

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.
February 8–9, 2018*

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*Georgetown University Law Center
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Thursday, February 8, 2018 – 8:30 a.m.*

**Session 1A:
Welcome and Introduction**

Prof. Jay Thomas
Georgetown University Law Center, Washington, D.C.

Prof. Robin Jacob
UCL Institute of Brand & Innovation Law, London

* * *

PROF. THOMAS: Good morning, everyone, and welcome to Georgetown. It is great to see so many old friends on my home pitch here at Georgetown. We offer you brisk weather, but at least the skies are clear, unlike last night.

We are going to have to scramble a wee bit because we had some French friends who cannot make it because of inclement weather in Paris. I have to admit I was a little skeptical of their accounts that they could not come, but then I heard the Eiffel Tower was closed due to snow. That implies a 325-meter tall snowdrift — an impressive achievement.

I am delighted to have helped put this conference together. I am grateful for the efforts of Brian Cordery and his team and Lisa Penfold of University College London, who have labored mightily to pull this together.

It is my task to impart certain stern admonitions to each of you.

First, there will be rigorous timekeeping. There will be draconian consequences if you do not observe your time limits. A timely conference is a beautiful conference.

There will be a transcript of this event. You will have a chance to review it, so just be aware that there will be some memorialization of your remarks.

Audience participation is welcome, and we do have a standing microphone over there. It is very helpful for these conferences if you identify yourself and your affiliation prior to speaking.

We do have Wi-Fi, but please no telephony during the events. If you can turn off your phone and keep it at a relatively low roar that would really be appreciated.

I have known Sir Robin Jacob for so many years, and it has just been wonderful to have a chance to work with him in person on this event. I present to you the doyen of international IP, Sir Robin Jacob.

PROF. JACOB: Good morning, everybody, to this quite extraordinary, different conference, a conference with so many different sorts of skills coming together with a single object. It is a conference with an object, not just a discussion.

The object is to try and find ways — or a way — of encouraging research into new uses for known medicines. If you find a new use for a known medicine, you have in fact really found a new medicine. You have put another arrow into the quiver of the doctor. It is just the same as if it had been a wholly new molecule or something else, a new treatment. That is why it is so important. And, because it is cheaper to do it than to find a wholly new molecule, it ought to be possible somehow to encourage it. That is the theme which we are following, and that is the reason we are going to do a book after this, a transcript.

I will just add a thing about the transcript. You will be sent the transcript pretty shortly after the conference by the shorthand writers, who are absolutely brilliant. Please correct it. It does not matter if you alter it a little bit to say what you wish you had said or whether what you said was wrong, because this is going to be part of the book, and then later a research assistant is going to try to turn this transcript into something like a book, and anything you think ought to be in there, any papers or anything, would be useful to send probably to me.

I want to say something about the sponsors. You will see them all named at the back. Again, it is a bit unusual to have pharma companies and lawyers. You can see why the pharma companies, and it is interesting that you have generic as well as innovative companies, as they are sometimes classed in two boxes.

But it is also interesting to see the firms of lawyers. They are not really here, and that is not the reason they contributed, because they want to advertise — yes, they want that, too — but it shows, I think, from these firms that they have a social interest, an interest in humanity, too. They are better than lawyers.

James Nurton, who used to run Managing IP and now is an independent journalist, is here. He will want to talk to many of you. If he comes up and says his name is James Nurton, talk to him. He is a very good egg.

That's about it. One other thing. I emphasize again timing. There is nothing worse than somebody overrunning, squeezing the people behind them. It is like standing on their toes. So the message to all of us is be very, very careful, don't say anything unless you really need to, and keep it short.

Away we go. First panel.

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*Georgetown University Law Center
600 New Jersey Avenue NW
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Thursday, February 8, 2018 – 8:45 a.m.*

**Session 1B:
Second Medical Uses: Missed opportunities,
clinical successes, and what the data tells us**

Moderator:
Dr. Marsha Rose Gillentine
Sterne, Kessler, Goldstein & Fox, Washington, D.C.

Presenters:
Prof. Graham Russell
NDORMS, University of Oxford, Oxford

Prof. Mondher Toumi
University of Marseille
[Transcriber's Note: Prof. Toumi was unable to attend this session, but made his presentation at 1:30 p.m. on Friday. The transcript of his presentation appears below at the end of the transcript of this panel.]

Panelists:
Dr. David Cavalla
Numedicus, Cambridge
Dr. Amitava Banerjee
UCL Farr Institute of Health Informatics, London

* * *

DR. GILLENLINE: Good morning. I am Marsha Rose Gillentine of Sterne, Kessler, Goldstein & Fox. I am a director in the biotech and chemical practice, and I work a lot with pharmaceutical companies dealing with patent and exclusivity issues related to their products.

Dr. Amitava Banerjee is a Senior Lecturer in clinical data science at the University College London, an honorary consult in cardiology at UCL in Bart's Hospital, and clinical lead for education at the Health Informatics Unit, Royal

College of Physicians of London. His interests in preventative cardiology evidence-based medicine and global health led to a Master's in Public Health at Harvard, an internship at the World Health Organization, and a Doctor of Philosophy in Epidemiology from Oxford. He has a longstanding interest in access to medicines, and his research particularly focuses on the Indian subcontinent and cardiovascular medications.

Dr. David Cavalla, founder of Numedicus Ltd, has thirty-one years' experience in various senior scientific and commercial roles within the pharmaceutical industry. He is currently involved with a number of biotech companies at board level. Previously he was founder and CEO of Arachnova, Ltd., a company focused on therapeutic switching. Previous affiliations include at Glaxo Group Research, Ltd. and Napp Research Centre. He is author of *Modern Strategy for Pharmaceutical R&D — Towards the Virtual Research Centre* and *Off-Label Prescribing: Justifying Unapproved Medicine*. He is one of the first advocates of drug repurposing and has used this strategy to create three first-in-class developmental products to have successfully passed Human Proof of Concept clinical stages. He frequently contributes articles on pharmaceutical strategy and is on the editorial board of *Drug Discovery Today*. Formerly he was Chairman of the Society for Medicines Research. He attained a first degree and PhD at Cambridge University and spent two years as a Visiting Fellow at the National Institutes of Mental Health (NIMH) in Washington, D.C. He is an author and inventor of over seventy published papers and patents.

Graham Russell is Professor of Musculoskeletal Pharmacology at Oxford and Sheffield Universities. He graduated in biochemistry from Cambridge University and spent his formative years in Leeds, Davos, Berne, Boston, and Oxford, where he completed his medical studies. He was Professor of Human Metabolism at Sheffield from 1977–2001, when he moved back to Oxford University as the first director of the newly established Botnar Research Center. His research interests are in skeletal biology and disease, and he is author of over 550 publications. His early work with Herbert Fleisch in Switzerland led to the discovery of the biological effects of bisphosphonates and to their eventual successful clinical use in the treatment of bone disorders including Paget's disease, cancer metastases in bone, and osteoporosis. Bisphosphonates continue to be the major drugs used worldwide to treat these disorders.

Graham very graciously stepped and agreed to do a presentation this morning at the last moment when our fourth panelist, Prof. Mondher Toumi, was not able to make it from France. His presentation is entitled "New Uses for Existing Drugs."

PROF. RUSSELL: Thank you, Marsha. Good morning, everyone.

