years—or more—investigating its "new" drug.
- An innovator rarely develops new uses for another innovator's drug, particularly once the generic versions of the drug enter the market.
- The development of new uses after generic drug entry by any of the generic manufacturers is unknown.
- If new uses of the medicine are developed in the post-IP era—and made immediately available to patients through low-cost generic versions—the potential exists to create enormous benefits for patients, their insurers, and governments as payors.

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Looking to non-IP-based tertiary incentives may be appropriate for other reasons. The medicine's originator by the time of generic drug entry normally has had twenty to thirty years or more to develop uses for the medicine. This reduces the likelihood that the originator will have discovered potentially viable uses that had not as yet been clinically investigated. Similarly, innovators rarely develop new uses for the medicines originally developed and approved by their competitors. The same is largely true for generic drug manufacturers with respect

to the drugs that they have copied. Generic companies rarely develop new uses for a dosage form that is already generic.

If non-IP incentives can be developed, it would mean that the generic drugs could remain fully generic drugs with respect to the new uses. The result would be that continued generic pricing for the new uses could provide enormous value for patients.

We have heard thus far in this conference ideas for tertiary incentives that might take the form of monetary prizes or transferable voucher benefits for such expedited regulatory review. Additionally, more market-based incentive mechanisms have been proposed that could allow for price differentiation among patients prescribed a generic medicine or otherwise create market segmentation for what otherwise would be fully genericized dosage forms.

As I have listened to these types of incentive proposals, I have registered concerns over both their feasibility and advisability. Prizes are difficult to translate into a viable business model and transferable vouchers tend to be highly inefficient in terms of the costs ultimately borne relative to the research that is stimulated.

The market segmentation and price differentiation models are — at their core — efforts to partially de-genericize what otherwise would typically be a fully generic market for the medicine to which the incentive would apply.

Before going down the de-genericizing path, we need to reflect on the practical, real-world issues that this type of incentive would engender. Consider two metformin patients, who perhaps are neighbors, one who is getting a medicine essentially free as a treatment for Type 2 Diabetes and the other who might be paying $300 a week for the identical but de-genericized pills because the medicine has been prescribed for a newly IP-protected use under some new scheme of IP-based incentives.

In effect, the identical drug in the identical dosage form would be being used identically by two neighboring patients, but with the sole difference as between the two neighbors being the disease or condition for which the medicine is being prescribed. Before going down the extraordinary path of partially de-genericizing a medicine and price differentiating the identical dose and dosage form — and burdening one neighbor with a cost that is 100 times the cost of the other — we should look hard at alternative incentives that do not "re-IP" an "IP-free" generic drug.

At the risk of being melodramatic, I do hope that, particularly in the United States, where prescription drug coverage is not universal and individual patients can be forced to pay for their medicines out-of-pocket, we do not foster a de-genericizing incentive under which the bedtime prayer of one of two neighboring metformin patients might be, "Dear God, please afflict me with diabetes so that I might be able to afford the cost of my metformin."

So how do we provide new incentives that do not depend on de-genericizing already generic drugs? We would appear to have many options.

Resources that could be focused on developing new uses for old drugs after generic drug entry

- ***National governments***—Agencies such as the National Institutes of Health in the United States have multi-billion dollar research budgets, some of which is focused on new uses for drugs.
- ***Disease-focused charitable foundations***—An array of foundations, largely dependent on private contributions, exist throughout the world. In the UK, for example, such charities include (1) Leukaemia and Lymphoma Research, (2) Breakthrough Breast Cancer, (3) The Brain Tumour Charity, (4) Myeloma UK, and (5) the Roy Castle Lung Cancer Foundation.
- ***Not-for-profit-research hospitals***—Organizations such as St. Jude's Medical Center raise funds for research into new uses of existing medicines. In 2016, St. Jude's alone reported $1.2 billion in contributions and grants.

• We have national governments on both sides of the Atlantic and both sides of the Pacific that could address the residual need for tertiary incentives. The U.S. National Institutes of Health (NIH) has a large budget for medical research. We need only to go on the clinicaltrials.gov website to find NIH funding for clinical trials for new uses for generic drugs.

• Around the world — and I have placed on the slide just five examples from the United Kingdom — there are private-sector, not-for-profit groups, that actually raise money to fund clinical studies that aim at new uses for medicines.

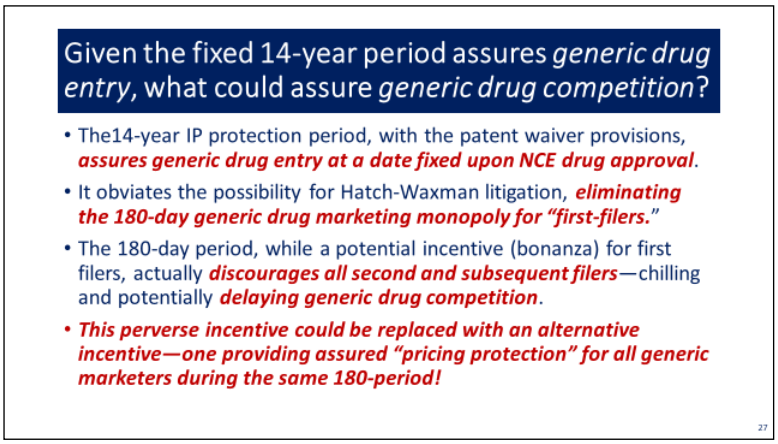
• Indeed, we have one research hospital in the United States that alone receives in donations per year $1.2 billion.

Resources that could be focused on developing new uses for old drugs after generic drug entry.

- Could the United States create an agency like the National Cancer Institute (NCI) focused on developing new uses for generic drugs, *i.e.*, ***the National Generic Drug Institute (NGDI)***? Such an institute could be entirely focused on the study of safety and effectiveness for drugs once generic drug entry has taken place or is approaching.
- ***Could an NGDI be partially or entirely industry funded?*** An industry funding mechanism including contributions from makers of any version of the drug, whether the original version or a generic version.
- Could such resources for developing new uses ***obviate the need for new IP incentives for already-generic medicines***?

Beyond these potential sources for funding clinical studies directed to new uses of established and already generic medicines, nothing would stop any country, including the United States, from creating an agency specifically dedicated to developing new uses for generic medicines. A National Generic Drug Institute (NGDI) could be established that could be entirely focused on the safety and effectiveness of generic drugs. Such an entity could be partially or completely industry-funded.

Someone today suggested raising research revenues from a levy of one cent per prescription. What if, under this ideal system we are discussing today, we were able to raise development funding revenues from the equivalent of a tax on all drugs that were in the "generic drug" bucket, say, a 20 percent surcharge that went into the NGDI? For drugs that are generic today, such a 20 percent surcharge could raise a significant amount of money that could be used precisely for this tertiary incentive. If we were to do this, I submit that we could obviate the need for new IP protections for already generic medicines



Lastly, if we are able to go down the path of a fourteen-year fixed IP protection period, we would fully moot one of the key features of the 1984 Hatch-Waxman Act, the 180-day period of generic exclusivity, which I sometimes refer to as the "generic drug marketing monopoly period." I know that some in the generic drug industry have lamented that this "incentive" to develop generic drugs — perverse as it is — was seriously impaired with the amendments made by the Medicare Prescription Drug, Improvement, and Modernization Act of 2003. Today, at best, it can operate functionally, rather than dysfunctionally, only in certain very limited circumstances.

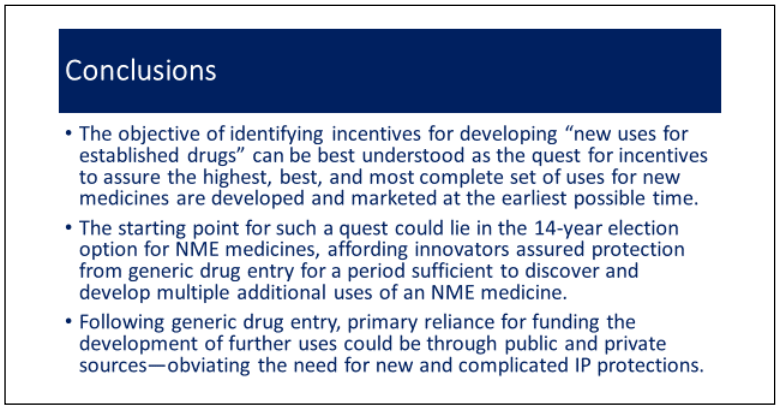
The 180-day generic drug marketing monopoly period was originally designed to as an incentive to challenge patents for the first-filer generic company. In the old days, it took a successful patent challenge to warrant 180 days of "generic exclusivity." After a number of iterations, the monopoly period today applies to protect each of the "first filers" that have not forfeited entitlement to the 180-day period. In this sense, it can operate like a prize, however elusive.

Unfortunately, today the monopoly period also has the perverse impact of discouraging any generic manufacturer that is not a first filer from ever deciding to seek regulatory approval. By the time the subsequent generic filers get to market, price competition may make the generic market barely profitable. The generic manufacturers coming to market late may face generic drug supply agreements and other first-marketer advantages that will chill any incentive to develop a late-to-market generic copy.

With the 180-day generic drug marketing monopoly period disappearing under the "ideal system," could Congress settle on a less dysfunctional and less perverse replacement incentive for generic companies to seek to be first to come to market after the fourteen-year fixed IP protection period ended? Could Congress address the issue of a generic-come-to-market incentive by simply providing for 180 days after the end of the fourteen-year fixed IP protection period when there could be price protection for all generic entrants, with the FDA setting a minimum pricing structure for all generic and non-generic manufacturers?

Such a price-protection incentive would provide a much more reliable and much more predictable incentive for every generic to be on the market during the 180-day period than exists under today's Hatch-Waxman Act. It would mean that after this 180-day period ends, the price competition among many generic

competitors would assure the type of commodity pricing that is consistent with a low-risk, low-reward generic drug business model.



In conclusion, dare we reframe what this two-day conference is all about? Could we decide that the "second use" issue is too myopically focused on one aspect of the broader issue of adequate incentives to develop rapidly both the best new medicines and their best uses?

Can we establish that many of the lost opportunities for developing "second uses" result from deficiencies in the existing framework of IP incentives, with its patent-centric character and the perverse consequences that patent centricity can produce? Can we focus our future discussions away from new "second use" incentives for established (and already generic) drugs that inevitably depend on some means for de-genericizing these already generic drugs and, in doing so, can we avoid grappling with all the issues that arise with any attempt to re-IP generic commodities?

I hope the potential advantages of the fourteen-year fixed IP protection period can move the dialogue on new "second use" incentives for established (and generic) drugs toward a discussion focused more broadly on incentives to develop the best new medicines and the best new uses for them, irrespective of the strength of their patent protection.

Most importantly, the ten-bullet-point patient "wish list" would suggest the need for just that type of broader focus that might produce a profoundly better system of incentives for new molecular entity drugs. It would assure the ability for developing the best medicines, not medicines with the best patents. Similarly, the best uses for those medicines could be developed during the decade following the initial regulatory approval for a new medicine.

If the economic case can be made for new, non-IP-based tertiary incentives, rather than trying to devise some elaborate system of unprecedented IP-based incentives that would de-genericize already generic drugs, with all of the administrative and other difficulties in titrating those incentives to reflect the right magnitude and duration of rewards, might we settle on something as simple as a public-funding mechanism? In this way, during the post-IP era for such medicines, they can remain inexpensively available as generic copies, thereby providing the maximum possible benefit for those new uses once they come to market.

Thank you.

MR. BARR: Thanks, Bob.

Let's move down our panel in order. Toni will give some remarks, then David, then Ben, and then we will have some questions.

MR. SANTAMARIA: Thank you. I will try to give the vision from a generic company mainly operating in Europe.

The European patent system is quite complex. Despite European national patent laws being generally harmonized by the European Patent Convention, common substantive provisions are often interpreted differently at the national level, resulting in different outcomes in different European countries. Yesterday, we heard about national courts handing down different decisions on the same product. At the end of the day, I believe that the ideal system is one that is able to provide both legal certainty and return on investment.

Companies need to have legal certainty. They need to know when they can come to the market and what their risk exposure will be in doing so. Consequently, generics need to know with certainty what acts are infringing. Obviously, from the innovator side, they need to know when they can expect generic competition.

The other thing that companies want is a return on their investment. If companies are investing money in developing new uses or reformulating products that are already on the market, they want to recover their investment. This can be achieved by regulatory exclusivities, price or tax incentives.

For new molecules there are already incentives. We have the supplementary protection certificate (SPC) system that provides an additional five years after the patent expiry as well as a pediatric extension of six months after initial SPC term.

There are also the data exclusivity periods. In Europe we have eight years of data exclusivity plus two years of market exclusivity and one additional year in cases where a significant new indication is approved. If you make that calculation, the total time for protection is fifteen years. That is not that far from the fourteen years suggested in the previous presentation. The fifteen years are calculated from the first marketing authorization and it is based on the SPC system.

We have seen that under the current system there are no clear indications regarding which actions are infringing and which are non-infringing. For example, yesterday it was mentioned that in the pregabalin case there were different requirements to avoid infringement in different countries.

There is a high burden of proof on the generic side to prove that they have not undertaken any infringing activities. Generics have in the past been required to send letters to doctors and pharmacies, but how many letters does a generic company need to send to be considered non-infringing? It was explained yesterday that even one single discussion between a sales representative and a doctor led to injunctions being granted.

Generics are also encountering difficulties carving out patented indications because no standard approach has been adopted by the national regulatory agencies. Centralized procedures can be filed at the European Medicines Agency (EMA) to obtain one single marketing authorization for all countries in the European Union. When some indications are protected by patent, it is possible to file a duplicate, one with the full range of indications and one with a carve-out.

However, if the decentralized procedure (DCP) route is used, it is necessary to discuss the carve-out with every single national agency, and each national agency has a different approach to the carve-out.

Another issue is the availability of information regarding the sales split by indication. Yesterday it was mentioned that in Denmark 80 percent of pregabalin's market was for neuropathic pain, in the United Kingdom the percentage was lower, and in other countries pregabalin was not even prescribed for epilepsy. Clearly, the sales split for each indication varies country by country and, because there is a lack of official data on the split of indications, it is difficult for generics to know the achievable market share on entry. On top of that there are the off-label uses.

There is also a lack of general awareness and understanding of the patent system. In Europe we do not have an Orange Book. We saw that in Germany tenders were issued for full indications for pregabalin. I believe that the tender authorities should be aware where there is patent protection in order to avoid these situations arising.

There are incentives to promote the substitution when generics are available, for example, and doctors, who do not necessarily know that there are patents in place, prescribe by International Nonproprietary Names (INN).

The European patent system is not perfect, but I do believe that there are actions that could be taken to bring about more certainty for companies that operate within this arena.

• In particular, clarity is needed around the additional steps, if any, that need to be taken by a generic company to avoid a generic product with carved-out indications being found to infringe a second medical use patent. European courts should be aligned in this regard and should provide some guidance. We have seen some initial guidance, but nothing sufficient or harmonized. In the pregabalin case, the UK courts gave some guidance,[4] and we will probably see more and more guidance coming out of other national courts that will be hopefully aligned.

• Market segmentation: Prescribing by indication could be a solution. There are electronic systems that would allow this option. But still, since in Europe there is no equivalent to the U.S. Orange Book, it would be difficult for software providers and regulatory agencies to know which indications are patent-protected. There are some EU countries — for example, Italy and France — in which innovators normally communicate the patent expiry dates to the agencies,

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[4] Warner-Lambert Company, LLC v. Actavis Group PTC EHF & Others [2015] EWHC 485 (Pat) (02 March 2015) (Arnold, J.), *available at* http://www.bailii.org/ew/cases/EWHC/Patents/2015/2548.html; Warner-Lambert Company, LLC v Actavis Group Ptc EHF & Others, [2015] EWCA Civ 556, *available at* http://www.bailii.org/ew/cases/EWCA/Civ/2015/556.html; Warner-Lambert Company 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 (Feb. 21, 2018), *available at* https://www.lifesciencesipreview.com/news/warner-lambert-v-actavis-a-summary-from-the-uk-supreme-court-hearing-2723.

but this is not an established practice in all of Europe. I believe that information regarding which indications are patented and when they will expire should be communicated to a body, such as EMA or another regulatory agency.

But this would still not be a perfect solution. For example, we have seen a case — and I think that it was mentioned yesterday — in Germany where there are infringement actions based on a use patent and the wording of the patent does not match with the wording of the approved therapeutic indication. In that case, the carve-out is not easy because the patent protects the use in a subtype of patients. Therefore, even with the electronic systems, the option of prescribing by indication will not provide the perfect solution.

• Data exclusivity: It is well established that for new molecules the 8+2+1 regime exists. But once the products become generic, there is no clear reward for any new use nor for getting official approval for off-label uses. We have had experience of cases where we were selling a generic product and we realized that the product was largely being sold off-label. The recompense to recover the money invested to get an official approval for the off-label use would have been minimal. The use probably would not have been patentable due to prior use and the exclusivity period would have been one year. This situation clearly discourages the businesses from investing in this kind of studies.

• There are special situations, like orphan drugs have special protection, and there are also the pediatric use marketing authorizations (PUMA) that provide ten years of exclusivity for these pediatric indications. Therefore, some sort of exclusivity packages for repurposing of drugs would probably incentivize the study and approval of these new indications, new formulations.

All in all, I believe that the system should be a mix of everything I have mentioned, and possible solutions have already been proposed in this forum. We need patents, we need exclusivities, and we need incentives in terms of prices or taxes that would encourage companies to develop these off-label uses into approved uses.

MR. BARR: Thank you.

Let's move on to David Korn.

MR. KORN: Thanks.

Bob presented an interesting proposal, rightfully focusing on IP. It would represent a new paradigm and it would require legislation.

There could be other approaches to addressing the issues, including improvements to existing systems. I thought it would be useful to step back and think through where this issue falls in the overall environment and where improvements would be helpful.

Our industry is committed to bringing new treatment advances to patients, as can be seen from our members spending $65.5 billion on R&D in 2016. IP is the lifeblood of the innovation in biopharma and drives the competitive marketplace.

As you heard before and are familiar with, the life cycle of a medicine begins with long-term, risky, and costly research potentially leading to a new medicine. During that process there is competition to be the first with a product to address a medical need, which does not necessarily mean that it would be the

best treatment option even if it is the first. If a medicine is first in class, there is competition from other products in the class within a few years, and eventually there is competition from generic drugs or biosimilars.

The framework we have, in the United States at least, is based on a policy and regulatory framework that seeks to balance the need for incentives for innovation with the desire to increase competition from generics and biosimilars. Once a generic is approved in the United States, there is rapid generic erosion, such that currently 90 percent of prescriptions in the United States are filled with generic products.

However, research and innovation do not stop after the initial regulatory approval. Patients can benefit from the addition of new indications to the labeling for medicines.

We have heard a lot in the past two days about drugs having a long period of usefulness and that the research into new uses can be quite expensive. Incentives can be important as companies choose where to spend research dollars, yet the political environment makes it challenging to obtain legislative improvements to incentives.

It has been discussed and shown that IP rights can be substantial pull incentives for innovation. Toni mentioned the European models. Just to refresh with respect to the United States, pull incentives include:

• Orphan exclusivity, which is seven years of market exclusivity for the same drug for the same use. So it is use-based as well.

• Pediatric exclusivity, which adds six months to other exclusivity protections and FDA's treatment of patent expiration for generic drug approval purposes.

• The Generating Antibiotic Incentives Now (GAIN) Act, which adds five years of exclusivity for qualified anti-infective products. This shows the importance of IP incentives, but also how complex the issue can be. The Department of Health and Human Services (HHS) just issued a report that the incentives in the GAIN Act are not sufficient to address all of the unmet medical need.[5]

There have been different approaches that have utilized different incentives. Patent rights and non-patent exclusivities have both been part of it. They are complementary and can work together, but there are issues with each when one considers new uses and new indications.