We have an idea that the snow in France has something to do with Brexit, making it less attractive to go to Europe, but never mind. [Laughter]

Thank you very much for inviting me to this conference. I went to the last one in Seattle, and I recognize a number of faces from there.

By background, as you heard, I am a chemist/biochemist who turned to medicine and I have been fortunate enough to be associated with a class of drugs called bisphosphonates.. I was involved in the initial discovery of the bisphosphonates and they have been a lifelong interest.

I will use what we know about these drugs to illustrate some of the themes of the conference about how drugs that start off with rather simple indications end up showing up effects that might be exploited in other areas, including things like cardiovascular disease and so on. I will try to illustrate this with some examples.

I wouldn't be among lawyers were it not for Sir Robin Jacob, who presided over the first patent case I ever got involved in, just about twenty years ago. He has a considerable sense of humor, as you know, and we have a number of things in common: age; St. Peter's College, Oxford. For those of you who have not read his book,¹ I thoroughly recommend it to you. This is an unsolicited advert for his book, which is a joy to read. I did check on Amazon. It is still available, and the price has not gone down.

New Uses for Existing Drugs
The role of Serendipity!

<p>Thalidomide</p> <p>From morning sickness and medical disaster to treating leprosy and myeloma</p>		<p>Sildenafil (Viagra)</p> <p>From anti-hypertensive to treating erectile dysfunction and pulmonary hypertension</p>
<p>Finasteride</p> <p>From treating prostate enlargement to male baldness</p>		<p>Aspirin</p> <p>From pain killer to preventing cardiovascular disease and cancer</p>

One of the themes here is the role of chance observation that leads to identifying things that drugs do that they were not expected to do. Thalidomide, for example, started out as a medical disaster and ended up as a blockbuster drug particularly for the treatment of myeloma. The other examples given here — Viagra, finasteride, and of course aspirin — are well known to you. And there are countless others. David probably has a list of about 100-plus such examples.

I work in the area of musculoskeletal diseases, and these are very common. How many of you have never had a problem with a joint or back pain or anything like that — or I should say, how many have? Lots of hands should go up. [Show of hands] There you go.

And how many of you have a relative who has had a hip fracture, for example, and possibly died from it or shortly afterward as a complication? [Show of hands]

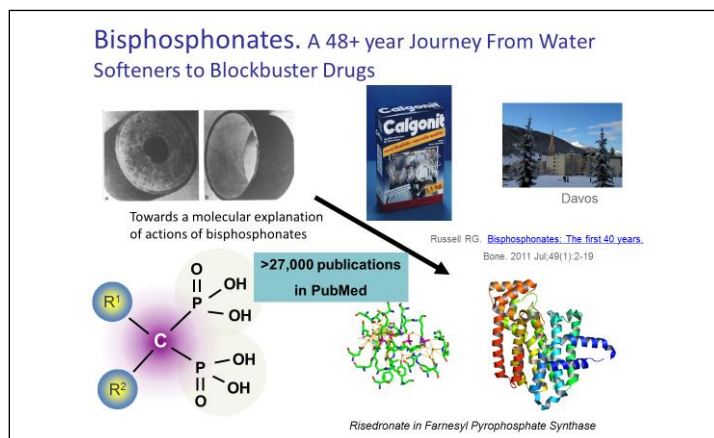
¹ ROBIN JACOB, IP AND OTHER THINGS: A COLLECTION OF ESSAYS AND SPEECHES (Nov. 5, 2015).

Musculoskeletal Diseases

- **Very common**
 - Fractures
 - Osteoporosis (>30% over 50)
 - Sports injuries
 - Consequences of trauma
 - Osteoarthritis
 - Rheumatoid Arthritis (1% of population)
 - Other types of arthritis (>100)
 - Pagets diseases (3% > 50 yrs)
 - Cancer metastases (breast, prostate), and myeloma
- **Less common**
 - >450 rare inherited diseases eg Brittle bones, dense bones etc

This is the area we are working in. There are a lot of very common bone diseases, and for osteoporosis in particular we now have effective treatments. They are not used as much as they should be for a number of reasons of patient identification and the rest of it.

But a really important area, too, which has some very interesting regulatory aspects, is rare diseases because many drugs for rare diseases are coming forward. There are 450 listed different genetic disorders of the skeleton, and at least a dozen of these now have very interesting new treatments. They are usually priced at an astronomical level, but, for whatever reason, payors seem prepared to pay, particularly because many of these sufferers are children.

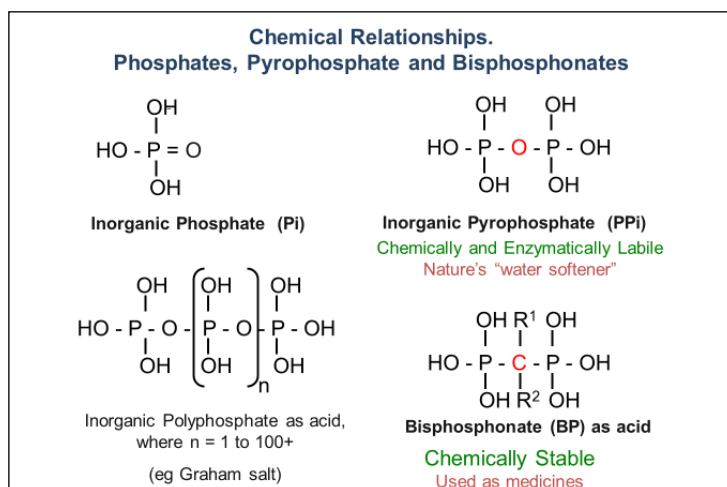


Bisphosphonates have a very interesting history, and you could call it serendipity. Davos these days is best known for the Economic Forum and so on, but it does have a research institute there that used to be devoted to researching tuberculosis. It was there that we hit upon the obser-

vation that bisphosphonate drugs could inhibit bone destruction and, therefore, be used to treat disorders of bone resorption.

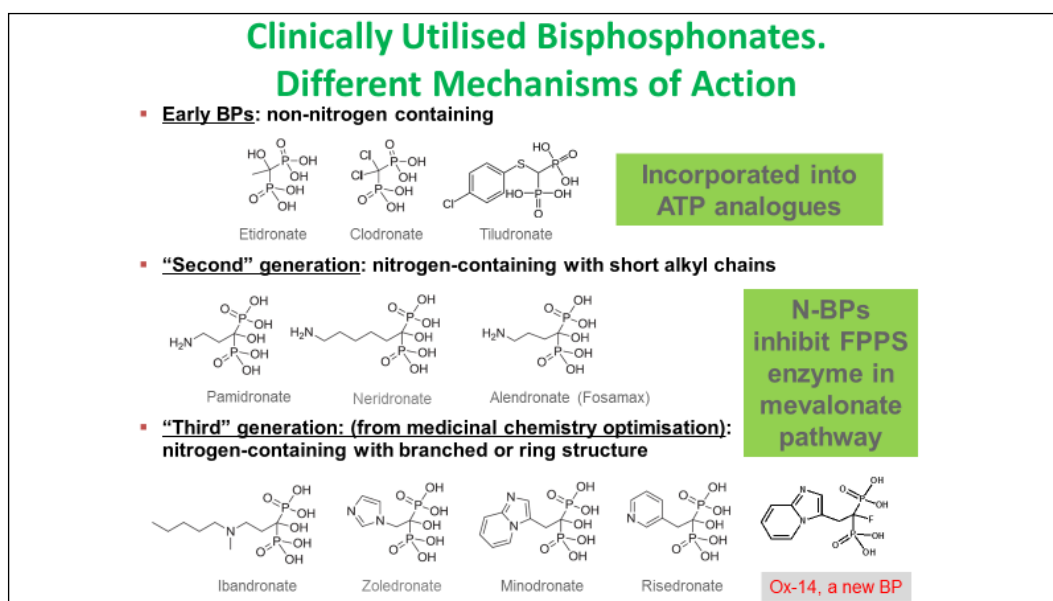
It started with a story about water softeners. Very closely related compounds, called polyphosphates, are used as water softeners, and you can see them in the old versions of things like dishwasher detergents.