The conference discussion thus far has focused substantially on patents and how they may not provide substantial incentives for new uses. There are timing considerations with compound patents, as Bob and Mark have described. There are also uncertainties surrounding patents in general, and even more with respect to methods of treatment. We heard yesterday about difficulty in even

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[5] Department of Health and Human Services, *Generating Antibiotic Incentives Now, Required by Section 805 of the Food and Drug Administration Safety and Innovation Act, Public Law 112-144 (2018), available at* https://www.fda.gov/downloads/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/UCM595188.pdf; *see also* Zachary Brennan, *Updated: FDA to Congress: Consider Changes to GAIN Act* (posted Feb. 7, 2018), https://www.raps.org/news-and-articles/news-articles/2018/2/fda-to-congress-consider-changes-to-gain-act.

obtaining patents. Depending on the type of claim, there could be difficulty showing infringement. There is also the regulatory carve-out issue — the "skinny labeling" issue — which impacts the ability to effectively enforce the patent. Inter partes review (IPR) challenges at the Patent and Trademark Office increase uncertainty. And, if a patent owner were able to be successful in patent litigation, there is a question about what remedies would be available in the litigation.

Data exclusivity (also known as regulatory data protection) is another incentive for new uses. Unlike in Europe, in the United States the three years is a separate period for the new use, it is not an add-on, and it can apply whenever the use is approved. But there are issues about applicability and its strength, and the issues about the regulatory carve-outs and the "skinny labels" are also an issue for such data exclusivity, and can even be an issue with orphan exclusivity.

As far as an ideal system, there is not necessarily any single ideal "one size fits all" system globally. As we heard yesterday, we have IP, regulatory approval, and pricing and reimbursement system differences worldwide.

If we are to incentivize second medical use development and approval, what is the goal? There is substantial unmet medical need that could be addressed through new uses, and developing such uses also could increase competition.

The incentives should encourage seeking regulatory approval of safe and effective uses and also accommodate policy goals concerning products for particular types of populations or uses. The best product for one patient may not be the best for another, and so encouraging alternatives is also important.

Could a government improve the current system by utilizing the currently available IP statutory frameworks and enhance the effectiveness of IP protections? Is it possible to strengthen the applicability and the role of data exclusivity? Could we strengthen the patent system's role by preserving the ability to obtain claims, defend them against challenge, and effectively enforce them? Is it possible to avoid disincentives in the regulatory approval and price reimbursement systems?

I know we have an upcoming panel on the policy environment, but policymakers can have a short-term focus on costs and there could be a lack of recognition by some policymakers of the value of new uses, especially over the long term.

There have also been attempts by some to weaken IP rights rather than make them a more effective incentive, such as for further R&D on new uses.

So it is a challenging environment in which to seek improvements in IP protections, but it is good to be able to have a forum to bring stakeholders and experts together to discuss ways to make progress on this important issue.

MR. BARR: I will turn it over to Ben.

PROF. ROIN: I am a big believer in having a much more predictable, much more consistent way of providing guaranteed market exclusivity terms to NME developers, or anyone who is developing a new drug. One thought is that we should focus on that, and that providing incentives independent of that for developing new uses for generic drugs is not the priority. That actually may be right.

Whether or not that is right depends on whether or not the existing arsenal of roughly 2000 generic drugs — and globally it is more than that — has in it a whole bunch of not-yet-discovered or discovered-but-not-tested really valuable treatments, or whether there are in that arsenal generic drugs a lot of personalized applications where we could really benefit from knowing which patients benefit most from these, what doses should they be given for that substitute; or if it is true that during the single monopoly term when the innovators have a new product they do not actually have spectacular incentives to develop all the different possible uses, perhaps because they can only charge one price or because different dosages are required for it, and there are other reasons that might affect it.

That would all suggest that maybe we actually want to do something on top of that, and maybe it actually is worth thinking about and dealing with a lot of complexities. I should talk about some of the complexities here because I think that is probably why I am on this panel.

Yesterday I alluded to the fact that you could have a system where we differentially price by indication. There is a pretty profound logic to doing that in general, because in medical practice you do not care what the drug is, you care what the indication is. It is all about the data supporting its use and for whom it is being prescribed and for what. The investment in creating the drugs is all about the production of that data, which is always necessarily specific to an indication. Having a pricing system that links that to the practice of medicine and the processes of developing a new drug probably makes a lot of sense.

Creating that system is easy to talk about doing in general. We have this nice proof of concept, and there is prior authorization, which tell us pretty clearly that it is in fact possible for a third party, in this case an insurer, to observe the indication and make discriminating judgments based on it that affect patient access. So we know it is possible.

But it will raise a whole bunch of issues and would require dealing with a bunch of complexities. I do not have time to get into details about all of them, but I want to talk about some of them at least and mention as many as I can.

The first one, which is actually the one that people talk about most, is: to what extent can we accurately identify the indication the prescription was given for and prevent doctors from lying? A legitimate concern.

We have to keep in mind that the system does not have to work everywhere. If it works somewhere, then you can do the differential pricing there, and if it does not work in other places, you just would not do it there, which is basically the way prior authorization currently works.

Another thing to keep in mind is the concern we have with misreporting of indications, that basically physicians would have an incentive to lie. In this case, they would have an incentive to lie because if you have expensive indications and cheap indications of a particular drug, you would think maybe there are higher co-pays for the expensive indications, so maybe doctors would lie to save their patients from having to pay a higher price. Of course, that actually seems a little less pronounced than the incentive doctors currently have to lie in the prior authorization, where they lie so their patients have access to the drug at all as opposed to not having any access to it. Nonetheless, there is an incentive to lie.

One thing you can imagine doing — or just negotiate individually — is not having different co-pays for the different uses. That might be necessary in some places.

That said, it is worth keeping in mind — and this is the reason why prior authorization works pretty well in a lot of cases — that there are a lot of diseases where you really can tell the different indications because the disease is associated with a diagnostic or a bunch of concomitant treatments or there are different physicians who prescribe it. Therefore, if you have an indication for diabetes and then another one for oncology, you can usually pick that up because oncologists do not usually treat diabetes, and vice versa.

There are places where it is going to be hard or impossible. The example I will give is that we will never be able to distinguish between mild and moderate back pain, so if someone wants to charge different prices for those, that is impossible. That will never happen.

Common co-morbidity, such as diabetes and high cholesterol, is a problem. If you have one drug that works for both — Lipitor is an example of that — charging different prices for that will always be hard.

Another concern people have — again legitimate — is privacy. If we are sharing medical information, basically you are telling more people about your diseases, which a lot of people, I think rightfully, want to keep private, there are two possibilities to think about here.

One is, instead of disclosing that information to a pharmaceutical company, we could have third-party intermediaries. Pharmacy benefit managers (PBMs), at least in the United States, already frequently use contractors to run their prior authorization outfits, so a third party is already doing that. It would just be a question of that third party not only having a contractual obligation with the insurance company or the PBM, they would also have one with the supplier, so you could have better disclosure. That is one possibility.

The other thing to keep in mind is that I think the only part of disclosing medical history that is not controversial, that is just inevitable, at least in the United States — and I imagine this has got to be true in Europe and basically everywhere else on the planet — is where we disclose and share information when it is necessary for billing. You just cannot have an insurance system in which the people writing the check cannot check to see whether the patient actually got this or whether this is a fraud where the doctor is writing prescriptions over and over for things that are unnecessary. The rules are all written so that anyone who is involved in the billing has access to that information.

If that is the case here, then it is natural extension of our existing privacy systems to include the billing operations of whatever companies are dealing with differential payments and then just put our standard protections in where they cannot share the data with anyone else, including their own internal firms for whatever other purposes, unless it meets a bunch of criteria.

There is an issue that Robin has brought up that I think is super-important. That is the question of what is the incentive for these things — is it patents, is it regulatory exclusivity periods? It turns out it is actually hard. If we are honest

and thought through it for a while, I think we would end up doing something a bit complicated.

Patents have the obvious problem in this context where there is going to be what you could think of as a lot of false negatives. There are a lot of things that you might want to develop but you would not have a patent on them because someone has already had the idea or it is inherently built into the way it is currently being used, so patent protection would not be available. Not to mention the fact that new use patents are less reliable because it is harder to be super-confident about the set of prior art that exists.

You could also potentially, by the way, have false positives, in that a company could patent a new use and not run any studies on it and just let clinical practice evolve where they start prescribing it and charge a higher price. That would strike most people as an abuse of the system, but there is nothing in the patent system to prevent that.

Regulatory exclusivity periods are super-nice, in that if you make the investment in clinical trials you get it. The problem is that we could have all sorts of uses that may be developed during the original patent term, which means we do not need the extra protection; or these are uses where doctors figure it out on their own and they were going to start prescribing it on their own, so we did not really need to provide an incentive for it. In those cases, if you start providing protection, it is going to seem like an abuse of the system. Thinking about some way to provide the right protection in that context is challenging, but there is going to be pressure to come up with a system for that.

The duration of protection is also an issue. We have fourteen years of patent protection for the original term. In this context, the set of existing protections we have for new medical uses is really absurd. You have three years for small molecules; seven if it is orphan; twelve for biologics; and then the patent system is twenty, but with no patent term extension, so it is twenty minus your development time. This creates the perversity that if you have a new use that moves super-fast through clinical trials, you are going to get eighteen years, whereas if it is a treatment for early-stage Alzheimer's, you are going to end up with six or five years because those clinical trials take forever. We probably would not want to just plug in our current system of durations and work with that; we would want to think that through.

I will end there. There are a few other things I could talk about, but I think that is enough.

MR. BARR: Thanks, Ben.

We are in the yellow zone right now and we want to have some time for questions. I will ask the first question and, hopefully, we will have a little bit more time for other questions.

This is a question for Bob. Henry Waxman retired in 2015 and Orrin Hatch we know is going to retire. In your solution the fix is a legislative one. Can you comment on the political viability of the proposal and what is it going to take to get that proposal to be taken seriously and potentially get it, or a version of it, over the goal line?

MR. ARMITAGE: The incentive proposal that I presented was built off the The Modernizing Our Drug and Diagnostics Evaluation and Regulatory Network (MODDERN) Cures Act, which was introduced in two Congresses. The last time it was introduced was in the 113th Congress when Representative Leonard Lance introduced H.R. 3116. It had a fifteen-year period rather than a fourteen-year period, and basically was available to innovators seeking to develop new medicines limited to serious diseases, specifically unmet medical needs.

It was a patient group-led initiative, developed by the National Health Council. There were ninety-five sponsors, forty-eight Republicans and forty-seven Democrats. So it was a sound proposal, soundly conceived, led by patients in the interest of patients, recognizing industry needs, and balanced between innovators and generics.

MR. BARR: We will let the audience ask some questions.

QUESTION [Sergio Napolitano, Medicines for Europe]: I have a couple of requests for clarification for Bob Armitage.

Your proposal of fourteen years for patent protection — I am not very familiar with the Orange Book in the U.S. system — would cover only the patents protecting the APIs/the molecule or all the patents? The extension of the patent up to fourteen years, or in Europe up to fifteen years (i.e. SPC), is only given to the molecule patents, not to all the existing and secondary patents. In that case, if your fourteen-year patent protection from the moment of the marketing authorization covers all the patents, that would go well beyond the protection we have today.

The second question is about the data protection package you mentioned. Maybe I did not fully understand. I understand that you were proposing that there would be a fourteen-year data protection package from the marketing authorization, which, if I am not wrong, is well beyond what exists today either in Europe or the United States.

If that is the case, would that be data exclusivity or market exclusivity? If it is data exclusivity, then the generic could not be approved before the end of this fourteen-year data exclusivity, and therefore before the end of the fourteen years of patent protection, so they would not be able anyway to enter the market at patent expiry.

MR. ARMITAGE: Right. The ANDA pathways would not be available until the end of the fourteen-year period, so it would be equivalent to the ten-year period in Europe, the eight plus two.

The patents would all expire on the same day as the data package protection period. For Orange Book patents — these are not just the API patents — the NDA holder is required to list in the Orange Book any patent that could be reasonably asserted against a generic company seeking approval of a generic copy of a new medicine. It would include the polymorph patents, the relevant use patents, the patents related to safety information, etc. So at the end of the fourteen-year period there would be no Hatch-Waxman litigation; there would be no remaining patents protecting that particular dosage form that was approved.

MR. BARR: Thanks, everyone, for listening to us. I hope we came somewhat close to the ideal system.

* * *

APPENDIX

Mr. Armitage's "ideal system" presentation is built on footnote 138 of his 2014 MODDERN Cures law review article giving an expanded justification for building IP incentives based upon a fixed period of combined patent and data package protection.

Robert A. Armitage, *The Hatch-Waxman Act: A Path Forward for Making it More Modern*, MITCHELL HAMLINE LAW REVIEW: Vol. 40: Iss. 4, Article 2. Available at:
https://open.mitchellhamline.edu/cgi/viewcontent.cgi?article=1585&context=wmlr

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 – 10:55 a.m.

Session 2D:
Plausibility and Second Medical Use Patents

Moderator:
Jane M. Love
Gibson, Dunn & Crutcher LLP, New York

Presenters:
Michael Eder
DF-MP, Munich

Frits Gerritzen
Allen & Overy, Amsterdam

Charlotte Jacobsen
Fitzpatrick Cella Harper Scinto, New York

Barry Schindler
Greenberg Traurig, New York

* * *

MS. LOVE: Welcome back. My name is Jane Love. I am pleased to introduce this panel.

This morning we heard about several new ideas to incentivize stakeholders to get known compounds back into the marketplace to treat patients. We are going to focus on an old idea, and that is to rely on the patent system. It is by no means perfect, as we have been hearing; however, the practical reality is that it has been established over hundreds of years in countries around the globe. There has been an effort across patent offices around the world over decades to harmonize their patent laws, to understand each other's patent laws, and to

attempt to get a system in place globally that will benefit incentivizing innovation and, in our case, hopefully protecting second medical use patents.

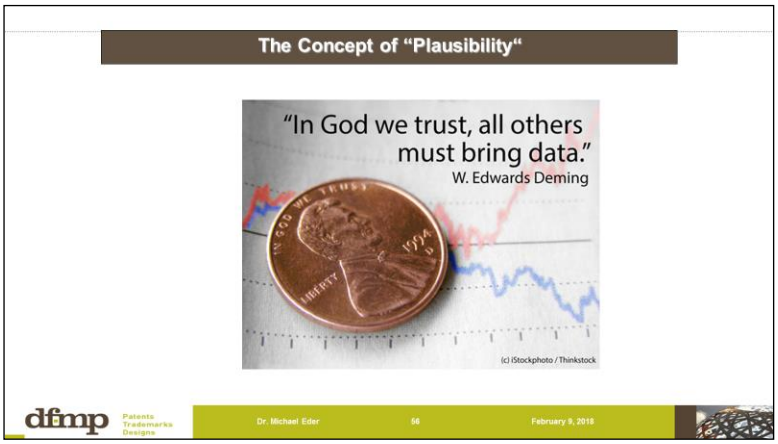
A point was made in the last session that a patent system may not help our question for this conference, and that is because there are many new uses for old compounds that would be deemed obvious or not novel or both, and that is true. But there is a large percentage of new uses for old compounds that are innovative, and if there was faith in the system and stakeholders recognized that, there could be filings that could automatically flow into an established system. That is what we will examine today.

There is one issue that we will focus on that can be problematic in terms of understanding a patentability standard. This is the so-called "plausibility requirement." Its shape and scope are not so clear.

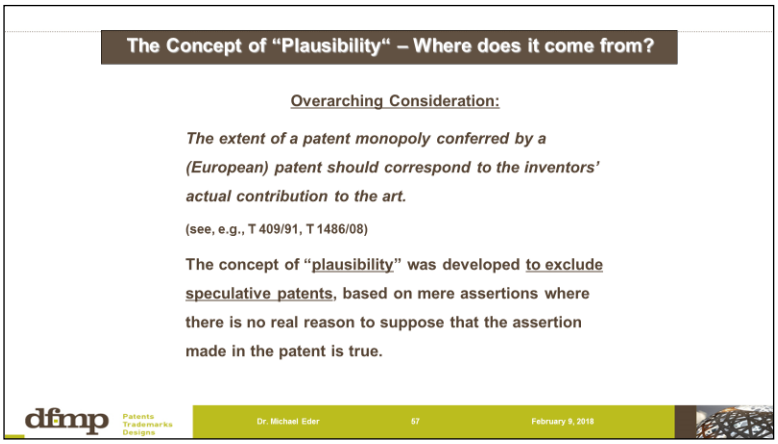
I am pleased to introduce our panel who will explore this issue. Our panelists are intellectual property specialists from around the world, and the hope is to have a global perspective on this issue. First, we have Michael Eder from DF-MP in Munich, who will give us a German and European Patent Office (EPO) perspective. Frits Gerritzen, from Allen & Overy, based in the Netherlands, will give us the Dutch, English, German, and French perspectives. Charlotte Jacobsen, from Fitzpatrick Cella in New York, is an IP litigator and will give us a U.S. litigation perspective. Finally but not least, Barry Schindler, just in from Israel this morning, working at Greenberg Traurig, practices in the United States and Israel and will give us both of those perspectives.

MR. EDER: Thank you, Jane, for the nice introduction. Let me also extend thanks to the organizers for inviting us to speak here.

Since I am kicking this off, I will try to give a little background on the concept of plausibility and how that concept developed.

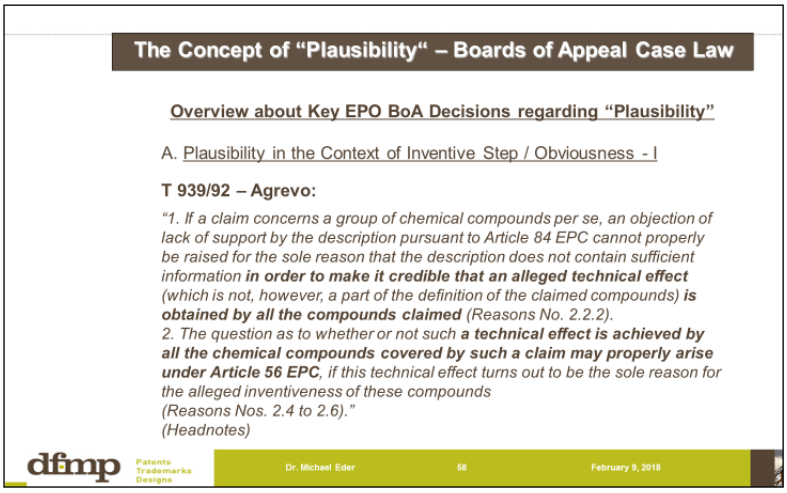


A nice quote from W. Edwards Deming: "In God we trust, all others must bring data" probably highlights somewhat that patent monopolies are not handed out just based on trust; we have to bring some kind of evidence that what we are trying to patent, what the patentee tries to obtain a monopoly for, has actually been in the hands of the inventors.



This concept is not really something completely new. It is rooted in the consideration that the extent of a patent monopoly should be commensurate to the actual contribution in the art. So if I make an invention, I should enjoy a patent monopoly; but if I actually do not have any invention or have not made it credible that I have an invention, that should not be the case. In a nutshell, that means it is there to exclude highly or purely speculative patents.

We have heard many times that plausibility seems to be a problematic, or even dangerous, concept to be introduced. I will, I think, destroy that fear because it is really a very low hurdle that, as I will show, is relatively easy for the applicants to overcome. It is rather an incentive and offers the possibility to gain patent protection for actual inventions, and prevents not being able to patent new uses, for example, just because someone speculated wildly about potential other uses in earlier patents.

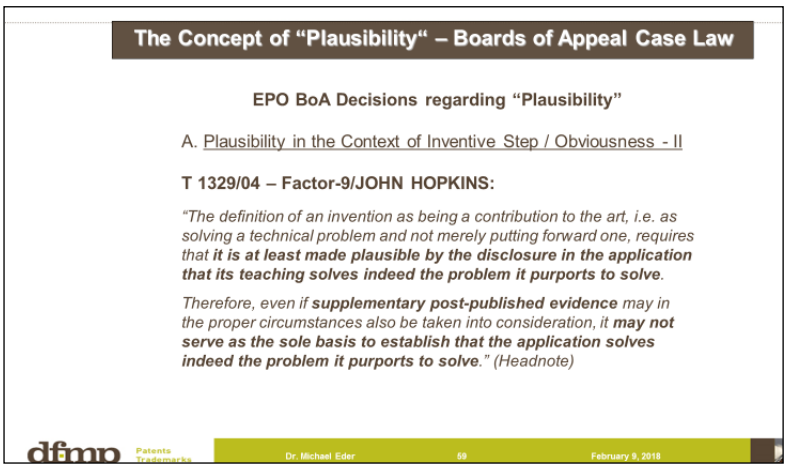


The first case in which the concept of credibility was developed is the often-cited *Agrevo* case from the EPO Boards of Appeal. Basically, the case was about a claim for a large number of compounds that had an asserted technical effect.

Here the question was whether the scope of the claim was credible according to the data in the patent that all of these claimed compounds achieved that technical effect. That is important. It was not a question to be dealt with under clarity, but it was a question that the Board concluded can be examined under inventive step because the definition of the objective technical problem as the EPO applies the problem-solution approach relies very often on what the compounds that are claimed are actually capable of providing in terms of a technical effect. This concept was later developed when the term "plausibility" was used. It was used in two different settings: one was under inventive step and the second under sufficiency.

The question whether the invention and the compounds you are claiming achieve a certain technical effect — for example, they work for treating a certain disease — might certainly be an important issue for sufficiency if that effect is a feature of the claim. But for pure compound claims, such as for new drug entities, the claim is directed to the compound itself. Examining that question under sufficiency is not going to work in this case because the sufficiency aspect for a pure compound claim is restricted to "can I make the compound?" which typically is not a big deal.

However, we are not contributing the compound just so we have another compound in the universe, but normally it is associated with achieving a certain technical effect and, therefore, this question has also been considered under inventive step.

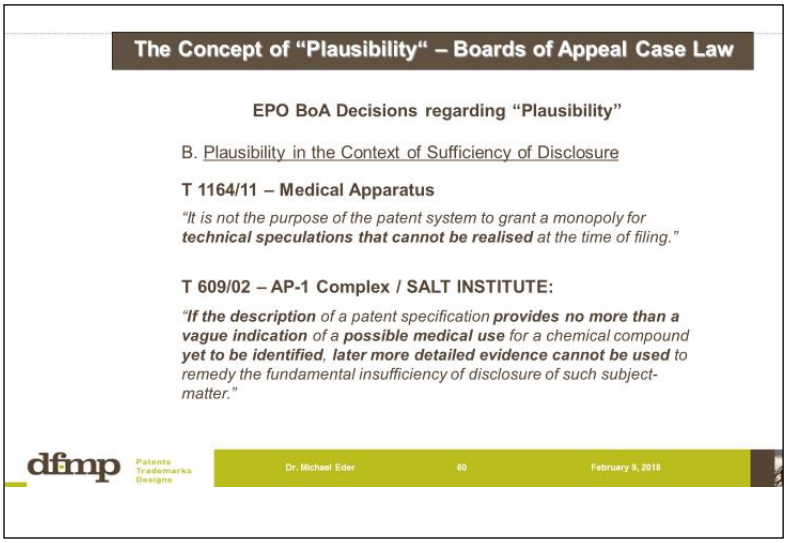


One of the leading cases is T 1329/04 – Factor-9/Johns Hopkins, decided by Board of Appeal 3.3.08, which is a biotech board. They concluded that it must at least be plausible by the disclosure in the application (the original disclosure) that its teaching actually solves the problem it purports to solve.

That was interesting because the plausibility hurdle was developed under the consideration "can I bring additional data to support my inventive step?" — or, as we will see later, sufficiency. Therefore, in this case, where it was not even made plausible, the Board said supplementary post-published evidence can only be taken into consideration if the plausibility hurdle is met, but may not serve as the sole basis to establish that the application solves the problem it purports to solve.

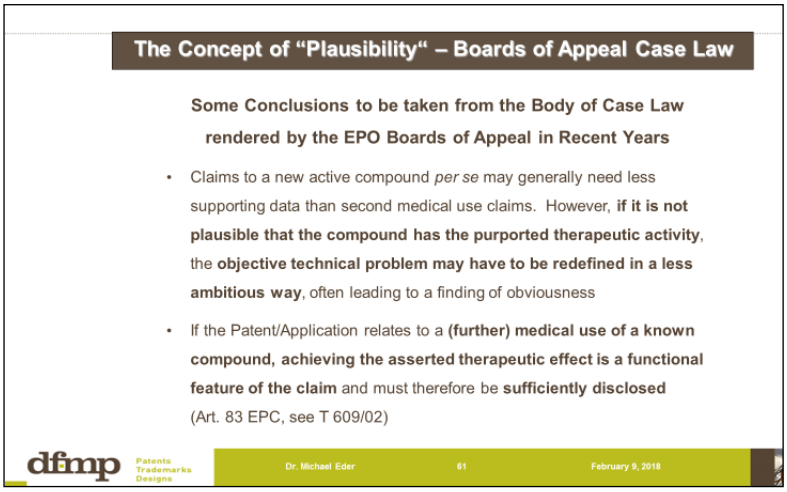
Because this plausibility concept was developed in the realm of biotech inventions, there was a discussion over many years whether that concept should also apply to small molecule patents. We have the answer now because we have cases — I will allude to them in a second — where this concept was also applied to small molecule compounds.

Plausibility also has been discussed under sufficiency, as I said before, so mere technical speculations that cannot be realized in practice should not be patentable. That was one take away from the headnote in T 1164/11.



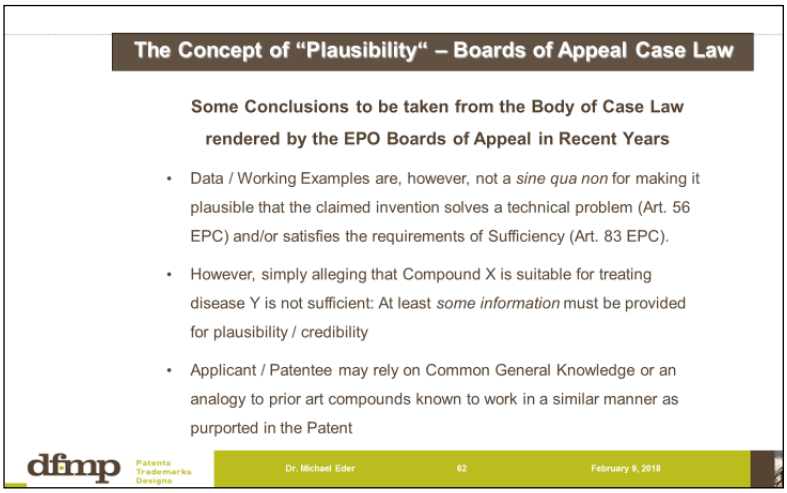
The leading case regarding plausibility under sufficiency is T 609/02 from the EPO, where the Board 3.3.08 concluded that "If the description of a patent specification *provides no more than a vague indication* of a *possible medical use* for a chemical compound *yet to be identified, later more detailed evidence cannot be used* to remedy the fundamental insufficiency of disclosure of such subject-matter."

That was a very extreme case because there the claim related to a compound yet to be identified by an assay, a screening method, and they were trying to patent that undefined compound for any possible indication being somehow related to the target used in the assay. That was basically too much for the Board, and in this case the EPO did not allow the patentee to provide additional data to overcome the plausibility hurdle.



What can be taken from this case law developed over the years is that for claims to a compound per se, in general it is fair to say that one needs less data in order to overcome the plausibility hurdle compared to second medical use claims. However, if the technical effect has not been made plausible under inventive step, the consequence is not a direct loss of the patent but a reformulation of the problem, which then means provision of a simple alternative; and if the compound does not solve anything, it is simply an arbitrary new compound and, therefore, also devoid of inventive step.

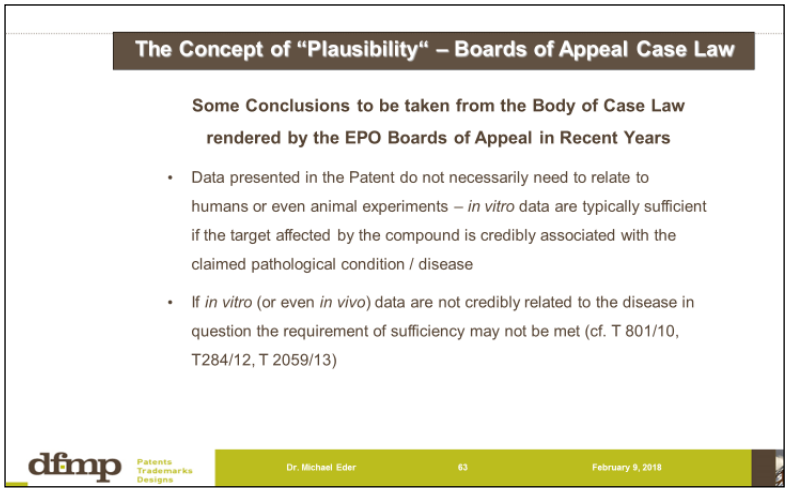
For a second medical use patent, the difference is that the asserted technical effect is a functional feature of the claim. Therefore, if that effect is not plausibly shown, it leads directly to invalidity under Article 83 of the European Patent Convention.



To recap, some conclusions can be taken from the body of case law rendered by the EPO Boards of Appeal in recent years.

• Data/working examples are not absolutely necessary — we will come to that when we discuss a pair of recent decisions — but more is needed than simply saying, "Compound X can be used for the treatment of Disease Y." That is not enough. You will have to bring some information that makes this at least plausible or credible.

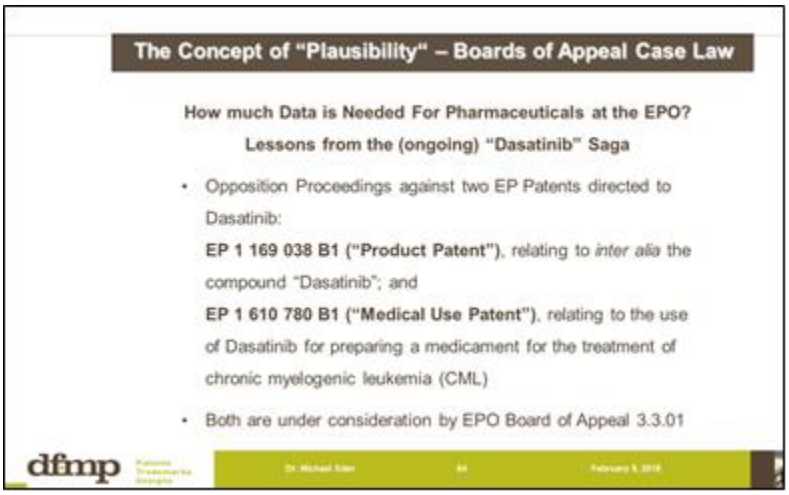
• What you will also see is that you may rely on common general knowledge or on analogies to prior art compounds that work in the same way to satisfy the plausibility requirement.



A final point: Most of you probably are aware that it is certainly not necessary to always have *in vivo* data, or even clinical data, to establish and to overcome that plausibility hurdle. Certainly, *in vitro* data typically are completely fine, provided of course that these *in vitro* tests have some kind of relation to the asserted treatment of the medical indication in our case.[1]

Now I want to discuss a few recent decisions, a pair of decisions relating to Sprycel®, the dasatinib product developed by BMS, that has received quite some attention in the last year:

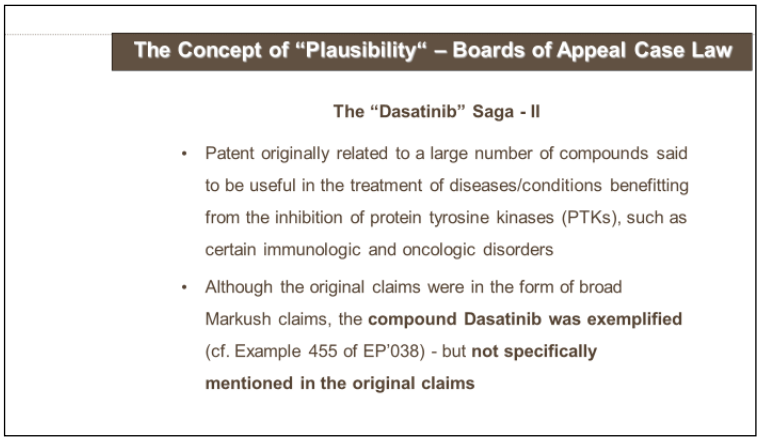
[1] *See* T 0801/10 (Use of Aripiprazole/Otsuka) (July 8, 2014); T 284/12 (Biodegradable Polyurethane/Urea Compositions) (Nov. 17, 2015); T 2059/13 (Aripiprazole against bipolar disorder/Otsuka) (Dec. 7, 2015).



A first case relating to what I will refer to as the "product patent," EP 1 169 038 B1, relating to dasatinib, but which originally broadly claimed a class of compounds as "potential tyrosine kinase (PTK) inhibitors";[2] and a second patent, a medical use patent, EP 1 610 780 B1, that quite specifically related to the use of a single compound already mentioned in the product patent for preparing a medicament for the treatment of chronic myelogenic leukemia (CML).[3]

The first case was decided last year, and I will discuss the outcome of that case in a second. To be fair, I should note that a petition for review has been filed, so it is not completely over and there may still be a chance that the conclusions will change. But, anyway, the Board of Appeal has decided the case, revoking the patent under inventive step, whereas the medical use patent was considered to be sufficiently disclosed. Basically, the same issue of plausibility was discussed in both cases; however, in the second case the same Board (3.3.01) came to the conclusion the patent was fine under sufficiency.

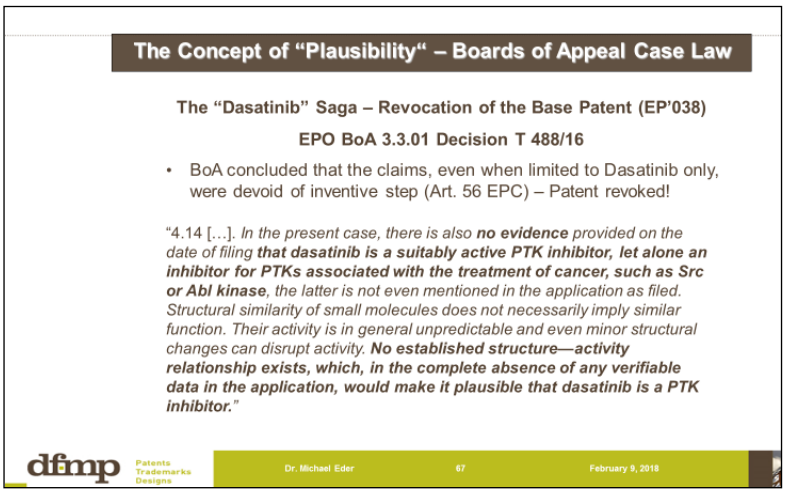
Now the case has been sent back to the first instance to discuss inventive step. I must admit that am a little biased because I am representing one of the parties in this case. But still, I think the general lessons that can be taken from these decisions are quite helpful for our discussion.



The Base Patent (EP '038) claimed a large number of compounds that were potentially seen as inhibitors of a large number of different PTKs generally known to be associated with immunologic and oncologic disorders. But there was no data in the patent. The compound dasatinib was exemplified but not specifically claimed. I have said that already, so we are clear here what the patent disclosed.

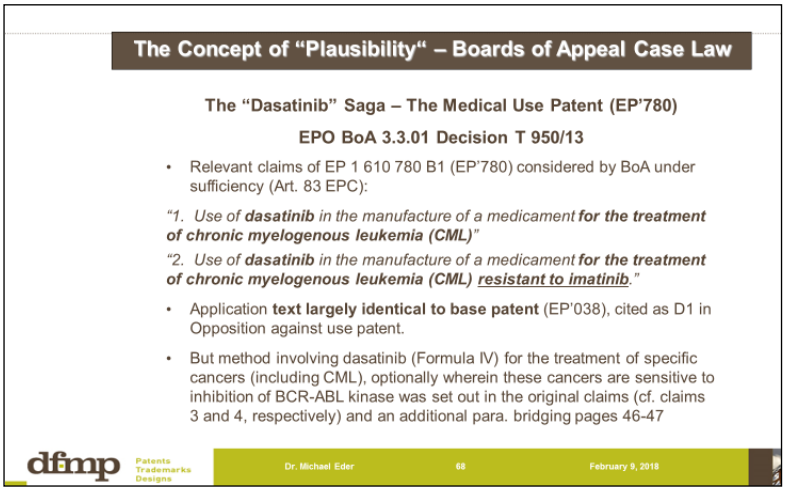
[2] EPO Board of Appeal 3.3.01 Decision T 488/16.
[3] EPO Board of Appeal 3.3.01 Decision T 0950/13.

It had some kind of general statement saying compounds that were tested in some of the assays showed activity. But that was basically worthless because you would not know which compound was tested, which PTK was inhibited, so so none of that was disclosed.



In the end, the Board of Appeal came to the conclusion to revoke the patent for lack of inventive step. They said: "In the present case, there is also *no evidence* provided on the date of filing *that dasatinib is a suitably active PTK inhibitor, let alone an inhibitor for PTKs associated with the treatment of cancer, such as Src or Abl kinase*; the latter is not even mentioned in the application as filed. … [thus, there was] *no established structure—activity relationship, which, in the complete absence of any verifiable data in the application, would make it plausible that dasatinib is a PTK inhibitor*." That was not sufficient to overcome the plausibility hurdle.

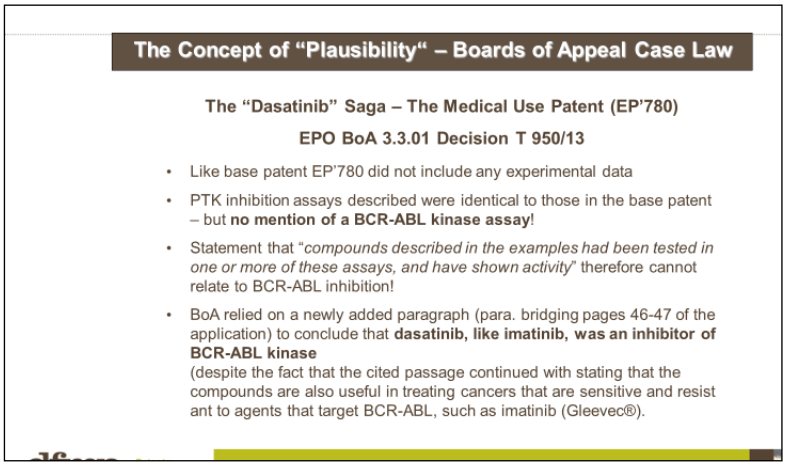
Of course, nowadays dasatinib is a marketed product. There was plenty of data to show it works that was published later, but these data were not included in the patent. and it was thus not made plausible at the time of filing. Therefore, that was the end for the patentee of the product patent.



I think the second case here is also interesting because it had two different types of medical use claims.

• The first claim was directed to the "use of dasatinib in the manufacture of a medicament for the treatment of CML."

• The second claim under consideration was basically in the same format, yet related to the "use of dasatinib . . . for the treatment of CML *resistant to imatinib*."