When we first started out using these stable chemical analogues, we did not know exactly how they worked, and it took another twenty years to work out the mechanism. There is another story in that: can you patent the mechanism and start all over again?



How many of you can look at chemical formulas and not slink beneath your seat? Any unhappy would-be chemists out there? [Show of hands] This is actually rather simple. The water softener on the bottom left is just a chain of phosphates joined together with loss of water. Inorganic

pyrophosphate, up at the top right, occurs in the body, and if you have low levels of this you get vascular calcification, and if you have high levels you have defective bone mineralization.



The bisphosphonates are chemically stable analogues of pyrophosphate, so they do the things that we might have expected pyrophosphate to do, but have the advantage that you can give them without them being destroyed in the body.

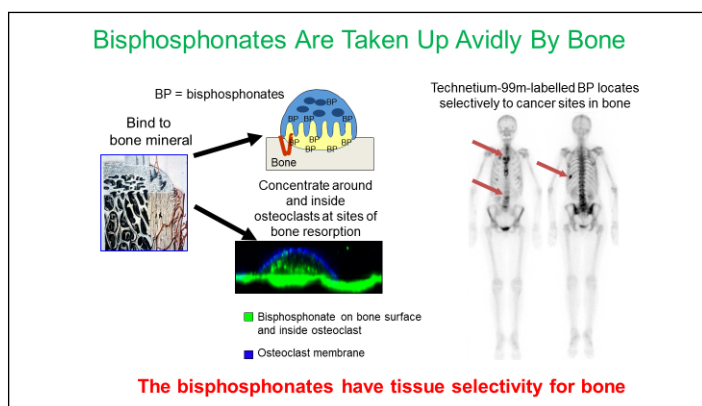
And there are lots of them. This table of formulas lists ten different bisphosphonates which have been approved for medical use in most Western countries, Europe, and the Far East. Almost all of them are now off-patent and, therefore, extraordinarily cheap. You can treat osteoporosis for less than \$10 a year with alendronate, for example.

Along the way, one of the things we have done is to understand how these drugs work chemically. They work through very interesting mechanisms. One of them fools the biochemical machinery in cells and creates Adenosine Triphosphate (ATP) analogues of bisphosphonates. But the probably more interesting one is the inhibition of the so-called farnesyl pyrophosphate synthase (FPPS)

enzyme, which is in the cholesterol biosynthetic pathway.

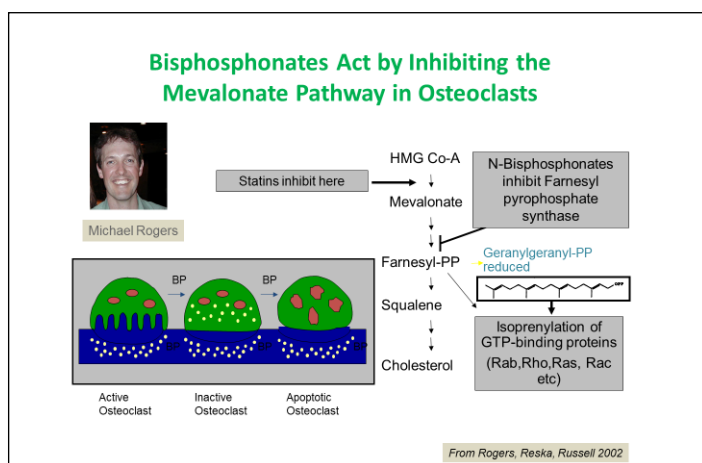
That ability to inhibit that enzyme leads to a lot of other potential effects. This is a very important pathway for internal control of biochemical signaling mechanisms. So if you can get bisphosphonate to work outside bone, you have the potential for a lot of other effects.

You can make new bisphosphonates, as we have done down on the bottom right. That is a super-super drug that is even better than zoledronate, but nobody wants it. The market is saturated with generic drugs. Nobody will develop that drug, even though it could be a lot better than zoledronate. If we were starting with none, it might actually be the leader of the pack.



What do they do? They have a high affinity for bone mineral, and this is the key to their action. They go into the skeleton, get attached to the mineral, and they get chewed up by cells called osteoclasts, which look like hungry cells chewing on the bone as it gets resorbed. The

bisphosphonate gets inside the cell and disrupts the internal machinery. You can put fluorescent labels on bisphosphonates and show them going into the cells. So it is very clear how they work and why they are specific for bone. One of the first uses was as bone-scanning agents, and fifty years later this is still a medical use. You can link them to technetium and image bone metastases and areas of high bone turnover. This illustrates the tissue selectivity for bone.



Working out the pathway was great fun. A key player in this was this a then-young man, Michael Rogers, who while a PhD student in Sheffield, actually nailed down the pathway very nicely.²

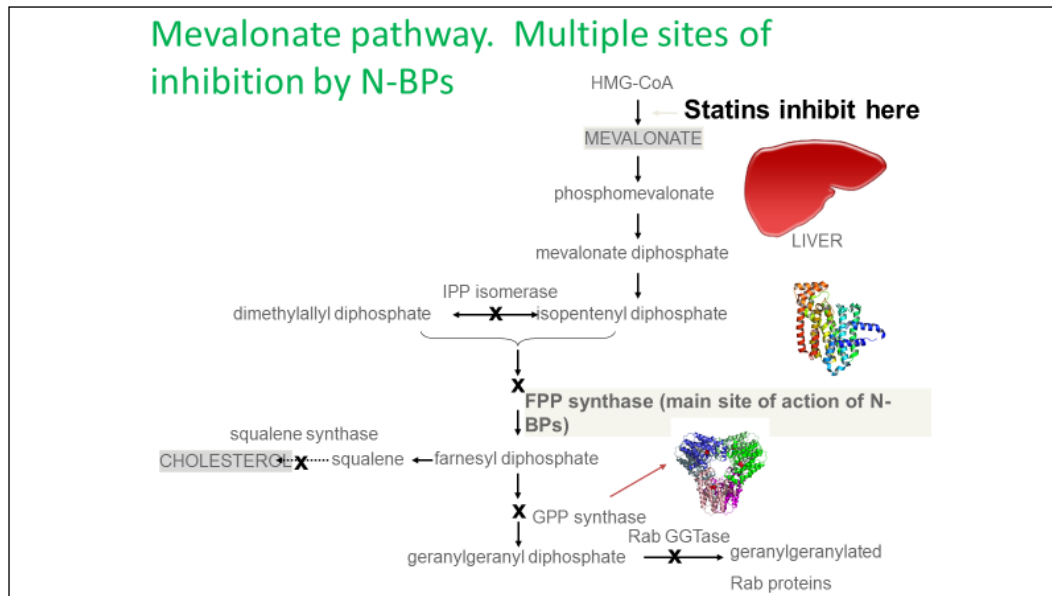
What you see here expressed very simply is the pathway leading to cholesterol biosynthesis. Statins work at the first step on the HMG Co-A

reductase and bisphosphonates work further down that pathway. You might

² See Michael J. Rogers, *New insights into the molecular mechanisms of action of bisphosphonates*, CURR PHARM DES. 2003;9(32):2643–58. Review. PMID: 14529538, available at <https://www.ncbi.nlm.nih.gov/pubmed/14529538>.