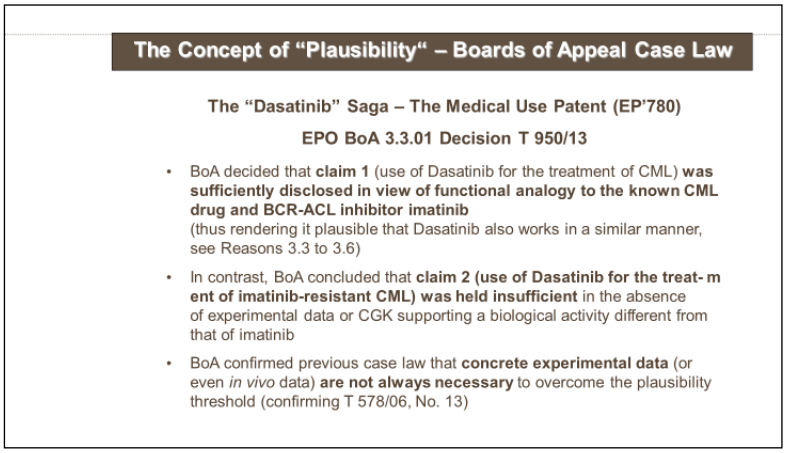


The disclosure of the use patent was largely identical to the product patent. Large parts of the description were basically copied from the base patent. There was only an additional paragraph in there saying now some compounds have been found to be very useful for the treatment of certain cancers, more specific than before (in this case BCR-ABL kinase inhibitors) and they were also said to inhibit cancers that are sensitive to and resistant to treatment with imatinib.

Imatinib (Gleevec®) was already known when the patent was filed. So the patent drew an analogy to a specific compound: — "dasatinib may work in cancers that are known to be treatable by another compound like imatinib." That was apparently sufficient for the Board of Appeal to conclude that there is a functional analogy to a known compound; therefore, it is plausible that the other inhibitor works in the same way, despite the fact that there was still no data for any of the compounds in the later patent.

Actually, the situation was even worse. The specific assay, the BCR-ABL kinase assay, was not even mentioned in the patent, so it was merely the same old kinase assays that had already been described in the base patent. The patent therefore did not even disclose the proper assay to find out whether the compound inhibits the PTK specifically associated with CML. But the Board did not find that problematic. They said: "Well, if the patent includes a statement that a compound works basically in the same way as a compound already known, we are satisfied."

The decision regarding claim 1 was that it was fine under sufficiency.



On the other hand, the second claim was rejected under sufficiency because that was a claim directed to the treatment of a cancer that was resistant to imatinib, which then raised the question: Okay, if it is resistant to imatinib, it probably does not work the same way; therefore, some evidence is

needed. As there was no data for it in the patent, claim 2 was found to be insufficient.

The Concept of "Plausibility" – Boards of Appeal Case Law

The "Dasatinib" Saga – The Medical Use Patent (EP'780)

EPO BoA 3.3.01 Decision T 950/13

- BoA's summary of the rationale applied for the subject matter of claim 1:

*"3.10.4 Concerning the **lack of explicit data**, the board reemphasises that in cases where the application **discloses a technical concept which is plausible in the light of the common general knowledge** at the relevant date, **but lacks concrete or tangible proof** that the claimed concept can be put into practice, **post-published documents may be used as evidence** that the invention was indeed reproducible without undue burden at the relevant filing date of the application (see T 1262/04, Reasons No. 5; T 157/03, Reasons No. 9)."*

- Re its finding that claim 2 was insufficient, BoA explained that:

*"3.13.2 […]. The **functional analogy to imatinib as BRC-ABL kinase inhibitor** is not helpful in this context and **cannot explain why dasatinib should be active, when imatinib is, or has become, inactive**."*

The Board confirmed it is not always necessary to provide experimental data. They relied here on a functional analogy, functional equivalence to a known compound to satisfy that requirement.

The Concept of "Plausibility" – Boards of Appeal Case Law

The "Dasatinib" Saga – Conclusions

- Lack of concrete data in application does not need to be detrimental: If a functional analogy to a known drug exists and is alluded to in the patent, chances are high that plausibility threshold is met
- Chances to overcome plausibility hurdle increased for specific compounds and for specific (or limited number of) medical indication
- However, the latter may not be sufficient if there is no functional analogy to an agent known to be effective in the claimed treatment (cf. EP'780 claim 2)
- Caution: Relying on a functional analogy to known agent may open up a possible attack under inventive step (although the concepts of plausibility and obviousness are clearly different from each other, cf. T 950/13, Reasons No. 3.8)

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In the end, I think it is fair to say that the plausibility hurdle is only the first step that needs to be overcome to then bring in further data, and it is quite a low hurdle for the applicant, which really aims at only forbidding patents that are entirely speculative.

The Concept of "Plausibility" – Conclusions

The EPO's approach to Plausibility – Take Home Message

- **Remedy of Art. 56 (Obviousness) & Art. 83 (Sufficiency) EPC deficiencies by post-published evidence: similar standard!**
  - *If post-published data cannot be used in support of sufficiency, they can not be used to support inventive step either*
- **Experimental Data in the original application not always required in particular if**
  - the application discloses a plausible technical concept and
  - there are no substantiated doubts (CGK, prior art) that the claimed concept can be put into practice

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The take-home message really is experimental data are not always required, especially if the application discloses a plausible technical concept and there are no substantiated doubts that the claimed concept can be put into practice.

MR. GERRITZEN: Thank you very much, Michael.

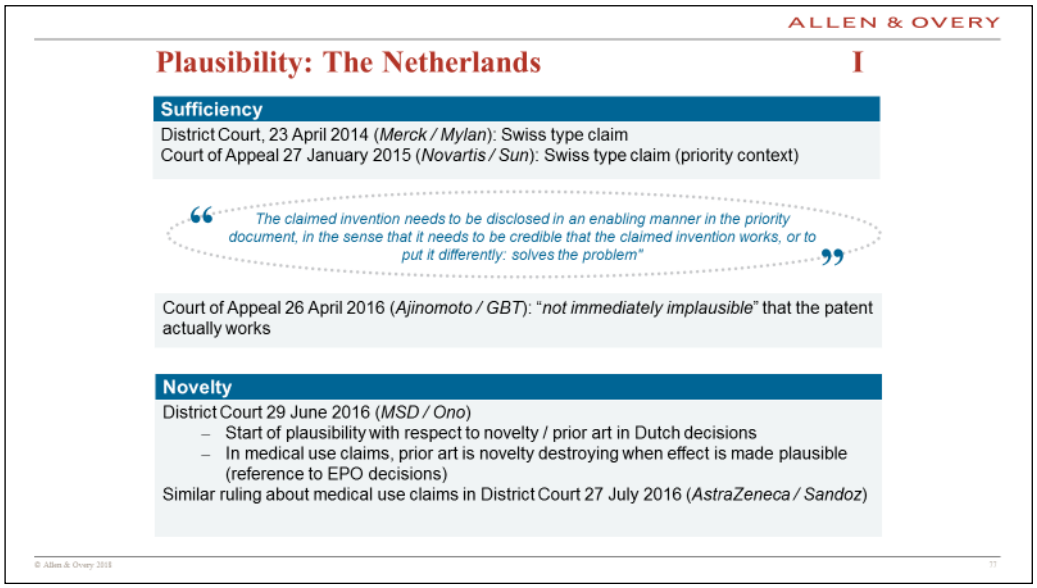
I will be discussing some of the highlights of the positions on plausibility in Europe. In order to stay close to the purpose of this conference, we are asked to look ahead instead of to look at what has happened in the past, but, as a lawyer, you cannot resist taking a look at case law and trying to make sense of that.

I think on a high level it is safe to say that also in national European courts plausibility has been around for quite a while. It was not always called that, and it is still not always called that everywhere.

In the past few years, we have seen an enormous uptake of an argument in national courts being raised related to some sort of plausibility. My position generally on that, before going into some of the specifics, is that you could say that plausibility is a bit of a craze. I think that can be shown from the national case law in Europe.

Also, looking at Europe, there is a bit of a divide between, on the one hand, the Dutch and the UK case law — actually, in those two countries there is a reasonable amount of case law in which plausibility is discussed — and, on the other hand, the French and German case law in which the term is not used as such and there is less clear legal guidance. However, the judges in all these countries in Europe seem to agree on one thing: this is actually about anti-speculativeness; we do not want to have patents that are merely speculative, and that is what plausibility is for.

Let me start by taking a look at the Netherlands, which is the country that I am from, and looking at some of the interesting decisions that have come out of that country. I am not going to be fulsome and discuss every country in full detail, because that is going to drive you crazy, and we only need to know that much to decide of course "what next?" because that is what we are here for.



I will start off with this first set of cases, which relate to plausibility in the light of sufficiency.

In the first case, *Merck/Mylan*,[4] the question was: is the invention plausible? The challenge was that the claimed effect of the patent would not actually occur; and that, even if it would occur, that it was not described plausibly within the patent. The court said: "Regardless of whether lack of plausibility would render the patent insufficient, I think that the invention is plausible," therefore leaving the question of what the connection is between the two. There were some indirect experiments within the patent that the court found to be sufficient for plausibility.

In *Novartis/Sun*,[5] the Court of Appeal looked at the plausibility of the priority document, and said: "The claimed invention needs to be disclosed in an enabling manner in the priority document, in the sense that it needs to be credible that the claimed invention works, or to put it differently: solves the problem."

There the word "credible" is used. I do not think there is any reason to think that "credible" is different than "plausible," but in the commentary there is a bit of a word game going on trying to figure out what words mean what, all under the assumption that if you use the same word it is probably the same thing and, therefore, if you use different words that must be a different thing. That is the way that lawyers like to view the world, but I am not sure that is actually accurate, as I will discuss a little later.

Here the Court of Appeal accepts an indirect disclosure of the common general knowledge to conclude credibility. The common general knowledge with regard to that patent was that an intravenous infusion of the medicament was common general knowledge and that dosing was such that that would only be efficient with that type of administration; therefore, the connection would be made by the person skilled in the art reading that for the disclosure and it was not necessary that those two would be put together in that document in the same way.

A good example of people being fussy over words is probably the next decision, *Ajinomoto/GBT*.[6] In that decision, the Court of Appeal used the term "not immediately implausible." That sparked a lot of debate in the Netherlands because people said, "Well, that must be something different surely," and articles were published about the differences between "plausible" and "not immediately implausible." People started raising theories about "plausible" meaning that there must be positive pointers to the invention in the description and "not immediately implausible" should mean the absence of negative pointers in the description.

I think that is a bit of a waste of time because, if you look at that decision, there were quite specific circumstances in which it was handed down. There was a debate about the burden of proof, and in the end there was no serious argument raised that the patent worked for at least a considerable part of the claimed subject-matter; therefore, the burden of proof was on the alleged infringer to show that there was a lack of plausibility; he could not reach that threshold, and therefore the court probably chose the term "not immediately implausible."

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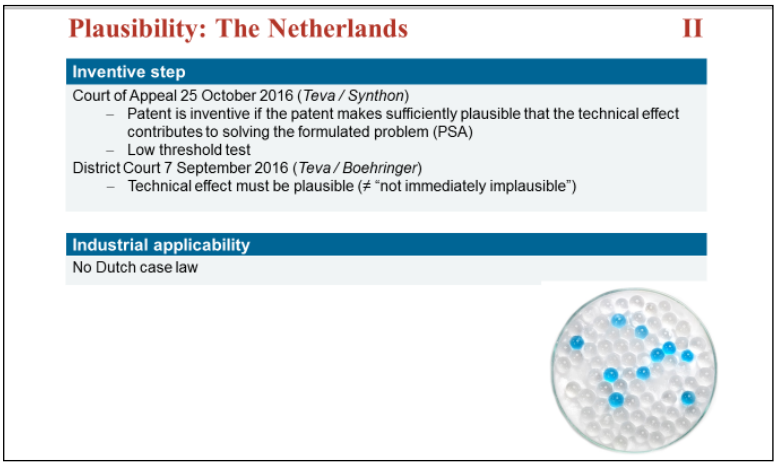
[4] Merck/Mylan, District Court of the Hague (Apr. 24, 2014).

[5] Novartis AG v. Sun Pharmaceutical Industries (Europe) B.V., Court of Appeal of The Hague, The Netherlands (Jan. 27, 2015), Case file number: Case file number: 200.1 50.713/01, see http://www.eplawpatentblog.com/eplaw/2015/02/nl-novartis-v-sun-skinny-label-injunction.html.

[6] Ajinomoto/GBT, Court of Appeal of The Hague (Apr. 26, 2016).

On novelty, in the *MSD/Ono* case[7] plausibility was assessed in two different forms: one with regard to the priority document, whether a valid right of priority could be invoked; and one with regard to the document as such. There were interesting points raised by the infringer there. The infringer said, "I think that the only test should be classical sufficiency and not also plausibility when you look at a potentially novelty-destroying document." And, he said, "Plausibility for prior art should not have a higher threshold than for the patent itself and the burden of proof should be on the patentee." Unfortunately, those points were not addressed by the court because they were filed late in the proceedings.



Teva/Synthon[8] was also interesting. This decision was handed down within the framework of an inventive step. The challenge was that the invention was not sufficiently plausibly disclosed within the patent. There the court actually takes some time to discuss the test, which refers back to the EPO case law that Michael just discussed. It explicitly recognizes that the threshold is low and it holds that the patent makes it sufficiently clear that the patented process is necessary for the desired technical effect, which was taking out a certain compound to avoid discoloring of the substance that they were trying to make.

The court found irrelevant that it was possible that there were other circumstances that could also influence the discoloration of the substance. It said, "As long as it is at least plausible that this substance is essential, then I think that is enough for plausibility."

In *Teva/Boehringer*[9] the test was described as "only the technical effect that is plausible can be relevant for formulating the technical problem," which also comes from the EPO case law. The court mentioned that plausibility can come from experiments, logical explanations, prior art, and the common general knowledge." So there are lots of sources that the patentee can pull from.

Now, it does recognize also — and I underline this— that it is not a separate test for invalidity, but that it can lead to lack of inventive step or insufficiency. I think it is very important when we talk about plausibility that we

[7] MSD/Ono, District Court of the Hague (June 29, 2016) (first Dutch decision on role of plausibility with respect to novelty/prior art).

[8] Teva/Synthon, Court of Appeal of the Hague (Oct. 25, 2016).

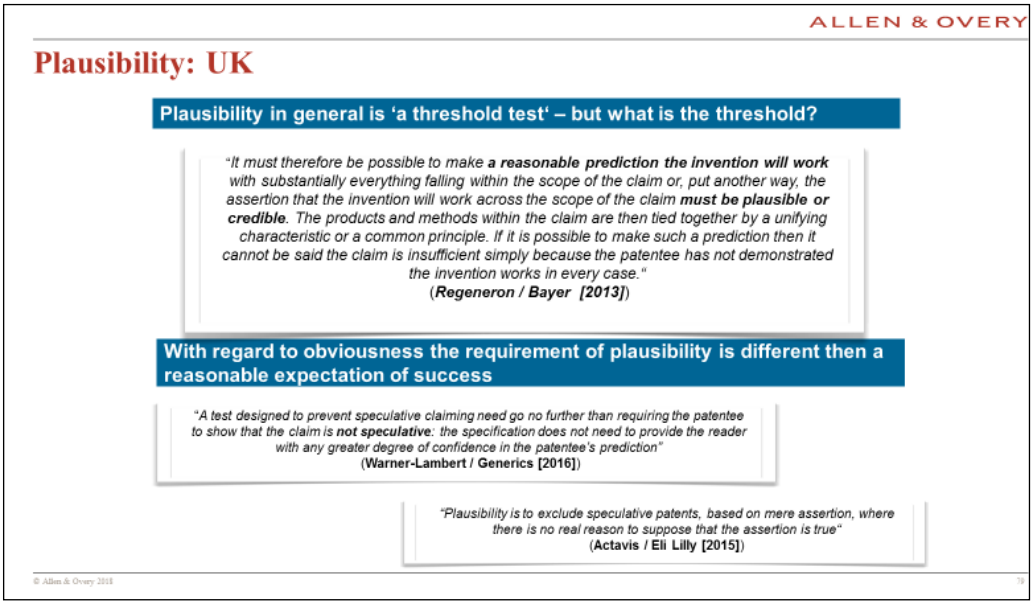
[9] Boehringer Ingelheim Pharma GmbH & Co. KG v. Teva Pharma B.V., Teva Pharmaceuticals Europe B.V., Pharmachemie B.V., District Court Utrecht/The Hague, Preliminary Injunction proceedings (Aug. 15, 2012, Case No. KG ZA 12-319 KG ZA 12-559; see http://www.eplawpatentblog.com/eplaw/teva/.

recognize that it is something that is within these distinct tests that we already have for invalidity.

Teva argued: "The goals of the invention that were actually put into the claim or that you argue, Boehringer, are not described."

Boehringer went on to file experiments that they had made after the application date of the patent, and they referred back to the Court of Appeal case law that I just mentioned, and said: "Well, it is no problem that we filed these experiments later because the test is 'not immediately implausible.' So as long as there are no negative pointers of a lack of plausibility within the patent, I am okay, and here you will see my experiments to underline that."

The court said, "No, that is not the test; the test is for actual plausibility." I think that is probably where the "not immediately implausible" thing ended in the Netherlands. It did not resurface again after that, and I do not think it will.



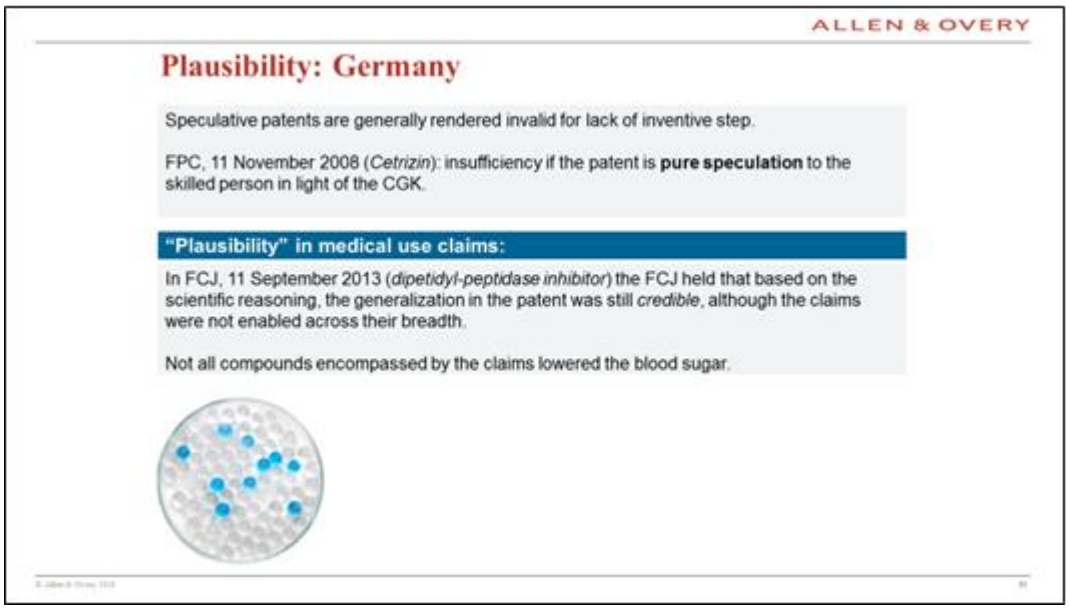
Looking a bit at the United Kingdom — and I am conscious of the fact that there are very experienced UK practitioners in this room so it is slightly dangerous for me to talk about the United Kingdom, but I will have a go and you can tell me when I am awfully wrong.

One of the first cases that actually was about plausibility but did not mention the term was the *Angiotech/Conor* case on appeal,[10] which held that plausibility is a threshold test, without actually mentioning what the threshold is. A lot of the decisions that came after that — and I list a few quotes from a few of those decisions — set out to try to define what the threshold should actually be. There is quite a broad range of terms that are used for that. I will give you a few: "A reasonable good-faith prediction"; "some real reason the statement is true"; "an educated guess"; or "a reasonably credible theory." There are, I think, various levels of plausibility that you can read into that.

[10] Conor Medsystems Inc. *v.* Angiotech Pharms. Inc. and others, [2008] UKHL 49 (July 9, 2008, https://publications.parliament.uk/pa/ld200708/ldjudgmt/jd080709/conor-1.htm.

In the end — and I think this is the overarching theme that you also see in the quotes that are on the screen here — this is about preventing speculation in the patent. You see that very clearly in the *Actavis/Lilly*[11] quote and you also see it in the *Warner-Lambert/Generics* quote.[12] I think they also show that the threshold is generally very, very low.

I think also in the *Warner-Lambert* case it was argued that plausibility should be the test that the skilled person based on the information in the patent would apply the invention with a reasonable expectation of success. The Court of Appeal said there, "No, that threshold is much too high."[13]



Moving on to Germany, if I understand my colleagues correctly, the word "plausibility" does not arise in German case law. It is not a big thing in Germany. I think the Germans basically say, "We've got our insufficiency test, we've got our lack of inventive step test, and that is what we will use."

I think there are two cases that could come close. One is the cetirizine case that I mention here. There the court said that a use claim might be insufficient if the claimed use is not clearly and unambiguously disclosed in the patent in a credible way and that is understood as pure speculation by the person skilled in the art on the basis of its common general knowledge. But then the court went on and eventually invalidated the patent for lack of inventive step. I think it is a good example that there the Germans say, "We will not get excited about plausibility. We've got our inventive step test. Thank you very much."

The dipeptidyl-peptidase inhibitor case[14] was interesting as well, where

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[11] Actavis Ltd. and Others v. Eli Lilly, EWCA Civ. 555 (June 25, 2015), http://www.bailii.org/ew/cases/EWCA/Civ/2015/555.html.

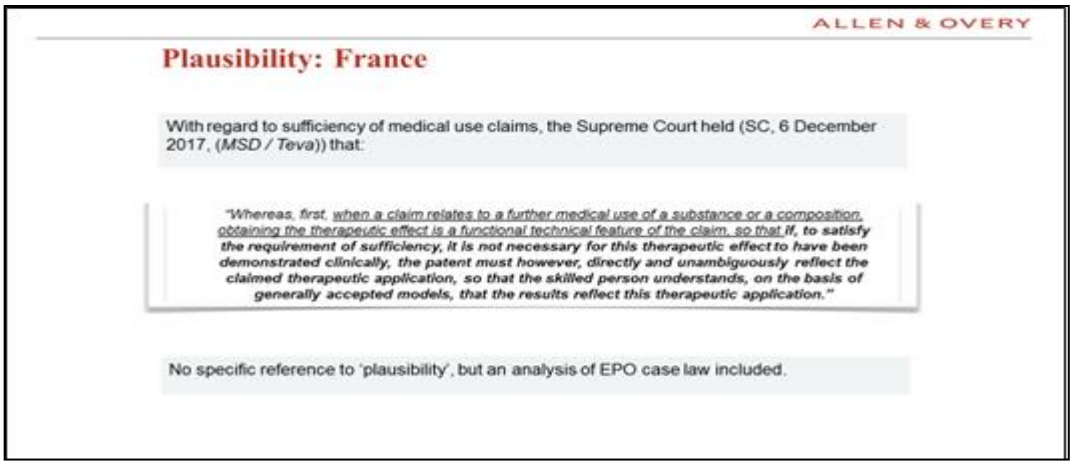
[12] Warner-Lambert Co., LLC v Actavis Group PTC EHF & Others [2015] EWHC 485 (Pat) (02 Mar. 2015) (Arnold, J.), http://www.bailii.org/ew/cases/EWHC/Patents/ 2015/2548.html.

[13] Warner-Lambert Co., LLC v Actavis Group Ptc EHF & Others, [2015] EWCA Civ 556, *available at* http://www.bailii.org/ew/cases/EWCA/Civ/2015/556.html.

[14] "Dipeptidyl-peptidase Inhibitor," Federal Court of Justice, BGH X ZB (Sept. 11,

there was also an issue of generalization of the teaching in the description. The Supreme Court in Germany went actually quite far, to say if there is a general teaching within the specification that is then generalized into the claim, there is actually nothing wrong with that as long as the person skilled in the art would find that credible, and it is not a problem that in the end not all compounds that are encompassed by the claims actually reach the effect that was intended.

I can safely talk about France because everybody is covered in snow in France so they will not hear me. I don't think that is really true.



Going to the French case law on plausibility, the route in France seems to be a little different than in other countries. I understand that between 2010 and 2012 there actually were cases that said that second medical use patents should have a higher threshold of sufficiency than other types of patents.

There is case law as to the amount of evidence that needs to be in the description of the patent between 2009 and 2015 in which the courts have said that you would expect some types of experiments or some types of tests to be included in the specification, not so much to show the results but to show that there is, if you will, a credible avenue that the patentee is actually pursuing to show that there is a plausible invention.

Luckily, that position was, I think rightly, corrected by the French Supreme Court in 2017. James Horgan mentioned the *Merck Sharp & Dohme v. Teva* decision[15] yesterday [see Session 1F]. I think this is the latest decision out of France that relates to this subject. There, interestingly enough, the French Supreme Court has gone back to EPO case law and took all the principles, some of which Michael just alluded to, and put them into its decision. The Court said that "to satisfy the requirement of sufficiency, it is not necessary for this

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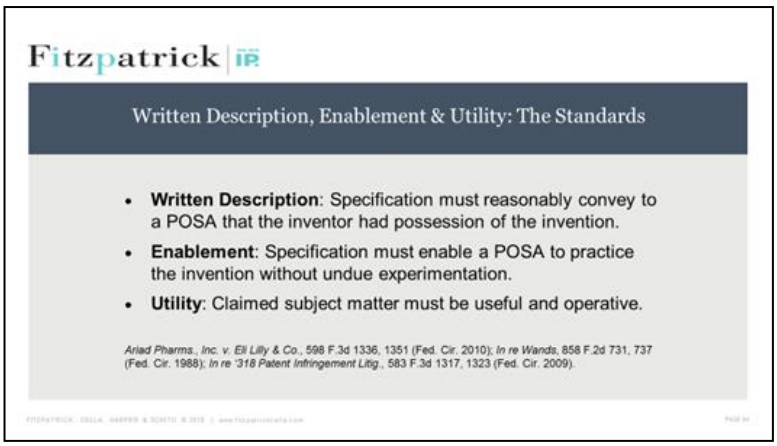
2013), decision in English available at http://patentblog.kluweriplaw.com/2013/12/05/broad-functional-claims-a-fair-reward-for-patentee-or-an-unfair-attempt-to-reach-through-to-future-inventions-by-others/translation-of-bgh-x-zb-8-12/.

[15] Merck Sharp & Dohme Corp. v. Teva Pharm. Indus., Inc., Cour de Cassation (French Supreme Court, Commercial Chamber), Decision No. 1514 FS-P+B+R+I (Dec. 6, 2017), available in English at https://drive.google.com/file/d/1FrjWB1PHFmn_egxSliLKih9erLEOcciq/view?usp=sharing.

therapeutic effect to have been demonstrated clinically, [but] the patent must however, directly and unambiguously reflect the claimed therapeutic application."

There is still slight uncertainty as to how that will eventually be applied and whether that is a full deviation of the prior case law that said that you need to have some start of experiments in France. But that will remain to be seen.

MS. JACOBSEN: Good morning, everybody. Don't be fooled by my accent. I am here to talk about the U.S. perspective.



In the United States under Section 112 of the Patent Act we have three requirements: written description, enablement, and utility. Now, some of you in the audience are all too familiar with these three requirements, but for our overseas friends who are not so familiar I will just quickly run through the standards and then we can talk about them in a little more detail.

• To satisfy the written description requirement, any patent, including a second medical use patent, must reasonably convey that the inventor has invented what is claimed. That is also known as having possession of the invention.

• The patent must also be enabling; that is, it has to enable a person of ordinary skill in the art to practice the invention without undue experimentation.

• And a patent must have utility. That means that it must be useful and operative.

What we see in the case law[16] in the United States — and it seems similar to Europe — is that one principle underlying all three of these requirements is that patents are not awarded for academic theories or research hypotheses. This principle is very important when it comes to second medical use patents because of the issues surrounding the timing of those applications that were raised yesterday and also by the previous panel today. The more time you wait to file your application, the more data you may have but the more prior art you may face; and, on the flip side, the earlier you file your application, the less prior art there may be out there but the less data you have to support that patent application.

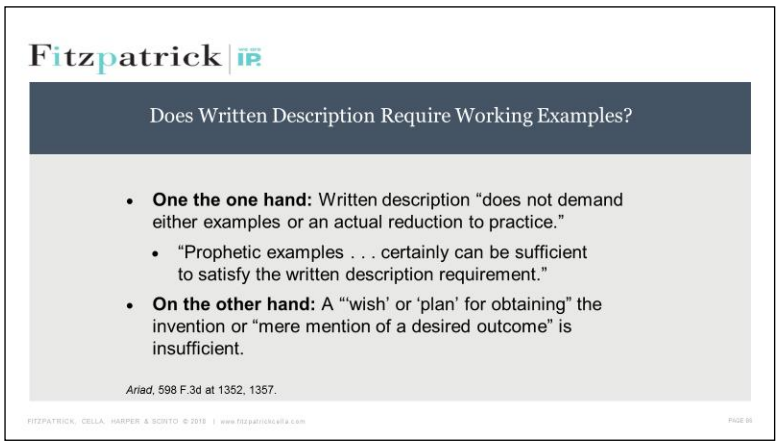
As we have limited time, I will focus on the first and third of these requirements and what data — if indeed any — you need to meet these requirements in the United States.

The U.S. courts have made clear that human trials are not required for a medical use to be patentable and it may be sufficient to have animal data or *in*

[16] *See* Ariad Pharms., Inc. v. Eli Lilly & Co., 598 F.3d 1336 (Fed. Cir. 2010).

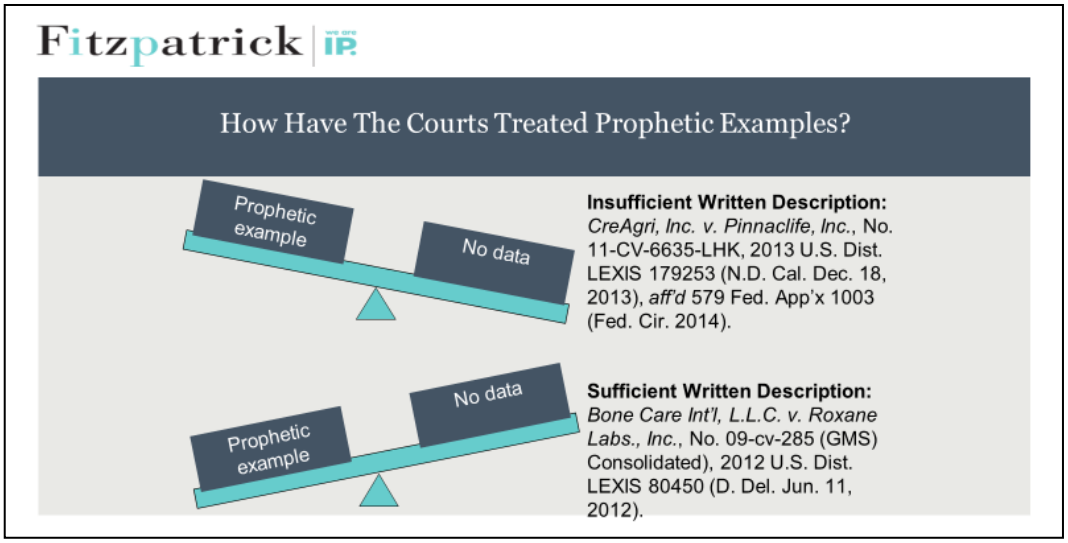
vitro data to satisfy the requirements of Section 112.

But what if you do not have that data? This may be because no animal model or *in vitro* model exists, which was the case in the Eli Lilly case that Mark Stewart discussed earlier [Session 2C], or it may be because for some reason you need to file your application early and you do not yet have the data available.



I will start with written description. On the one hand, our case law expressly states that written description does not demand either examples or an actual reduction to practice; prophetic examples certainly can be sufficient to satisfy the written description requirement. So far so good. But on the other hand, the case law also says that "a 'wish' or a 'plan' for obtaining" the invention or "mere mention of a desired outcome" is insufficient.

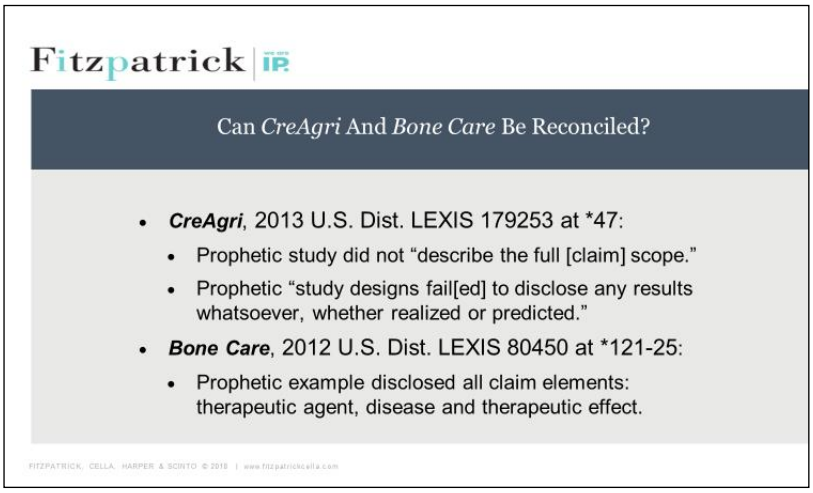
How has this apparent conflict played out with respect to second medical use patents?



Here we have two cases which appear to have highly similar facts. The *CreAgri, Inc. v. Pinnaclife, Inc.* case concerned a method for using hydroxytyrosol, which is an olive oil plant extract, to treat inflammatory disorders. The *Bone Care* case concerned Hectorol,® which has the active ingredient doxercalciferol, and the patent was on the use of that drug to treat secondary hyperparathyroidism in patients with chronic kidney disease.

Neither patent in these cases contained any data to support the use of the drug for the claimed indication, but both patents contained one or more prophetic

examples. In the *CreAgri* case, those prophetic examples were not enough and in the *Bone Care* case they were. The question is: how can these cases be reconciled?

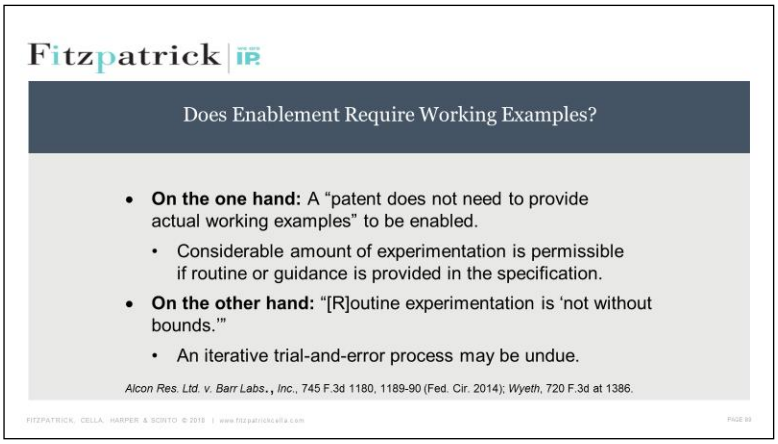


Two factors that appear to have tipped the balance in the *CreAgri* case were: (1) that the prophetic examples were not commensurate in scope with the claim; they related to only one type of inflammatory condition, not all of them; and (2) the prophetic examples did not include any predicted results. In fact, the closest that the *CreAgri* specification came to describing the invention was an almost-verbatim recitation of the claim language in the specification.

But, under *Ariad*, simply repeating the claim language in the body of your specification may not be enough. In *CreAgri* it was not sufficient because the specification contained no explanation why the inventor believed that his invention would be effective to treat any inflammatory condition, let alone all of them as recited in the claim.

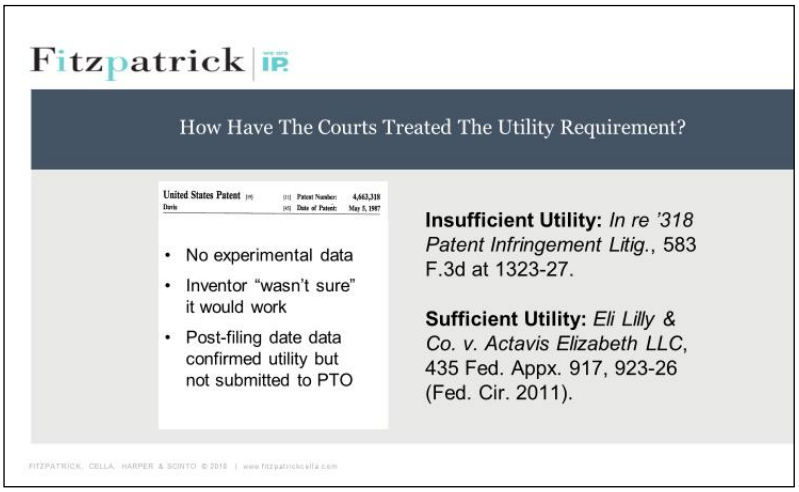
By contrast, the *Bone Care* prophetic example was sufficient because it was a detailed, twelve-month clinical trial protocol. It described the relevant patient population, their disease state, the drug, how it was to be used, and the anticipated outcome. It was this detailed nature of the trial, combined with what was known in the art regarding the drug and its mechanism of action, that tipped the balance in that case.

And, as we will see next, the state of the art is also important in the utility requirement under Section 112.



Turning to utility, while neither written description nor enablement require that the patentee actually prove that his invention will work, the utility requirement ensures that an invention is useful and operative. A patentee

can show utility either by providing test results or by demonstrating that a person of ordinary skill in the art as of the filing date would have recognized the utility of the invention based on the specification (*Alcon Research v. Barr Laboratories; Wyeth and Cordis v. Abbott*).



Here again we have two cases that appear to have highly similar facts. First, *In re '318* concerned a patent on a method for treating Alzheimer's disease using galanthamine. The second was the *Eli Lilly v. Actavis* case, about which we got a preview earlier this morning, which concerned a method for treating ADHD using atomoxetine.

In both of these cases the drug was known. In fact, as Mark Stewart explained, atomoxetine had undergone Phase II and Phase III clinical studies, although neither of those had been successful. And in both cases: the patent lacked any data relevant to the claimed indication; the inventors of each of the patents had admitted at deposition that he did not know whether or not the drug was going to work for the claimed indication; and there was post-filing date data that confirmed the utility, but in neither case had that been submitted to the Patent Office during prosecution.

Despite those similarities in the facts of these cases, we have the opposite outcomes. Again, can we reconcile these cases?

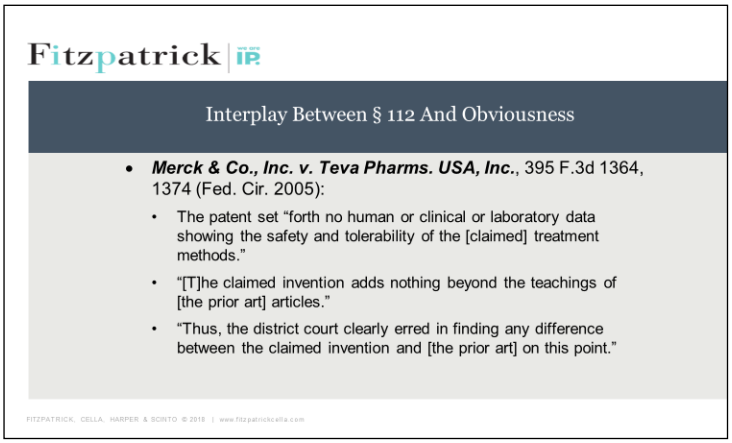
Importantly, in *In re '318,* there was no reasonable correlation between the drug's activity and its asserted therapeutic use. The specification simply summarized six prior art publications that the inventor admitted had no relevance to Alzheimer's treatment. As such, the specification just set forth a hypothesis and described animal studies that could be used to test it. While those animal studies had been started, they had not been finished and there were no results available during the prosecution of the patent.