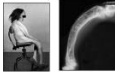

therefore expect that both drugs would actually do the same thing. They do not do exactly the same thing, and that is probably because they go to different places. Statins go to the liver and bisphosphonates go to the bone.

But the bisphosphonates, by working halfway down that pathway, block the production of isoprenoid lipids, which are used to attach to proteins to get them into membranes in cells. If you interrupt that pathway, you stop intracellular control molecules from going to the right place in the cell, and that is the basis for how they work.



This is shown in slightly more detail. There are several enzymes in this pathway that bisphosphonates inhibit, but FPP synthase is the major one. We at Oxford have done the crystal structures of these enzymes and shown that bisphosphonates bind into the active sites of these enzymes, and those are the rotating pictures you see there.

Bisphosphonates are Used to Treat Many Bone Resorption Disorders

Paget's Disease	
Myeloma	
Bone metastases	
Osteoporosis	

The diseases I think many of you will be familiar with are shown here:

- Paget's disease, interestingly, is becoming less common. It has a genetic basis, and is associated with bone deformity and pain, and bisphosphonates are extraordinarily effective in treating that.

- Myeloma is a rather horrible malignancy, and you can stop the bone destruction with bisphosphonates.

- Bone metastases, common of course with breast cancer, prostate cancer, and so on.

- And of course osteoporosis, which probably affects 30 percent or so of the elderly population. Fractures are associated with osteoporosis, and what you

are aiming to do with bisphosphonates is to reduce fractures.

Bisphosphonates are Used to Prevent Fractures In Osteoporosis

Wrist Spine Hip

Oral "blockbuster" BPs

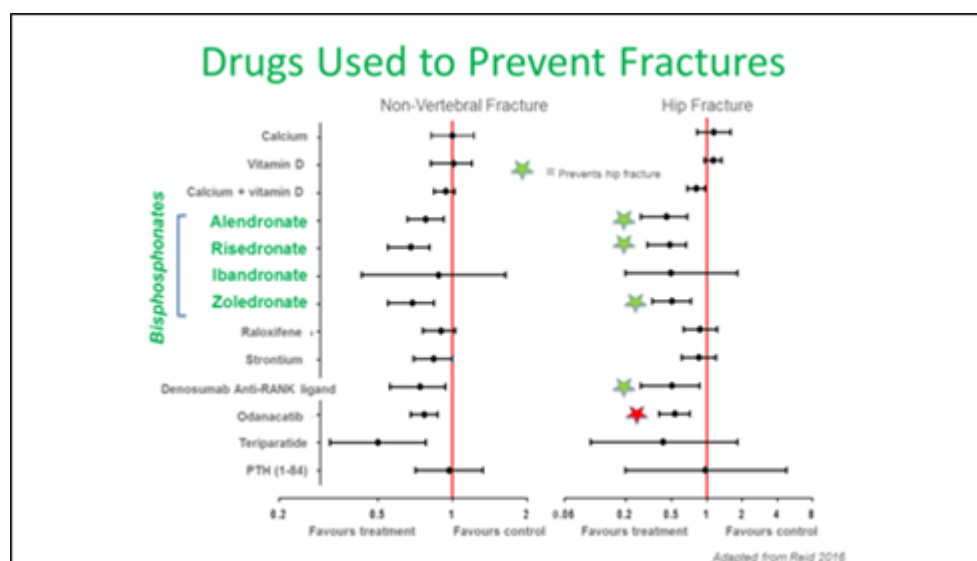
Alendronate **FOSAMAX**
(alendronate sodium tablets)

Risedronate **Actonel**
(risedronate sodium tablets)

Ibandronate **Boniva**
(ibandronate sodium tablets)

Zoledronate is given once yearly iv
Atelvia
(zoledronic acid injection)

This is the use in osteoporosis. Four of these drugs became block-buster-level drugs: alendronate, risedronate, ibandronate, and zoledronate. They are all now off-patent. Big companies were behind all these. They are the standard of care for osteoporosis.



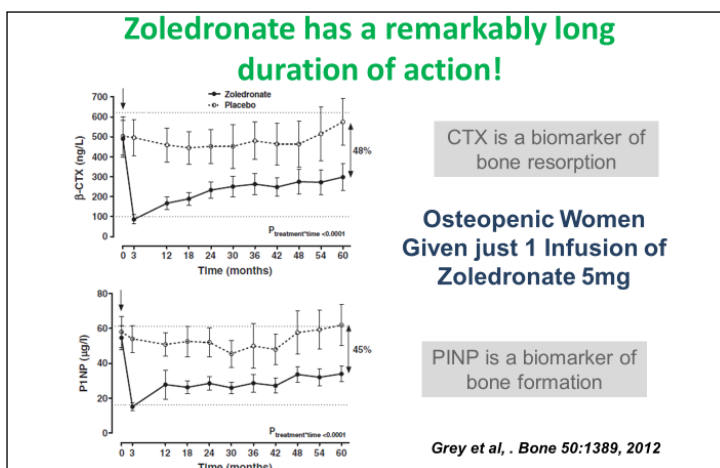
When you look at what drugs we have available to prevent fractures, there are actually quite a number of approaches and drugs, one or two of which have failed to pass the last hurdle of safety and so on after Phase III trials.³

The intention of showing you this is that if you look for nonvertebral fractures — that is everything not in the spine — which is an important group of fractures, and particularly hip fractures (on the right), all the lines to the left of the vertical red line indicate a significant reduction of fracture.

You will see that the drugs that accomplish this are either bisphosphonates or Denosumab from Amgen, which is an anti-receptor activator of nuclear factor-

³ See R. Reid, *Efficacy, effectiveness and side effects of medications used to prevent fractures*, J INTERN. MED. 2015 Jun;277(6):690–706. doi: 10.1111/joim.12339, available at <https://www.ncbi.nlm.nih.gov/pubmed/25495429>.

kappa-B ligand (RANKL) antibody. Because of that, these are the drugs that tend to be used to try to prevent hip fractures in particular.



One or two nuances to this are really fascinating. One is zoledronate, which is in my view a wonder drug. I know there might be people here who think that is a good statement to make. The more we have learned about this drug, it is quite extraordinary. The standard treatment is one infusion of 5 mg once a

year. How many drugs do you give just once a year?⁴

If you dig deeper, you actually find that you do not even need to give it as often as that. In this graph you can see it reduces bone turnover or bone resorption for at least five years after one dose. There are not many drugs that have that long an effect.

Somebody might ask why. The glib explanation is that the drugs go into bone and stay there for a long period of time and continue to act. I think there is probably more to it than that, but it is remarkable. For therapeutics this is extraordinary because you can treat people who might fracture with one infusion and then come back three or five years later if you are still alive.

This is now in my view the standard of care for osteoporosis prevention, to give people one dose or a yearly dose of zoledronate. The price is down to about \$30 a year or something like that. The biggest cost is associated with bringing the patient to hospital for the infusion.

Bisphosphonates (esp Zoledronate) Are Used to Prevent Skeletal Related Events (SREs) In Cancer (Hypercalcaemia, Bone Loss And Fractures etc)

Humerus with lytic lesions in breast cancer

Skull with lytic lesions in myeloma

Zoledronate (iv)

Note that alendronate and risedronate were never developed for treating cancer, despite being oral drugs

The other huge area of application is in cancer. The aim is to prevent bone destruction, which causes pain, fractures, and possibly hypercalcemia, which can be life-threatening.

These are pictures of lytic

lesions in bone, in breast cancer, and in myeloma.

⁴ A. Grey et al., Five years of anti-resorptive activity after a single dose of zoledronate – Results from a randomized double-blind placebo-controlled trial. BONE 2012;50:1389–1393, available at <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3727770/>.

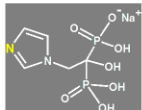
Again, both drugs were Novartis drugs, pamidronate first and then superseded by zoledronate. Here the drug is given more often, every month or six weeks, so you seem to need a bit more of the drug to keep the bone destruction suppressed, but they are extraordinarily effective in that. Again, that is now standard of care. And there is evidence that you improve the survival of patients with breast cancer if they are given these drugs early, even before there is a suspicion that they might have bone metastases.

Interestingly, in drug development, even though companies like Merck and Procter & Gamble had alendronate and risedronate as oral drugs, for whatever reasons they never applied them to the cancer world. In one case, I think it was because they were afraid that if you started using them in cancer patients, the occasional patient might die and that would contaminate the use of the drug for non-killing conditions like osteoporosis. Osteoporosis is a killing condition because a hip fracture can be associated with increased mortality. It is an interesting reflection on how commerce plays into the availability of drugs.

I thought it was worth putting together one or two comments about zoledronate.

The Zoledronate Story

- A Novartis Invention
- Given Iv only, not oral
- Standard of care for bone metastases and myeloma
- Very effective in osteoporosis
- Remarkably long duration of action (>1 year after only one dose of 5mg); basis for patent, contested, and patent revoked
- Extensively studied for biological effects
- >3700 refs in PubMed
- Several potential medical uses not developed because of patent expiry**
- eg Bone erosions in rheumatoid arthritis,
- New applications, DNA repair etc



Zoledronate (iv)

I should have said earlier that all ten, to my knowledge, of those approved bisphosphonates have been the subject of one sort of litigation or another. I have been involved in one or two of those and learned the little bit of law I know as a result. I've met interesting people along the way, of course.

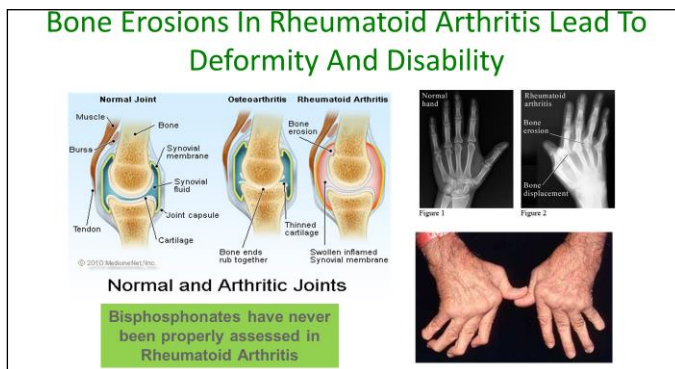
Zoledronate is a Novartis invention. It came out of a

program of making lots and lots of compounds and selecting the best. It is given intravenously, not orally, so you know the dose you are giving. It is the standard of care for bone metastases and myeloma, and very effective in osteoporosis.

One area of litigation that several people here were involved in is the patent that tried to protect the use of the once-yearly treatment, which was the only drug that could be used in that mode. The patent was contested, and it eventually was revoked last autumn at the European Patent Office. Some of us feel — I need to be careful what I say because I am on the record — it was a pity, to say the least, that something as good as that could not be protected by the patent system.

There are lots and lots of effects of zoledronic acid biologically, and some of these can be converted to other uses. I am going to run through some examples of that in the rest of this presentation.

One of the big areas that never got developed was stopping bone destruction in people with rheumatoid arthritis. That was a life cycle management issue. The patent was sufficiently close to expiry that embarking on new clinical studies was not worthwhile because the company would not see the benefit of success.



This slide shows what we are talking about in arthritis. These are extremely florid old textbook-type pictures of deformed hands in rheumatoid arthritis. There is evidence that bisphosphonates will block some of that bone destruction, particularly if you get in early. The

anti-tumor necrosis factor (TNF) therapies do not do it 100 percent, so there is a place for giving them in addition to the other drugs, but bisphosphonates have not been properly assessed in rheumatoid arthritis, and that is a gap. Any of the bisphosphonates used properly might achieve that, particularly zoledronate.

Old Dogs and New Tricks

Examples of potential additional medical uses of Bisphosphonates

- Rheumatoid erosions, inflammatory bone loss
- Osteoarthritis,
- New formulations (eg oral zoledronate)
- Combinations with other drugs
 - In osteoporosis
 - Combination with chemotherapeutic agents in cancer

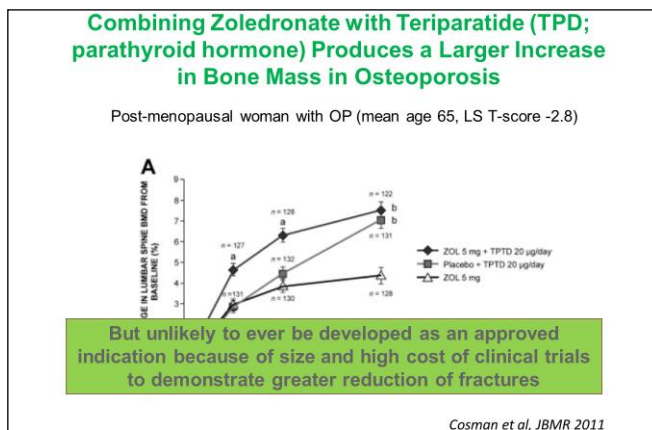
“Old Dogs and New Tricks” — this is really the theme of part of the meeting, isn’t it?

There are some major examples here:

- Rheumatoid erosions and inflammatory bone loss.
- For osteoarthritis, which is the main reason people have hips and knees replaced, you can prevent the pain and progression. In osteoarthritis experimental and clinical observations with bisphosphonates suggest that they can be effective. This is not being developed because nobody is behind these drugs from the pharma point of view to do the necessary studies.

- New formulations: It would be quite neat to have an oral zoledronate that you did not have to infuse, and people are working on that. That is a difficult area to get traction in.

- And then combinations with other drugs.