By contrast, in the *Lilly* case, the prior art suggested that the mechanism of action — norepinephrine reuptake inhibition — was relevant to ADHD, the patent disclosed the safety of the drug at issue, and the specification contained a full and accurate description of the utility.

Also relevant in the *Lilly* case was that experimental data confirming the utility was available before issuance of the patent. And, as I just explained, that is different from the *In re '318* case, where that data could never have been used during prosecution because it was not available until after the patent was issued.

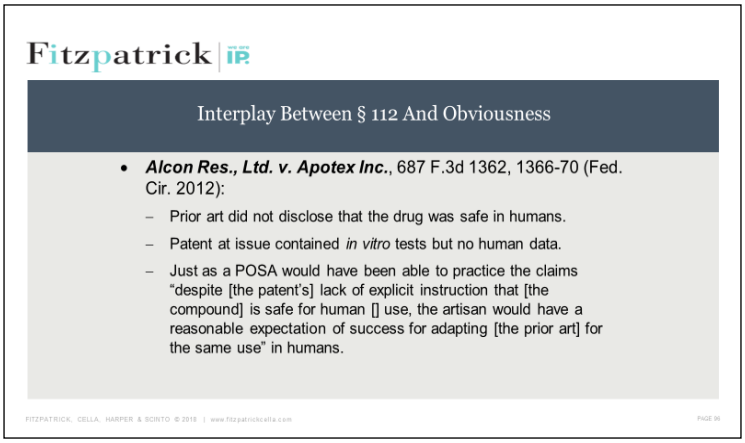
Thus, it appears that timing is everything, including in the use of post-filing date data to support a claimed utility.

In my last one minute I want to discuss a couple of cases that, it has been argued, blurred the lines between Section 112 and obviousness.

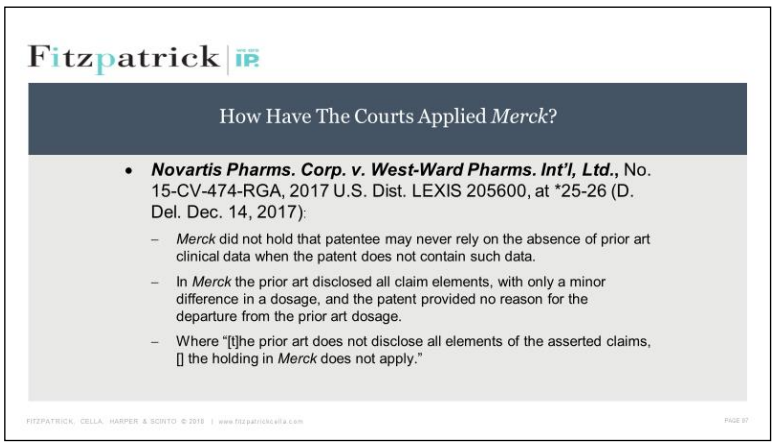


The first case, *Merck v. Teva*, concerned Fosamax and a patent on a method for treating osteoporosis using a specific dose of alendronate administered once a week. In this case, there was no dispute that the prior art disclosed every aspect of the claimed method but proposed a slightly higher dose. The issue was whether a person of ordinary skill in the art would have been discouraged from practicing the prior art due to safety concerns.

Rather than simply compare the prior art with the claimed invention, in this case the Federal Circuit considered the patent specification in connection with this issue. The court noted that the specification set forth no human, clinical, or laboratory data showing the safety and tolerability of the claimed method, and for that reason the claimed invention added nothing over the prior art, and thus the district court had erred in finding a difference between the claimed invention and the prior art on this point. Ultimately, the Federal Circuit held the patent obvious.



The *Alcon v. Apotex* case is very similar and I will not dwell on the facts of that case because time is limited.



I will just note the *Novartis v. West-Ward* case that was recently decided by Judge Andrews in the District of Delaware. This case is interesting because the defendants in that case sought to apply *Merck* beyond the specific facts of that case. The *Novartis* case concerned two methods of using a known drug, everolimus, for the treatment of two different cancer indications. As of the priority date of those two patents, everolimus was a known drug that was already in development, but it was in development as an immunosuppressant for the prevention of transplant rejection.

The defendant West-Ward argued in the *Novartis* case that the absence of data in the prior art, specifically clinical data in the prior art, could not be relied on in support of a nonobviousness argument because the patent itself did not include any such clinical data.

Judge Andrews rejected that argument. He said that the holding in *Merck* was not so broad. He relied on the very specific facts of the *Merck* case and found that in the *Novartis* case there was no prior art disclosing the use of everolimus for the treatment of either indication, and both method-of-use patents were upheld.

This case is now on appeal to the Federal Circuit. So watch this space. We will see what happens next.

MR. SCHINDLER: I am going to take a different perspective. I am also a U.S. patent attorney. Charlotte looked at the areas of indefiniteness, enablement, and Section 112, and I am going to look at more the issues of obviousness and anticipation.

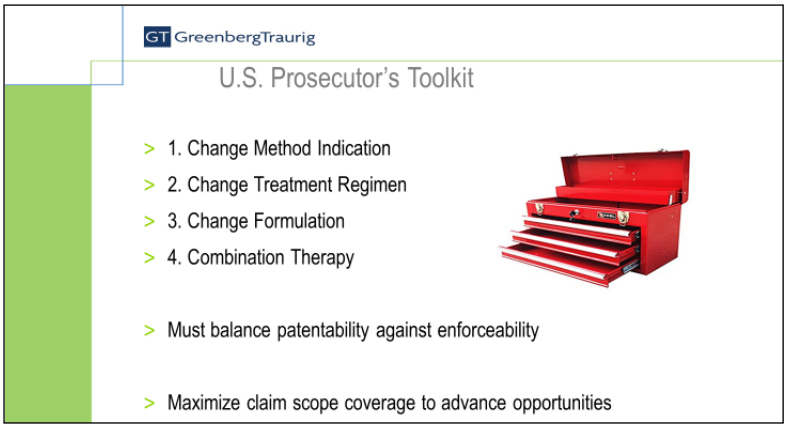
But before I do that, I want to take a step back and I want arrows to be shot at me. I am one of the people who is going to say that the patent system is working. I know that we have sat through two days of "it's not working." Why I say that is, as somebody who works in the startup world, it is absolutely critical that a company has a patent.

I work both in the Artificial Intelligence for Disaster Response (AIDR) world and in the life science world. The answer is any investor needs to see a patent. The first question they will always ask in the startup world is, "What is the life of the patent?" Many times I am working with a startup that is licensing a patent from a university and there may have already been maybe eight years that the patent already has and we are now looking at twelve years possibly. So the first question they are asking is, "What are the improvement patents you can do?"

Part of my presentation today is to say what the patent system in the United States is looking at and what are our tools that we can look at with regard to how we answer this investor. In the startup world I need investments, and everybody knows here that no company will survive without that.

There was a lot of discussion here and everybody understands there is great work being done in universities — great stuff — but it is the hand-off, and it is the hand-off possibly before you go to the Mercks and so forth. I heard a statistic, and maybe it is true or maybe it is not: Merck said they believe that 50 percent of its profits came from Israeli companies or universities, to give you the idea of the hole that needs to be filled.

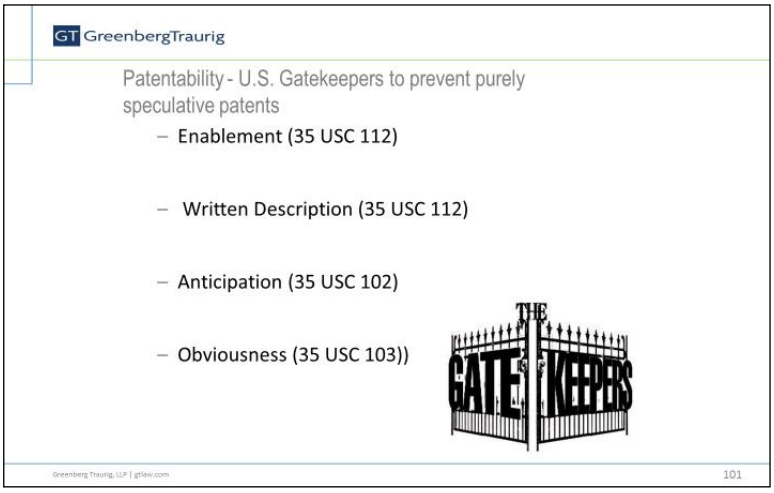
I think I fill part of that hole by being able to get some type of patent that an investor can look at. We can argue the strength or not, but it is a patent that an investor feels that at least we are extending the life of a patent. That is what today's presentation is about.



I call this my "U.S. Prosecutor's Toolkit." I view that there are four areas that I can get a patent in the life science area. I am going to go through each one of these and talk about their strengths and their weaknesses:

- Change method indication;
- Change treatment regimen;
- Change formulation; and
- Combination therapy.

I think when an inventor comes to me I can put it in one of those buckets.



Enablement, written description, anticipation, and obviousness we have talked about. In the United States we do not really have what is called plausibility. The closest thing to plausibility would be these four elements plus utility.

GT GreenbergTraurig

Enablement & Written Description

- Written Description
  - The written description requirement serves "both to satisfy the inventor's obligation to disclose the technologic knowledge upon which the patent is based, and to demonstrate that the patentee was in possession of the invention that is claimed." Capon v. Eshhar, 418 F.3d 1349, 1357, 76 USPQ2d 1078, 1084 (Fed. Cir. 2005).
- Enablement
  - "The test of enablement is whether one reasonably skilled in the art could make or use the invention from the disclosures in the patent coupled with information known in the art without undue experimentation.". *United States v. Telectronics, Inc.,* 857 F.2d 778, 785, 8 USPQ2d 1217, 1223 (Fed. Cir. 1988)

Again, Charlotte talked about enablement and written description, so I am not going to touch those. I am going to very quickly through these slides.

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Anticipation

- A claim is anticipated only if each and every element as set forth in the claim is found, either **expressly or inherently** described, in a single prior art reference." *Verdegaal Bros. v. Union Oil Co. of California,* 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987). (Emphasis added)
- The claiming of a new use, new function or unknown property which is inherently present in the prior art does not necessarily make the claim patentable. See *Atlas Powder Co. v. IRECO Inc.,* 190 F.3d 1342, 1347, 51 USPQ2d 1943, 1947 (Fed. Cir. 1999).)
  - However, the discovery of a new use for an old structure based on unknown properties of the structure might be patentable to the discoverer as a process of using. *In re Hack,* 245 F.2d 246, 248, 114 USPQ 161, 163 (CCPA 1957).
  - However, when the claim recites using an old composition or structure and the "use" is directed to a result or property of that composition or structure, then the claim is anticipated. *In reMay,* 574 F.2d 1082, 1090, 197 USPQ 601, 607 (CCPA 1978)

I will start with anticipation. In the United States the reason a method-of-treatment claim is very hard is mere recognition of an inherent property is not patentable. That is a very fundamental principle we have in the United States. Again, if somebody is working in the cancer area and they have a compound and they determine that now it can be used for lupus, the first problem I have is if that cancer patient also suffered from lupus, then I've got an inherency problem because I have the same patient that was treated and all I am doing is merely recognizing an inherent property.

The biggest problem in the United States that we have is being able when you are getting a new use or a new method and I will go to a claim on that.

Obviousness

- *Graham Factors for determining obviousness (Graham v. John Deere Co., 383 U.S. 1 (1966))*
- *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398 (2007) – Supreme Court invokes "common sense" and "Obvious to Try" as rationales for obviousness.
  - Common sense teaches us that familiar items may have obvious uses beyond their primary purpose, and in many cases a person of ordinary skill will be able to fit the teachings of multiple patents together like pieces of a puzzle."
  - "When there is a design need or market pressure to solve a problem and there are a finite number of identified, predictable solutions, a person of ordinary skill has a good reason to pursue the known options within his or her technical grasp. If this leads to anticipated success, it is likely the product not of innovation but of ordinary skill and common sense. In that instance the fact that a combination was obvious to try might show that it was obvious under § 103." (Emphasis Added)

The other area is my friend *KSR*. Everyone knows *KSR*. We live with *KSR*. *KSR* I said changed the world. My biggest argument to an examiner was "it was obvious to try." The U.S.

Supreme Court turned around and said, "Obvious to try is the greatest way to show obviousness." So *KSR* has really changed our world in every area, but clearly in the life science area.

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A Glimmer of Hope?

> Genzyme v. Dr. Reddy (Fed. Cir. December 18, 2017) - When a USPTO Examiner relies on an article (e.g. a journal article) that includes an **"isolated sentence, without explanation," and without supporting testing** to allege that the article is a teaching for obviousness purposes, *Genzyme* may be useful to counter that this teaching **does NOT provide a "reasonable expectation of success"** when **combined with evidence of unpredictability in the art**.

But there is very recent case law, *Genzyme v. Dr. Reddy*, December 18, 2017, from the Federal Circuit, that gives me a glimmer of hope. I will read this decision because I think it is a wonderful case dealing both with anticipation and obviousness. The court said: When a USPTO Examiner relies on an article (e.g. a journal article) that includes an *"isolated sentence, without explanation," and without supporting testing* to allege that the article is a *teaching for obviousness purposes*, *Genzyme* may be useful *to counter* that this teaching *does NOT provide a "reasonable expectation of success"* when *combined with evidence of unpredictability in the art*. So they basically said reasonable expectation of success means reasonable, so simply an isolated sentence is not reasonable in the unpredictable art — which, luckily, in the life sciences you guys are living in.

Why is that extremely critical? Because many a time when I am dealing with a university professor who writes an article, in the last sentence of her article she usually speculates that "by the way, in addition to cancer this can be used for ……" and every single indication in the world. We fight that every day. The examiner will look at that paragraph and say, "Hey, they did say it was for lupus."

I think this is a glimmer of hope. There are a couple of cases like that in the Federal Circuit in the last year that go after that same principle, that you can at least argue that that is not obviousness.[17] Now, anticipation is different, but for obviousness it gives me a glimmer of hope.

Change Method Indication

> Compound A is a known cancer therapeutic and you discover that it can be used to treat lupus
  - What's the evidence? Incorporate into Specification:
    - Need art accepted in vitro model of disease or animal model of human disease (enablement/plausibility)
    - Emphasize and develop evidence of surprising results
  - What's next? Know the Prior Art:
    - Think about potential overlap in patient populations
    - Understand doses used, modes of administration
    - Teaching away from your indication
  - Being overly inclusive can be problematic in future

Change of method indication: basically in other words — let me put up a claim because I am a patent geek and I love claims.

[17] *See, e.g.*, *Metalcraft of Mayville, Inc. v. Toro Co.*, 848 F.3d 1358 (Fed. Cir. 2017); *Meiresonne v. Google, Inc.*, 849 F.3d 1379 (Fed. Cir. 2017); *Rovalma v. Bohler-Edelstahl GmbH & Co. KG*, 856 F.3d 1019 (Fed. Cir. 2017).

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Draft Claims Based on Understanding

A method for treating a subject afflicted with lupus, the method comprising administering a therapeutically effective amount of Compound X to the subject.

A method for treating a subject afflicted with lupus, the method comprising administering a therapeutically effective amount of Compound X to the subject, wherein the subject is not known to be afflicted with cancer.

Common Obstacles: Anticipation (Inherency), obviousness.

You have a claim: "A method for treating a subject afflicted with lupus, the method comprising administering a therapeutically effective amount of Compound X to the subject."

Or you can write it negatively: "A method for treating a subject afflicted with lupus, the method comprising administering a therapeutically effective amount of Compound X to the subject, wherein the subject is not known to be afflicted with cancer."

Common Obstacles: Anticipation (Inherency), obviousness. Again, this is the world we are living in — anticipation.

This is my classic method-of-treatment claim. The only way I can get around it is to make sure I exclude another group. Again, a very hard claim to get because when you are taking over something, if someone talks about cancer, they are typically talking about another area; or, even if it is not, if they are afflicted with that, you have inherency. So in my view this is the most impossible claim to get, but I also posit that I am not sure it is the claim I want.

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Change Treatment Regimen

- Mode of administration: systemic v localized; oral, intravenous, subcutaneous, localized (via e.g., injection), topical (skin, lips), aerosolized, anal, vaginal, intrathecal
- Timing /frequency/duration of administration
  - Example of Claim: A method for treating a subject afflicted with lupus, the method comprising administering a therapeutically effective amount of Compound X to the subject, wherein the Compound X is administered at less than 50 mg/kg at a frequency of twice per day.
  - Reasoning: Compound X is used at higher doses (e.g., > 75 mg/kg) and 3X per week) – cancer treatment requires higher dose and greater frequency (=higher toxicity)
- Common Obstacles: Written description and enablement.

Change treatment regimen — I love it. These are the greatest claims in the world. Now I've got all the parts in my toolbox.

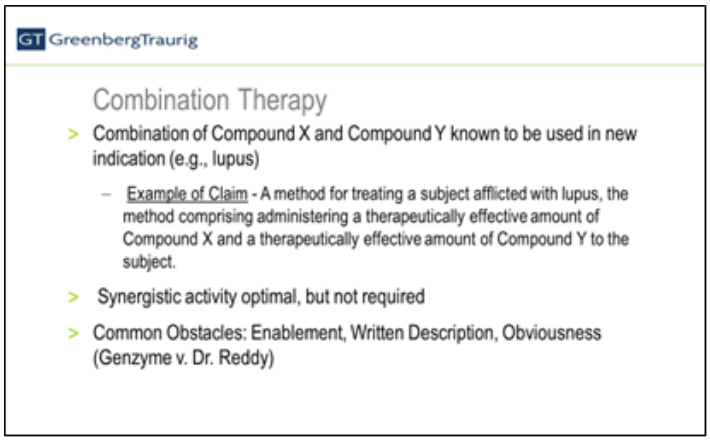
If it was orally given before, now I've got intravenous; if it was subcutaneous, now I've got localized; if it was topical, now I've got aerosol; if it was vaginal, now I've got other directions. This is a great claim. This is the claim that I love because it is a broad claim because now I am just changing the treatment regimen.

The other treatment regimens are like "something for five days over five hours" and so forth. I hate that type of claim because, as has already been said, that is a claim that a doctor can write off-label. If there are 50 milligrams of a certain drug that is being made, now if all I am doing is just a different treatment

regimen, that doctor can go off-label and I cannot get that doctor." Of course I can sue the doctor, but I would not want to do that.

That is why that claim that everybody thinks is a great claim, that says "X times per day for five days" is a problem. Again, the law of inducing infringement in the United States is problematic because we have a higher hurdle for inducing infringement.

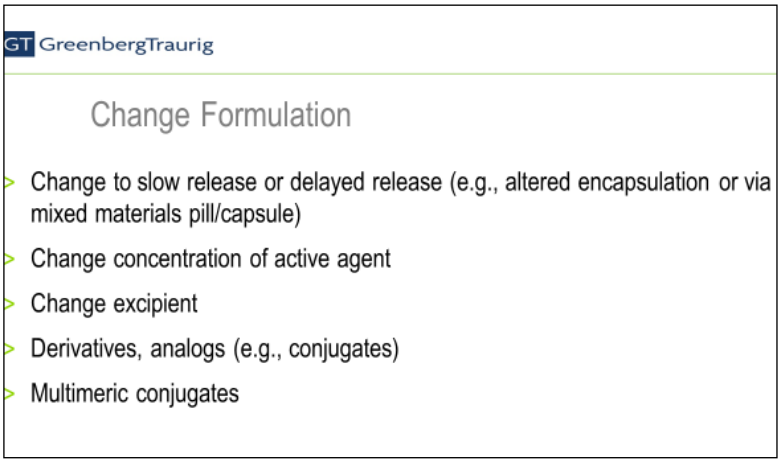
So again, treatment regimen is a cool claim because I can go after different administrations.



The next type of claim is combination therapies — fantastic claims. Again, I am trying to pitch that there are a lot of ways the U.S. system can extend. Combination patents are great. We constantly say, "Okay, using Compound X, can you use Compound Y with it and can we find some synergy?" I am a patent lawyer. The researchers have to go do that. But the answer is lots and lots of patents in that area.