One example of this: If you combine zoledronate with other good agents in osteoporosis, teriparatide (TPTD) or parathyroid hormone (PTH), also the subject of recent litigation, you get a bigger increase in bone mass.⁵

But the purists do not like the idea that you would do that because you have

not shown that that bigger increase in bone mass equates to a reduction in fractures. I think most people feel that this is unlikely to ever be developed as an approved indication and registered as such because of the size and high cost of clinical trials to formally demonstrate that you get a better effect with a combination. So this would be a case for off-label use, but getting it approved is going to be difficult.

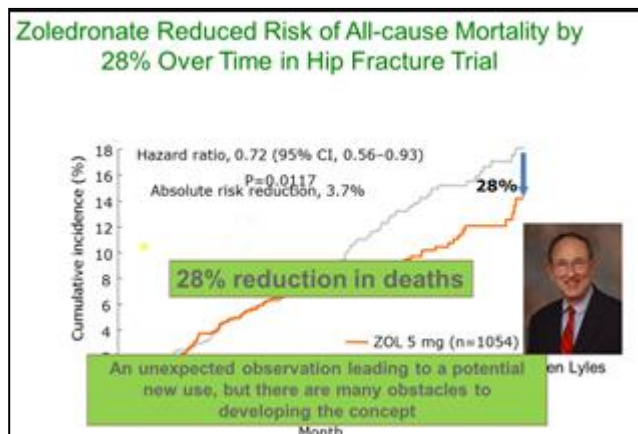
Examples of Potential Non-Skeletal Effects of Bisphosphonates
(derived from clinical observations)

- Reducing colon cancers
- Reducing heart attacks and heart failure
- Increasing survival in intensive care units
- Preventing radiation damage by enhancing DNA repair and tissue regeneration.
- Reducing mortality and extending life span ("senolytics")

Finally, a quick romp through some of the fascinating so-called non-skeletal effects of bisphosphonates. These are effects outside the skeleton, but based on observations from population studies.

- There is quite good evidence that people on bisphosphonates have fewer colon cancers and die less from colon cancers,
- There is pretty convincing evidence from several studies of reducing heart attacks.
- Increasing survival in intensive care units.
- More experimentally, there is evidence that you can prevent radiation damage.
- Reducing mortality and extending lifespan in certain situations. I am going to show you one or two examples of this.

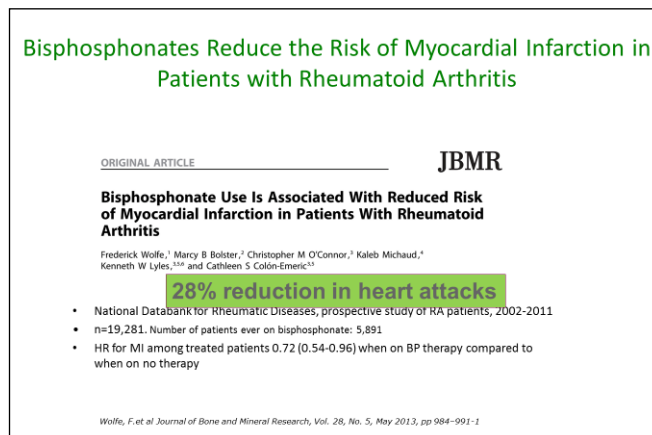
⁵ F. Cosman et al., *Effects of intravenous zoledronic acid plus subcutaneous teriparatide [rhPTH(1-34)] in postmenopausal osteoporosis*, J BONE MINER RES. 2011 Mar;26(3):503-11. doi: 10.1002/jbmr.238, available at <https://www.ncbi.nlm.nih.gov/pubmed/20814967>.



The first comes from a clinical trial, which again is a Novartis trial, conducted by Ken Lyles from Duke University.⁶ They observed a 28 percent reduction in mortality in people who were given zoledronate. These are people coming in with a hip fracture. Half get placebo; half get zoledronate. The zoledronate group have fewer

subsequent fractures, but they also die less often — not that you die more than once, but fewer of them die. [Laughter] There is a 28 percent reduction in deaths, which is a really striking effect from a clinical trial. This is a wonderful example of an unexpected observation leading to a potential new use.

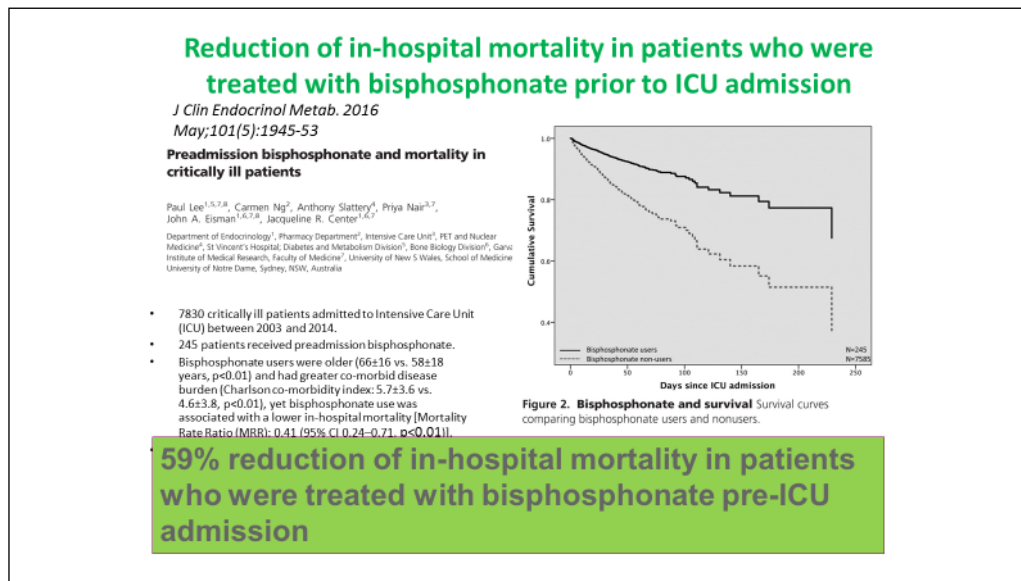
Unfortunately, almost ten years after this observation, there are many obstacles to developing this. Ken Lyles is a very tenacious guy and he is still trying to get clinical trials in place to see whether you can actually do this on a wider scale.



Another study he did was to go into a database of rheumatoid arthritis patients who are prone to get myocardial infarcts. This is a big database, nearly 20,000 people. Interestingly, the ones on bisphosphonate had a 28 percent reduction in heart attack. So these are quite big effects coming from observational studies.⁷

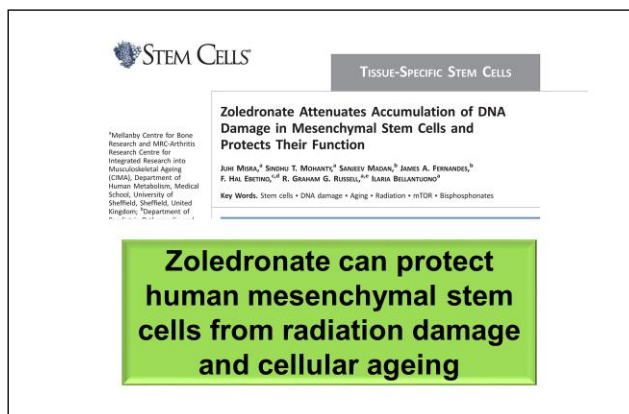
⁶ See Kenneth Ward Lyles, *Zoledronic Acid and Clinical Fractures and Mortality after Hip Fracture*, NEW ENGL. J. MED., 2007; 357:1799-809, DOI: 10.1056/NEJMoa074941, available at <http://www.nejm.org/doi/full/10.1056/NEJMoa074941>

⁷ Frederick Wolfe et al., *Bisphosphonate Use Is Associated with Reduced Risk of Myocardial Infarction in Patients with Rheumatoid Arthritis*, J. OF BONE & MINERAL RESEARCH, Vol. 28, No. 5, 984-991 (May 2013), available at <http://onlinelibrary.wiley.com/doi/10.1002/jbmr.1792/epdf>.



This is a fascinating study from Australia.⁸ These folks looked at more than 7000 admissions to intensive care units over a ten-year period in Sydney and showed a very significant improved outcome in people who went into intensive care units for whatever reason being on a bisphosphonate drug, a 59 percent reduction in the in-hospital mortality.

This is so counterintuitive that it just seemed very strange. If people are on a bisphosphonate, they obviously have some other disease. Why should they survive better than people going in for other reasons into an intensive care unit? This observation could be converted into practical use where if you go into an intensive care unit for anything, you automatically get zoledronate on day one when you go in. It is just crying out for a clinical study.




How does all this work? We have got interested from the scientific point of view in how this works.⁹ There are all sorts of possible mechanisms. For example, you can extend the lifespan of stem cells by putting them in a medium containing zoledronate; you can irradiate them and show that you can prevent irradiation damage in terms of

⁸ Paul Lee et al., *Preadmission bisphosphonate and mortality in critically ill patients*, J. CLIN. ENDOCRINOL METAB. 2016 May;101(5) 1945–53, available at <https://academic.oup.com/jcem/article/101/5/1945/2804745>.

⁹ Juni Misra et al., *Zoledronate Attenuates Accumulation of DNA Damage in Mesenchymal Stem Cells and Protects Their Function*, STEM CELLS. 2016 Mar;34(3):756–67. doi: 10.1002/stem.2255. Epub 2015 Dec 22, available at <https://www.ncbi.nlm.nih.gov/pubmed/26679354>.

DNA damage, cellular aging, and so on. So we are groping toward explanations for why you might see some of these beneficial effects.

Accelerated Ageing
Hutchinson-Gilford Progeria Syndrome (HGPS).



HGPS is due to a genetic defect in prenylation
Life span in mouse model is doubled by giving zoledronate plus a statin
Clinical trials in progress

A final example is progeria, the genetic condition that leads to premature aging. These “little old men,” children who are ten years old and look seventy, get all sorts of complications, like cardiovascular disease and other things, and die prematurely. There is a very clearly defined

genetic defect, which is a prenylation defect, which makes it logical to use a bisphosphonate or a statin in treatment.

A mouse model of that showed that you could double the lifespan of mice with this genetic disorder by giving them a combination of statin and zoledronate. In these types of patients, who are very rare, there are clinical trials going on with that drug combination. It is difficult to do controls, of course, in that situation.

“New Tricks”, “Repurposing”
New Uses for Existing Drugs



Can we all live to 100?!

Metformin	From Type 2 diabetes to anti-ageing and Alzheimers
Rapamycin	From immunosuppressant to anti-ageing
Resveratrol	Red wine
Bisphosphonates	From bone diseases to anti-ageing and DNA repair

Can we improve lifespan even on a more general scale with drugs that we have around?

Bisphosphonates are at the bottom of that list. But in passing I should mention that there are some old drugs which have similar effects on increase-ing lifespan in experimental studies in worms and fruit flies and various other

organisms: Metformin, the diabetes drug; rapamycin; resveratrol; red wine, of course, good health to everyone, but you need to drink an awful lot of red wine to get an adequate dose. Of course, if you are British, the objective for living to 100 is you get this treasured telegram from the Queen.

Can We Change the Road Signs?!



Osteoporosis
Osteoarthritis
Frailty

The serious bit of this is: can we really change some of the late-life problems and the outcomes? It is a telling observation that the street sign for the elderly, “Beware of Walking Elderly Roaming Free,” shows a woman probably

with osteoporosis and a stoop and a man with hip pain with a walking cane. She is possibly picking his pocket if you look closely. [Laughter]

To the obvious things of osteoporosis and osteoarthritis we would add frailty, because there is this phenomenon of becoming weaker as you get older, and a lot of those drugs that are being used or thought of for aging are actually working on mechanisms that may lead to frailty, loss of muscle, and so on.

Bisphosphonates approach 50th Birthday! Party in 2019



50 years of successful and safe clinical use.

Many new uses for unmet medical needs are possible if current legal, commercial, and logistic barriers are reduced.

To end on a happy note, next year will be the fiftieth birthday of the bisphosphonate discovery, and we plan to have some sort of party. There is a moral to this tale too, that drugs that were first introduced fifty years ago are still the main drugs used for bone disease.

The take-home message is here is a class of drugs that have had successful and safe clinical use, safe in spite of one or two now recognized very rare side effects — not killing ones but rare events, which the media love, of course — but they are on the whole very successful drugs.

There are many, many new uses and unmet medical opportunities for these drugs. We have to overcome the barriers — legal, commercial, and logistics, just doing the trials — if these are ever to be put into practice.

So that is my message to start the day. Thank you.

DR. GILLENLINE: David has identified a number of well-known drugs that have been repurposed, but perhaps now we can discuss what are some of the hindrances to the second medical uses or repurposing an old drug for a new use.

DR. CAVALLA: I would say that repurposing is a very heterogeneous field, and also a very, very, very large field, probably much larger than any of us know about. I have spent twenty years in this field and I had never heard of bisphosphonates being used for Hutchinson progeria disease. Indeed, there are over 8000 rare diseases. There is an enormous pool of opportunities here.

Misconceptions

- DRP does not identify ground-breaking drugs
 - Alemtuzumab (formerly CamPATH for CLL; now MS)
 - Pirfenidone (formerly anthelmintic for IPF)
 - Ketamine (from anaesthesia to severe depression)
 - Espindolol (hypertension to cachexia)
- Big pharma is not interested
 - Access to failed assets and data from pharma companies (MRC, NCATS)

I would say that repurposing is often characterized as “new tricks for old dogs.” But it is not always like that, and in some cases repurposing can give rise to ground-breaking new treatments. I will go over a few examples here.

- One which I like very much is the use of an antibody called alemtuzu-

mab, which was discovered in Cambridge and used for chronic lymphocytic leukemia (CLL). Very early on it was thought there might be an opportunity in multiple sclerosis. The company involved spent ages trying to get commercial interest in this, and also at the same time treating a few patients with multiple sclerosis, and it had a dramatic effect in these few patients: some of them went into remission for up to ten years, sometimes even fifteen years.

Whilst this was going on, they were touting their story around to pharmaceutical companies, with very little success because of the difficulties in commercialization and the longevity (and cost) of multiple sclerosis trials.

Ultimately, one of the people who had been treated with alemtuzumab for multiple sclerosis accidentally met a representative for Bayer who was coming out of a meeting to discuss a potential license for this product. They met fortuitously in the car park. She was a very erudite and forceful woman, and she explained how beneficial this drug had been to her condition. She alone convinced the Bayer representative to develop alemtuzumab for multiple sclerosis. It was then taken on by Sanofi, and it was introduced in 2015.