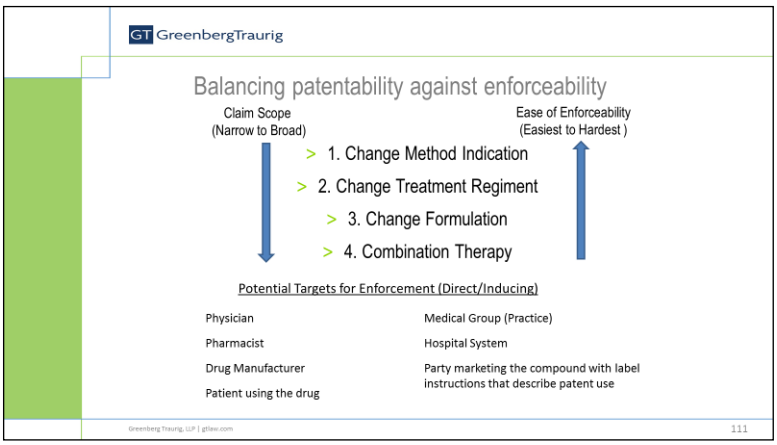
Synergy is found. Is it hard? Yes. But if you find synergy it is a home run with regard to the Patent Office.

That is where we try to talk about, "Okay, you have thought about this compound; can we put it with this compound?" In other words, two compounds off-patent but now we have combination. Combination patents are wonderful patents and patents we get all the time.



Finally, change the formulation. This is the classic patent we all get. The idea of slow release, delayed release, concentration of active agent, changing the excipient, derivative analogues — this is also another thing in my toolbox.

Great claims. I can get lots of these different claims.



I am going to finish with this slide. I know there was talk yesterday about enforceability. When you are looking at scope of claims, the broadest scope of the claim is change of method indication. But those are the hardest claims to assert against someone because, again, with a method claim how do you know that the doctor is prescribing the same compound that is off-label to other people for other areas? Very hard to get.

Combination therapy claims, on the other hand, the exact opposite: if no one has ever put those two compounds together and I have a pharmaceutical company or a pharmacist or a hospital group putting those compounds together today, if they never worked together before, I've got them for inducing infringement.

When you are thinking of scope of claims you have to think about different ways. My takeaway is I think the U.S. system is somewhat working and is helping the startup community substantially.

MS. LOVE: Great. Thank you, everyone.

Are there any questions from the floor?

QUESTION [Chris Loh, Fitzpatrick Cella]: This is a question to Dr. Michael Eder and Frits. In the United States, we see a lot of the plausibility/ operability law being confined to the pharma area. In Europe and in other jurisdictions, do you also see the trend where operability is a unique burden for pharma patents, or do you see it in other areas, and are there other teachings from other technologies that might shed light on how to better apply this principle?

MR. EDER: I think it is relatively specific to at least the chemical area, so all the mechanical arts and electronics patents do not know about this; thus, the problem is unheard of. But in the chemical field I would say it is universally applied.

MR. GERRITZEN: The specific patents that we are talking about today have, of course, the background of being filed by those who are in a bit of a rush to get a patent application, and that needs to be balanced with should we wait for more data. So you might have patents in there that are more open to such arguments being raised.

MS. LOVE: Great. Let's thank our panel, and they will be available during lunch if anyone has any other questions.

[Session adjourned: 12:05 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 – 12:08 p.m.

Session 2E:
The Politics of Incentivizing SMUs – Presentation & Discussion

Moderator:
Sarah Frederick
Partner, Goodwin Procter LLP, Boston

Presenters:
Tim Molino
Peck Madigan Jones, Washington D.C.

Prof. David Ridley
Faculty Director, Duke University Health Sector Management Program, Durham

Panelists:
François Houÿez
Director of Treatment Information and Access, Policy Advisor, EURORDIS, Paris

Suzanne Munck
Chief Counsel for Intellectual Property and Deputy Director of Office of Policy Planning, Federal Trade Commission (FTC), Washington D.C.

Margaret Kyle
Chair of the Intellectual Property and Markets for Technology, MINES ParisTech, Paris

* * *

MS. FREDERICK: Good afternoon, everyone. We are the panel about the politics of incentivizing secondary medical uses.

We have heard a lot of potential solutions and we have heard a lot from economists, physicians, pharmaceutical companies, and other stakeholders. This panel is directed toward how do we achieve some of these and what are the incentives and what are the obstacles.

I am Sarah Frederick. I am a Partner at Goodwin Procter in Boston. I focus on pharmaceutical litigation, mainly in the regulatory, antitrust, and product liability space. I am excited to be here in the nation's capital during an interesting time to be talking about politics.

Our first panelist and presenter is Tim Molino. He is a biologist and a lawyer, a former patent litigator, who then transitioned over to Congress, where he worked on antitrust policy in the Senate Judiciary Committee before becoming Chief Counsel for Senator Amy Klobuchar, which coincided with the passage of the America Invents Act (AIA). He is now a lobbyist with Peck Madigan Jones, and is tasked with trying to get people who agree on nothing to agree on something. He has prepared a few remarks to set the stage for our discussion this afternoon focused on today's political environment and how that poses challenges, and perhaps opportunities, for the subject of our conference.

MR. MOLINO: Thank you. I am glad that we can be here.

I actually had an email conversation last night, to show how well politics is working in the United States, with Suzanne Munck from the Federal Trade Commission (FTC), who said, "You have to excuse me, but I may not be there tomorrow because if the government is shut down I am not allowed to come to this event," highlighting where politics is right now in the United States and the challenges that anyone has when trying to make changes to the law to improve our policies in an environment where we have had two government shutdowns over just funding the government in the last month. It is challenging.

A little background. I am a patent attorney by trade, near and dear to my heart. Although I call myself a recovering patent attorney, it is the best thing I ever did — no offense to those who are out there still working in that field.

Most importantly, my time in politics has taught me that making policy changes is not easy. Everyone in the room can sit here and say they agree with the ultimate outcome, but it is not easy.

Let's start by looking at the American Invents Act and how long that took. Bob Armitage is here, who has been stalwart in that effort. It started in 2002 or 2003, when the first real effort to get something moving on patent reform started, and it did not get signed into law until 2011. It was a large, sweeping piece of legislation. What we are talking about here we could say is focused on only one aspect of patent law, but that just shows you the challenges of trying to get something together.

There were many machinations of the America Invents Act, or patent reform, before it actually was signed into law. When you look at the law, some of the discussion today is nobody is certainly happy with where it ended up, although I agree with those who thinks that patents are still important and that the patent system overall is still working.

One thing to think about as we discuss the challenges on the political front, making policy changes that help advance the goals of the medical and

pharmaceutical community, is during the entire process that we went through in the America Invents Act a lot of things happened. A lot of those things would not have happened but for the political environment in Washington, D.C. I do not mean the political environment of the dysfunction, but the idea that Congress was constantly talking about patents and patent reform.

Because of that, you can certainly look at the Supreme Court, which took up more patent cases in the last fifteen years than it had taken up in the thirty years before that. You had regulatory agencies getting involved in trying to hone in on abuses within the patent system. You also had at the time a Patent and Trademark Office (USPTO) Director who was respected by both sides of the debate and who was willing to put a lot of his political capital into getting something over the finish line. As many of you may know, as of this Monday Andrei Iancu was confirmed as the new USPTO Director, so that is another step in the right direction.

My major point is that it is very hard to actually make a real policy change that helps the world. But, at the same time, I think it is possible, and people should think about it not just in the short term or not just fall in love with whatever idea you come up with today or you come up with in the next month or two or next year. This is a long-term project, as you are always constantly coming up with ways to improve the system.

Thank you.

MS. FREDERICK: Thank you, Tim.

That is a good segue to the panelist to my left, Prof. David Ridley. You heard earlier today about his role in both the paper in support of priority review vouchers and then getting it through Congress in eighteen months in 2006−2007. I think there is an interesting story to tell there in terms of how that actually was achieved, with all the different stakeholders and players at the time.

Now that we can look back at it, here in 2018 — how has it worked? Has it worked as intended? And, over time, are there things that we should think about when implementing new solutions or crafting solutions for the future?

With that, David, I will let you speak.

PROF. RIDLEY: Thanks, Sarah.

I think there were four important steps taken by Henry, Jeff, and me as we tried to move our paper[1] to law. Let's go from easiest to hardest.

• The easiest was identifying interested legislators, although, as outsiders, we didn't immediately know the relevant legislators. I presented our proposal at a press conference, and a reporter told me afterwards that Senator Brownback would like it, and he did. However, Senator Brownback is a Republican and Democrats controlled the Senate at the time, so it was key that he brought in one of the more progressive members of the Senate, Sherrod Brown, and they worked together. That bipartisanship was special, I think.

• Second, we needed a legislative vehicle. We were lucky that in 2007 (and then again in 2012 and 2017) Congress was reauthorizing the Prescription

[1] David B. Ridley, Henry G. Grabowski & Jeffrey L. Moe, *Developing Drugs for Developing Countries*, HEALTH AFFAIRS, Vol. 25, No. 2 (2006) at 313−24, *available at* https://faculty.fuqua.duke.edu/~dbr1/research/developing-2006-preprint.pdf.

Drug User Fee Act (PDUFA), so we just tagged along with that. We were lucky that there was already legislation to which we could attach.

• Third, it might have helped that we were outsiders and that pharma kind of shrugged at the priority review voucher. Pharma shrugged, in part, because we were not talking about a huge prize. We predicted that it could be worth as much as $300 million. So pharma was not that interested. In some respects that might have helped, because I do not know that Senator Sherrod Brown would have sponsored the legislation if it looked like it could be a handout to large pharmaceutical manufacturers. So maybe being an outsider helped, although I can also see that having the backing of pharma would attract different members.

• Fourth, a key component — and this is a little harder to replicate — was that the voucher was free; it was off-balance sheet. We identified an inefficiency, and that was the value of faster review. Priority review can be worth hundreds of millions of dollars while the cost to FDA is only a couple million dollars. So pay an extra user fee to FDA of a couple of million dollars and we think we have something.

• Earlier, Connie talked about closing inefficiency. However, I like that the inefficiency existed because then we could grab it and use it over here. But, in general, if you can find some inefficiency and/or find something free and/or find something that is not so transparent, that is a helpful mechanism.

• You also asked about lessons. We got some things wrong, such as FDA notification and the language on unlimited transferability. We fixed those, but other problems remain. We continue to try to figure out access: now that we've got a drug; how do we get it to people?

• Finally, we got more vouchers than we expected. We did not realize that Congress would extend eligibility to rare pediatric diseases. We expected maybe one voucher per year and instead we see five vouchers per year. In many ways that is helpful for establishing the market, making investors feel more comfortable about it. But we do worry about the price being a little low as a result.

MS. FREDERICK: Thank you very much.

Next is François Houÿez. There was a comment yesterday that people were interested in hearing from the patient perspective. I am happy to say that François comes from that perspective. He is a patient advocate. He has been working in the field since the early 1990s, when he worked with HIV/AIDS advocacy groups to ensure earlier access to what became lifesaving medicines for them. He is based in France and works at the European Organization for Rare Diseases (EURORDIS). He has prepared some remarks on how patient groups can play a role in advocating for faster access to medicines for unmet needs.

MR. HOUŸEZ: Thank you, Sarah, and good afternoon.

The irony is that I left HIV and AIDS in 2002, when the debate was much more on access issues in the developing countries, discussing patent rights and intellectual property, and for my brain that was far too complex. So I decided to leave HIV/AIDS and I moved to rare diseases where patients were advocating for

innovative products. I thought that now I could get rid of these complex issues on patents and IP. So here I am (ironic).

Thank you to the organizers for inviting me to these fascinating discussions, which of course we understand the importance of.

EURORDIS was really created precisely not at the request of patients but of Member States that were pushing in the European Union for the adoption of an Orphan Drug Regulation. They quite rapidly noticed a stronger position from parts of the European society that were opposed to new incentives for industry, which they called "gifts to industry," saying, "They have enough; it should be mandatory for them to develop orphan medicinal products; we should not give them any rewards for that; it should be easy and automatic." This opposition had some voice at the European Parliament. Some Member States called some existing patient organizations and said, "Maybe the voice of the patients should be heard at the European Parliament. Is there a way a coalition of patients could be organized?" That is how EURODIS was created in 1997.

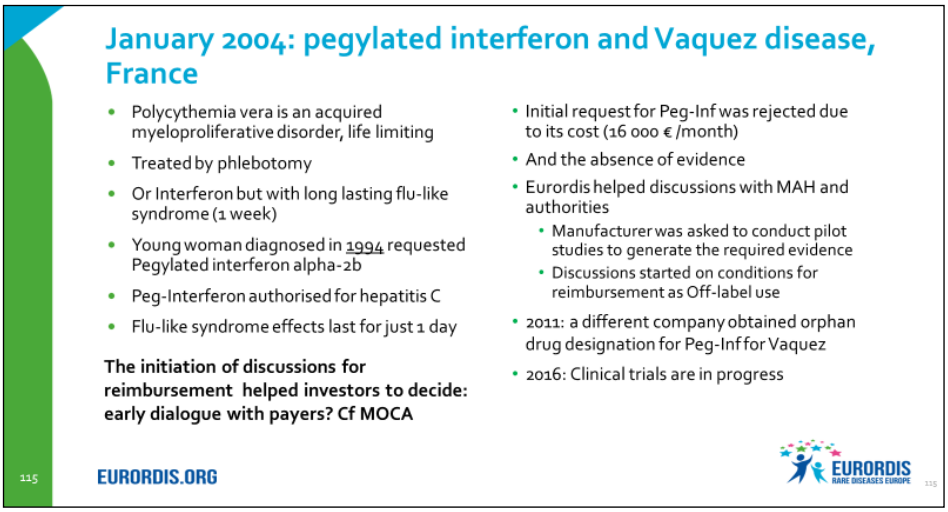
We rapidly identified 120 other patient organizations in Europe, and we decided to support that legislation because we saw the point of that legislation, but by doing this we wanted to participate through this effort in providing a favorable environment for the development of these medicines.

The incentives are one thing, and they certainly are very important, but the fact that society is sending a message to all investors — "we are now ready to help and support the development of products for these diseases" — apart from the incentives, certainly had an effect.

We proposed to play a role. We want to have full responsibility in these policies, not only by supporting the adoption, but now all members participate at the European Medicines Agency (EMA). Members of the committee that designates orphan medicinal products and other committees, like the Pediatric Committee, accompany all members to scientific advice and protocol assistance discussions at the EMA. We continue to contribute to policy reviews in the field of pharmaceuticals, and to tackle and address all the difficult issues that we are encountering for the development of more products.

In two weeks we will invite all interested parties to a series of regular workshops precisely on the issue of incentives for rare disease therapies.[2] Do we get what we incentivize? Do they bring what we expected they would bring, not only for second medical use, but for other types of incentives?

I would like to show you a few examples of some activities that can generate proposals for new policy developments.



This case was brought by a patient who contacted us in 2004. That person had Vaquez disease, which is treated by phlebotomy or interferon. At that time she could only get daily injections of interferon and she was asking for pegylated interferon as an off-label use. That was authorized already for hepatitis C. The difference for her was that with the pegylated interferon she would have the side effects only for one or two days instead of continuously with the other one.

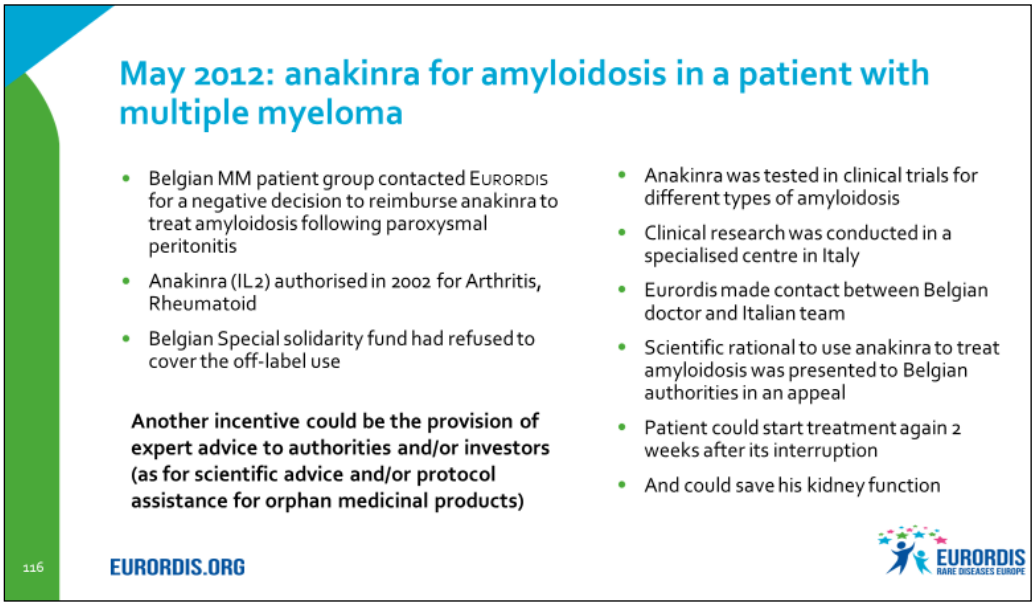
The initial request was rejected due to the cost and the absence of evidence. After she contacted us, we started negotiations with the manufacturer — "could you maybe develop clinical trials for this new indication?" — and, at the same time, with the authorities to see if there were possibilities to reimburse this pegylated interferon for Vaquez disease systematically, not just on a case-by-case basis, to facilitate the life of patients.

What happened is that a different company obtained the orphan drug designation and now it is conducting clinical trials. I think this had an impact on the second company, that patients themselves engaged in discussions with the authorities about finding a way this second use can be supported by authorities.

Now in the French regulation we have what they call the Recommendation for Temporary Use (RTU), which is not a marketing authorization for an off-label use or a second medical use, but which temporarily authorizes a company with a duty of collecting data on efficacy and safety to provide this treatment for the second use, and the patient's treatment can be reimbursed and covered by the healthcare system.

[2] See EURORDIS, 26th EURORDIS Round Table of Companies Workshop, Rare Disease Therapies: Do We Get What We Incentivise? (Feb. 21,2018), https://www.eurordis.org/publication/26th-eurordis-round-table-companies-workshop.

In addition, we are participating in the Mechanism of Coordinated Access (MoCA), which is a very early dialogue among investors, developers, and the payors, where the developers present their project and explain which issues they can anticipate in terms of high cost or complex organizational aspects of the treatment delivery so that the payors and the healthcare systems can prepare themselves for the arrival of those kinds of products.



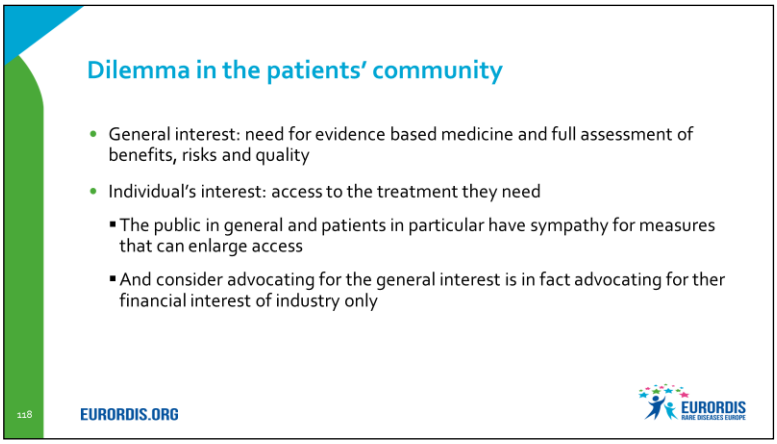
Another example was a patient with multiple myeloma. We were contacted by a Belgian organization for multiple myeloma about a patient who had difficulties being reimbursed for a product for treating amyloidosis.

We learned that the product was in fact tested in clinical trials and there was a specialized center in Italy conducting research. We made the contact between the Italian researcher and the Belgian doctors to make an appeal to the Belgian authorities. We provided all the information. In some cases, clinicians were surprised to realize that there was this discussion because for them anakinra was a treatment of reference already. Finally, the patient won the appeal and could start treatment two weeks after its interruption, and that saved his kidney function.

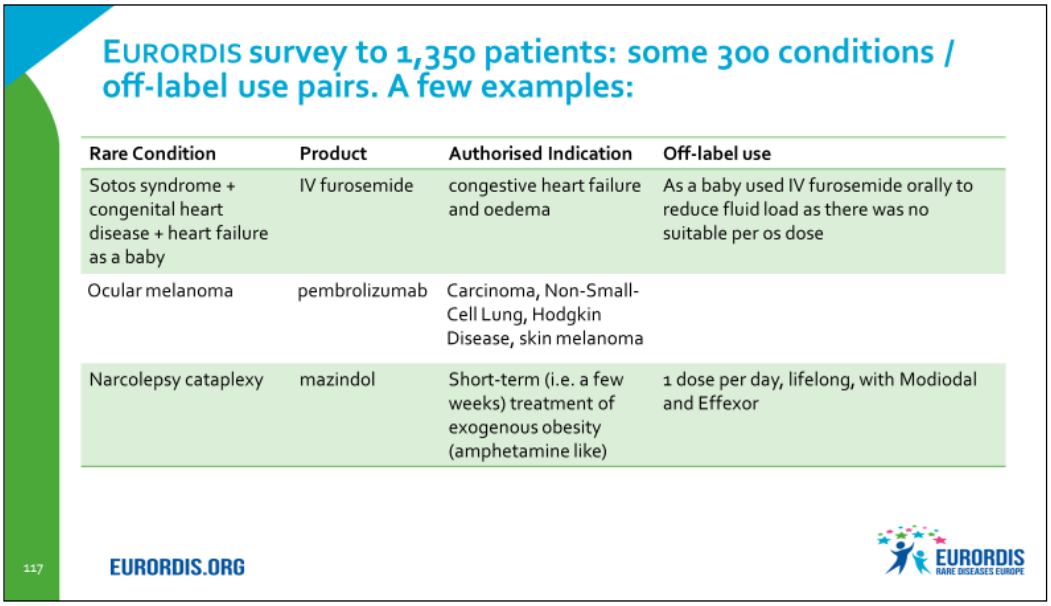
This is how we generated the idea that maybe we need a group of experts — they could be, for example, experts at the EMA — who, on the request of some Member States, would have such discussions as would this off-label use be of interest to patients and what new evidence needs to be generated for this second medical use not to become fully authorized, but with enough presumed efficacy for authorities to accept that use.

We have collected many, many other cases from patients about different off-label uses, some which are being explored, some which could be explored.

The International Rare Disease Research Consortium (IRDiRC) has different projects, like DrugNet or Homopharma, to analyze which repurposing of medicines could give birth to second medical use in rare diseases. It is making great progress in the scientific aspect, but what is lacking is the policy development to accompany this research effort, with all the difficulties that you know.



I would like to finish this brief introduction with the dilemma in the patients' community. There is a lot of sympathy among many patient groups for Member States which take initiatives to substitute for an authorized product an unauthorized product at a lower price. This is a debate we have with them because, even if it can enlarge access to the treatment — and we understand why patients are pushing for that — there is the general interest which says, "We need evidence, we need marketing authorization for these off-label uses, particularly when they concern a certain number of patients."

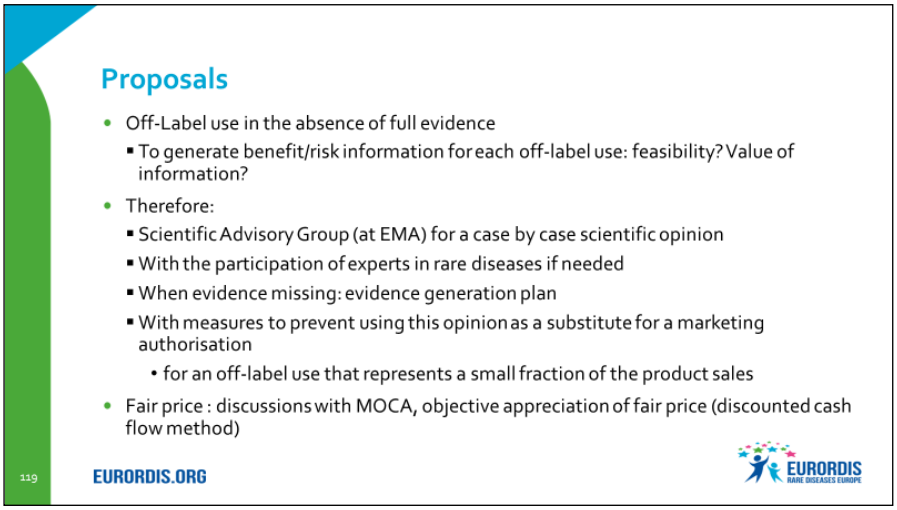


Rare Condition	Product	Authorised Indication	Off-label use
Sotos syndrome + congenital heart disease + heart failure as a baby	IV furosemide	congestive heart failure and oedema	As a baby used IV furosemide orally to reduce fluid load as there was no suitable per os dose
Ocular melanoma	pembrolizumab	Carcinoma, Non-Small-Cell Lung, Hodgkin Disease, skin melanoma	
Narcolepsy cataplexy	mazindol	Short-term (i.e. a few weeks) treatment of exogenous obesity (amphetamine like)	1 dose per day, lifelong, with Modiodal and Effexor

It would be detrimental to the general interest if this research for second medical use would not continue to the marketing authorization. That is when patients say: "Okay, but if then the price is higher afterwards, there is no benefit for us even if the treatment is reimbursed." We have many cases of that kind; for example, a second medical use for Celebrex to treat a rare disease, where, even if the price difference was only 5 percent, no patients were receiving the product as authorized for the second medical use.

As opposed to another one, which was sildenafil (Viagra) second medical use for treatment of pulmonary hypertension. The price difference was 30 percent, but in a completely different context. Patients who needed it to be treated for pulmonary hypertension did not feel comfortable receiving Viagra boxes. The men and the women were not comfortable using Viagra, knowing what the

product was for. When the generic of Viagra came out, then all patients switched from Tyvaso to Viagra because the package was not called "Viagra" anymore but sildenafil-something, and they were comfortable using that product. A different story of the product and the environment, the context, in which the patients are living, where they would accept, more or less, to use a product on a different basis.



To finish the discussion that we are having, we cannot have marketing authorization for all possible off-label uses in rare diseases, but there is probably a threshold, a number of uses of prescriptions above which the companies should generate evidence, should collect data, and we should push that company to obtain marketing authorization. Where to put this threshold and what to do for the others?

Patients with rare diseases are entitled to the same quality products as other patients. So can we accept this gray zone of off-label use with uncertainty on the evidence of efficacy and safety? This is still an open debate that we have.

Thank you.

MS. FREDERICK: Thank you, François.

Actually you raised an issue at the end of your presentation which is one I want to turn to Margaret Kyle to talk about.

Margaret has joined our panel. She got out of the snowdrifts of Paris and made it here today. She is Chair of Intellectual Property and Markets for Technology at MINES ParisTech. She is a prolific researcher and writer, including on R&D productivity in the pharmaceutical industry, but also interacts regularly with health ministers in France, and I think throughout Europe as well, on issues related to the industry and pricing.

I am curious what your take is from your perspective on the issue of differential pricing. The idea has come up a few times throughout the last two days that someone may have been getting a drug and paying a $10 co-pay (which is how we would refer to it here in the United States), and then, perhaps the next month, because of the indication it is being used for, all of a sudden the patient is

being asked to pay $50. Has that ever come up in discussions with ministers in Europe and how has that played out?

MS. KYLE: I think actually when you discuss this with health ministers they are primarily concerned about what the health ministry is paying rather than the patients, because, in general, for patients the system is fairly generous in most European countries and governments have more control over the prices patients face than in the United States.

I want to also echo the point that François made about a concern that changing some policies in Europe is being perceived as a "gift to industry." There is a lot of resistance to that, particularly when it involves an extension to intellectual property of some sort.

The case of differential pricing is one that is a struggle both in thinking about different prices for different indications as well as different prices for different patient groups, because often drugs work better in some patient subpopulations than others. Indeed, differential pricing across countries remains something that Europe struggles with.

Pricing is a national competence. There is some recognition that probably the poorer countries — Bulgaria, Romania, etc. — should have lower prices than the Netherlands. But at the same time, if you are the health minister of the Netherlands — and when the Dutch had the EU presidency of the Netherlands, the health minister made drug pricing one of her main issues — it is difficult to explain to your own population why we are supposed to be in a common market and these other countries are getting much better prices on the same drug than you are in the Netherlands, or how do you justify spending all that money when these other countries are not.

For that reason, let me talk about the politics of second medical uses and what kinds of policies we could realistically expect, at least in Europe.

First, let's distinguish between the case of new chemical entities (NCEs) and generic drugs. For the NCEs, I think it is a hard case to make that there is a big market failure for the following reason. If you look at drug development projects over the last twenty years, more than 80 percent of them were in development for multiple indications. It is not like firms were not looking for multiple uses of a drug that they were working on. To me that is evidence that there is market expansion. Firms have an incentive to seek out new uses for the drug if that expands a market that they expect to have some protection around. Now, I do not know what the counterfactual is. Should it be 100 percent instead of 80 percent? I don't know.

But I think it is easier to make the case that for generic drugs there is a market failure, that there is not sufficient interest for industry to invest in developing new uses for these drugs that have generics already on the market. Where there is interest, I think, is the health ministers. Then, even though this is not a policy that is off-balance sheet or off-the-books, like David was talking about, it does have the lure of: "Look, if we can use cheap drugs to treat a new condition, that could generate lots of savings to the health system." That is an argument that might work.

We have with the European Union a mechanism for trying to coordinate this across multiple Member States, so there is pooling across countries. That actually in this case works perhaps in favor, because, in some sense, "it is somebody else's money; at least it is not all my money; this is a cost that is shared across lots of Member States."

That is where I would actually push to say: "Okay, the European Union, maybe through the EMA or maybe through one of the various directorates, can commission clinical trials looking for new uses of generic drugs. They do that for economic studies all the time, so surely they can do this for clinical work."

That might also provide some information about the true cost of running these trials, because I will say that the costs that are quoted for running clinical trials are met with some skepticism by most health ministers. So they can try and see if they can pull it off for a lot less than the quoted costs that we have heard.

MS. FREDERICK: Thank you.

Dr. Banerjee's presentation yesterday [see Session 1B] referred to nine drugs that have been fully genericized for which, through public funding, new uses have been developed. I am curious what that cost was, as just one data point.

I want to introduce our final panelist, Suzanne Munck, who comes to us from the enforcement side and, thankfully, was able to attend today. She is Chief Counsel for Intellectual Property at the Federal Trade Commission. She is a litigator and practices at the intersection of antitrust and patent law, which has been a big area in our country for the last several years. She was the patent lead on several high-profile cases where the FTC had alleged that generic entry was delayed due to an alleged payment from the brand to the generic company. We are very happy to have her perspective here today.

I want to pose to you a question, given your enforcement background. Of course there are no perfect solutions, but many solutions have been tried and have been implemented — things involving exclusivities and vouchers and tax credits. From your perspective from the FTC, are there any perhaps unintended consequences that happened that are learnings that we should take from those for the future when we are thinking about potential legislative or regulatory fixes?

MS. MUNCK: I will get to your question about the unintended consequences in a moment.

Thank you very much for including me here today. I am thrilled to be here. These are my own views, not necessarily those of the Commission.

What has been interesting to me, listening throughout the course of the day, is: how do you achieve changes and how do you explain that those changes are necessary?

If you are not familiar with the Federal Trade Commission, we have an enforcement obligation under the antitrust laws and the consumer protection laws and then we have a policy mandate through our statute.

In antitrust, when you are trying to establish that there is a need for an antitrust case, you need to establish that there has been harm to competition, not harm to you as a competitor. I think that framework carries over to the policy side of the mission. We frequently hear folks saying, "XYZ is either a harm to

innovation" or "XYZ policy could benefit innovation." But oftentimes that is being framed in terms of the benefit to a particular innovator.

Building on what other people have said today, I think it is important when you are looking at — as you mentioned, David — inefficiencies, cost, and transparency to think about your fix in terms of the potential benefits and harms to innovation across the board.

When we were preparing for this program we were talking about exclusivities. Several of you I have known for more than ten years because we were working together pre-passage of the Biologics Price Competition and Innovation Act of 2009 (BPCIA). I think that is a good case model for how the FTC from its policy side, from its commitment to strong patents and commitment to empirical research, will evaluate a presentation.

If you go back to 2007−2008, in the data exclusivity discussion of the BPCIA there was a question over how many years are necessary for that exclusivity, and ultimately we settled on twelve. The FTC used its policy role to really take a look at some of that research. Ultimately we did not take a position on the term, but we recommended that if you have data exclusivity of twelve years, what you are looking at is a pure profit state for the brand after the twelve-year period. That is an important data point to consider as Congress is evaluating what the potential benefits and costs are of certain behavior.

It is always hard to know what the unintended consequences are looking forward, right? That is kind of the nature of how they work.

When you look at the FTC's enforcement work, whether it be in pay-for-delay — I do not think anyone predicted pay-for-delay in the mid-1980s — Hatch-Waxman has obviously been tremendously beneficial for consumers, tremendously beneficial for generic competition, but you do not see that.

Then, when you were looking at the interchangeability provisions in the 180-day requirement, you saw a different type of 180-day provision in the BPCIA that was not keyed to entry of the generic.

To wrap up, I think my lesson is: When you are trying to persuade government actors to engage, focus on the benefits to the economy, focus on the benefits to innovation, focus less on how it is going to impact your specific company. While obviously that is massively important to you and your shareholders and that is the right position for you to be in, taking a step back and explaining why this intervention is necessary and why this intervention is better than where we are today are both going to be requirements for engendering change.

MS. FREDERICK: I think those are really good points and actually transition well into a question I want to pose to the panel, which is about stakeholders. Change does not happen without people who are there to drive the change. There are, obviously, a lot of different players in the market for pharmaceuticals — from the manufacturers and those people formulating and developing drugs; to the payors all the way down the line, a whole layer of payors; pharmacy benefit mangers (PBMs) in the United States who help negotiate prices; down to the patient; and the people who will benefit beyond the patient, the taxpayers, people who are funding these drugs for everyone.

I am curious to hear from the panel who has the biggest stake in this. Who might be the drivers here for some kind of change?

MS. MUNCK: I think it has to come from a coalition. You have to have people who appreciate the different roles that they play in the distribution system working together and each respecting that they are going to have to make some concessions in order for it to move forward.

MR. MOLINO: I would totally agree with that idea. It is not just a coalition, but you have to have — and to get a coalition you have to have this — some type of consensus. It cannot be viewed as a one-sided policy because we live in a world where no one side is going to get rolled. I think bringing multiple groups together and seeing if you can come up with something that satisfies or benefits a lot of them is important.

MS. FREDERICK: Related to that, are there any groups that people need to be particularly aware of that could be a block perhaps, that certainly need to be essential and onboard for any potential solution here?

MR. MOLINO: It is ironic to me. It was a big surprise when I got into the political side of patent reform to find out how important universities were. I think at some level if senators or congressmen did not want to choose between tech and pharma, they could always look there — "everybody has a university, so therefore we are safe and we are caring about constituents."

But I would say that once universities decided that they were okay with a certain provision or the overall legislation, that was very interesting to me. I thought that turned the tide of actually getting it done, after eight years of gridlock. That has always been a very interesting one for me, in addition to the usual players of the pharma industry, the generic industry, and patient advocates.

MS. FREDERICK: Margaret, you spoke earlier about a potential solution involving public funding in Europe and coordination among Member States for developing new uses for drugs that are generic. I am curious on a couple fronts about that: (1) is that a kind of solution that would be workable in the United States in today's political environment; and (2) if the information and the data were to come from the public side, is that the only speedbump that needs to be overcome in order to get those secondary uses out into market? Another role that pharmaceutical companies play is to spread knowledge about new uses for drugs. Were it to come from the public sector, how does that then translate into use and adoption by doctors and by patients?

MS. KYLE: That is a good point. I think that there are clearly some important differences between the way the U.S. market operates and the way the European markets tend to operate.

In particular, most European health systems already provide a lot of information to doctors to try to guide their prescribing habits. There are health technology assessment bodies that try to push the use of the most cost-effective drugs, etc., in part, because when you have roughly universal healthcare, the state has such a big interest in achieving those cost savings; whereas in the United States, because it is divided across many different payors, it is harder, I think, to get everybody onboard with a solution like that.

One other point which is related — should the United States be doing this; should Europe be doing this? — is David and I have looked at the ques-tion of public funding and the potential for free riding of governments on the spending of other governments. I think that is an impediment that we definitely should be talking about.

One response to my proposal from Europe might be, "Why should we pay for it, because information is a public good, and that information is going to benefit not just Europeans, that is going to benefit the Americans who have not paid anything to provide that information?" Of course, that is the argument that you might use against telling the National Institutes of Health that they should fund studies like this, because then that is going to benefit people in other countries, etc.

I think cooperation, at least among developed countries, on some of these kinds of points is certainly an impediment that we need to work on as well.

MS. FREDERICK: I now want to open up to questions from the audience.

QUESTION [Bruce Bloom, Cures Within Reach]: Margaret, what about thinking of what you just talked about, but do it in a social finance context, where the European governments do not have to pay until the success is proven? Private funds will fund the repurposing research and then the governments are only paying when there is success, and only for constituents in their own countries. We could set it up so that a country would never pay for the fact that it was helping people in other countries, although there would be benefits around the world. If you think there is a pan-European opportunity for moving this forward, social finance would remove a couple of the obstacles, such as "Why should we do this to benefit other people?" and "How much money is it going to cost up-front?" What do you think about that?

MS. KYLE: Why not try? I think, in general, one of the issues that we face here when dealing with multiple countries trying to reach consensus — we see the same thing with determining a prize: everyone agrees that we probably should move to some kind of prize for antimicrobial resistance, but there is a struggle as to how much each country should contribute. And, even if we have an estimate *ex ante, ex post* you might suddenly discover this huge patient population in a country that did not contribute very much but nevertheless benefits a lot.

I think it is easier said than done, obviously, but certainly something worthwhile pursuing as an option.

MS. FREDERICK: Are there any other questions from the audience?

QUESTION [Dr. Amitava Banerjee, UCL Farr Institute of Health Informatics]: As a physician in public health, looking globally at the things that have made HIV/AIDS, for example, work in terms of the politics was when access and human rights and the broader public was mobilized.

Another example which seems to work is a public health emergency in this country, like when there was a threat of anthrax or, recently, globally in terms of Ebola.

Third, whether we like it or not, we have a hierarchy of how we perceive diseases. So cancer is more emotive than other diseases. We talk about medical

need, but, in terms of science or objectivity, you could argue for other diseases as well.

I wonder if the panel could comment on those three and how they play out in the politics in relation to secondary use.

MR. HOUŸEZ: I think something which is key for any success of a coalition or a campaign to make advances in second medical use is, first, a name for that campaign. For rare diseases or orphan medicinal products, the simple terms "Orphan Drug Act" or "Family Health Care Decisions Act" legislation were really self-explaining for the public. The public could understand what that was because the word "orphan" is quite easy to understand. But "drug repurposing" or "second medical use" in itself is not enough to really mobilize troops in the population.

We certainly need a campaign. We certainly need to educate patient organizations and patients themselves so that they understand the issues which are at stake. Without that, I doubt we can make much progress.

For example, if we want to introduce prescription monitoring and to have patients disciplining themselves, and doctors as well to use one product for one indication and not the other one, for that we really need huge communication efforts.

MS. FREDERICK: Thank you very much. Our panelists will be around during lunch to speak further.

MR. CORDERY: Thank you, Sarah.

[Session adjourned: 12:52 p.m.]