Interestingly, all of these drugs — alemtuzumab is one of them — are slight modifications of the standard generic drug being used for a new condition. In the case of alemtuzumab, they actually had to take the product for chronic lymphocytic leukemia off the market in order to generate a commercial opportunity for the new product in multiple sclerosis, and then it was, of course, introduced at a much, much higher price, and there was public debate about that.

- Pirfenidone was never approved originally as a pharmaceutical. It was an animal health drug which was the first drug approved for idiopathic pulmonary fibrosis, a rare and fatal condition.

- Ketamine is an unusual drug originally used as an anesthetic. Its use in depression has been predominantly studied in an academic environment. There are many examples of repurposing which are discovered in an academic environment. In fact, I would actually say that the purpose of this meeting is not really to enhance the discovery of repurposed medicines. There are plenty of drugs out there which have been discovered and are potentially useful. The challenge is how to create an environment for their development. That is the real problem. Ketamine is being developed as a single enantiomer for major depression and prevention of suicide in depressed patients.

- Espindolol is a drug I have been working on, which is a single enantiomer of pindolol. It has been through a Phase II trial and is the most effective drug that we know about for cachexia.

One of the ways — apart from these minor changes to the original product that enable development to occur — is by developing failed assets or things which have stalled. These would then not have a generic comparator to compete with and face that commercial challenge.

A number of big pharma companies have put some of their abandoned assets into libraries of compounds, which were then taken up by either the National Institutes of Health (NIH) through their new division of National Center for Advancing Translational Sciences (NCATS) or in the United Kingdom through the Medical Research Council (MRC).

No money in repurposing?

- Tecfidera (dimethyl fumarate); Namenda (memantine)
 - Peak sales \$2.91bn; \$0.8bn
- Modafinil, thalidomide, gabapentin
 - Repurposed for various orphan (& non-orphan) diseases
 - All billion-dollar products
 - Companies developed sales franchises
 - Thalidomide became lenalidomide (PYS \$4.28bn); modafinil became armodafinil; gabapentin became pregabalin
 - Indications expanded with new CoM-protected analogue
- Raloxifene
 - Original discovery objective to identify alternative SERM to treat tamoxifen-resistant breast cancer
 - Repurposed to osteoporosis
 - Retrospective evidence showed it prevented breast cancer recurrence
 - Peak sales \$1.09bn

Because of the heterogeneity, whilst many of the repurposing opportunities are not commercially successful and are never taken forward, there are a number of others that are very successful in a commercial sense.

Two salient examples are dimethyl fumarate (Tecfidera®), which is one of the very few pharmaceuticals without a nitrogen in it, which has been introduced for multiple sclerosis; and memantine (Namenda™), which is a drug for Alzheimer's disease. Both of these are billion-dollar drugs.

Some of the commercially successful examples of repurposing have not only been successful of themselves, but have also enabled the establishment of franchises for the companies. Thalidomide became lenalidomide, which is another Celgene product, an improved version of thalidomide; modafinil became a single-enantiomer amodafinil, R-modafinil; and gabapentin became pregabalin.

The third thing is that sometimes drug discovery and histories of drugs go full circle. Raloxifene originally came out of a discovery program which was to identify an alternative to tamoxifen to treat tamoxifen-resistant breast cancer. It went through an early clinical trial and the results were not very positive, so they switched to develop it for osteoporosis. Then, in the course of marketing, it became clear that it prevented the recurrence of breast cancer, a marginally different kind of effect on cancer which had not been picked up in the original case and it is now given for that condition.

Acetyl salicylic acid, 2000 years after Herodotus

- Aspirin first marketed by Bayer in 1899, for pain
- In 1970s, John Vane shows it disrupts platelet aggregation; effective for MI & stroke
- In 2010, shown to prevent GI and other cancers (25,000 pts) [Rothwell, 2010]
- Hazard ratio for pancreatic cancer = 0.25

The last thing is how long this all takes. Some refer to repurposing in a somewhat derogatory fashion — talking about “new tricks for old dogs” — but aspirin is about the oldest dog there is and we are still finding things out about it. Of course, as the patent envelope, the

commercial opportunity, secedes, you do not have rapid advancement. Whilst aspirin was first introduced at the end of the 19th century for pain, it was discovered in the 1970s to have an effect on platelet aggregation and it was shown

to be effective for heart attacks and for stroke.¹⁰ But it has also in more recent times been discovered to have a preventative effect on cancer.¹¹

So here we have something which is so common — it is in all of our medicine cabinets at home — and yet it does not just treat mild headaches; it potentially prevents us getting the most demonic of conditions, cancer. The effect in pancreatic cancer is really quite profound.

Retrospective evidence in cancer

Cancer type	Drug type
Breast	Beta-blockers
Colorectal	Calcium-channel blockers
Liver	HMG CoA inhibitor
Lung	Na ⁺ /K ⁺ ATPase inhibitor
Melanoma	Metformin
Oesophageal	NSAIDs
Ovarian	PPAR agonists
Pancreatic	Quinolone antibiotic
Prostate	TNF antagonists
Stomach	

...but sometimes not repeated prospectively (metformin in pancreatic cancer)

This is retrospective evidence in cancer. I will talk about this in my presentation later on this afternoon. I think that is a very powerful means of uncovering potential new uses for existing drugs.

DR. GILLENLINE: I know you research big data. What does the big data tell us about these missed opportunities?

DR. BANERJEE: The word that Graham used a few moments ago was “serendipity,” and aspirin is a good example of how long it can take. Now, in an era where there is more electronic data or more cooperation between different owners of data sets, might it be possible to speed up this process and to remove some of the serendipity?

Part of the problem in research and in clinical practice is that we work in silos. I am a cardiologist; Graham works in orthopedics and rheumatology, in musculoskeletal diseases. The trials concerning our respective disease areas might not gather the data in as much detail on the other outcomes, so we are relying increasingly on observation or retrospective data sets where you can do so-called “data mining” to look for potential signals.

Maybe we can have a discussion about how we can move on from the classic randomized control trial paradigm that has been used to the new designs where we can move forward using this newer type of observational data or electronic health records to try to facilitate things more quickly. At the moment,

¹⁰ See John R. Vane, *Inhibition of prostaglandin synthesis as a mechanism of action for the aspirin-like drugs*, NATURE 1971;231:232–35, available at <https://www.ncbi.nlm.nih.gov/pubmed/14592543>; see also National Heart Lung and Blood Institute, *Aspirin to Prevent a First Heart Attack or Stroke*, <https://www.nhlbi.nih.gov/health-topics/aspirin-prevent-first-heart-attack-or-stroke>.

¹¹ Peter M. Rothwell et al., *Long-term effect of aspirin on colorectal cancer incidence and mortality: 20-year follow-up of five randomised trials*, LANCET, Vol. 376, No. 9754, 1741–50, 20 November 2010, available at [http://www.thelancet.com/journals/lancet/article/PIIS0140-6736\(10\)61543-7/abstract](http://www.thelancet.com/journals/lancet/article/PIIS0140-6736(10)61543-7/abstract).

in terms of costs, in terms of regulation, and in terms of serendipity, it is not going to move quickly enough. I think there are data opportunities.

Another opportunity in the data is not just different diseases, but people do not present with one disease. A person who has a hip fracture may well have a predisposition to heart disease and hypertension and diabetes, and yet our trials put these people into single-disease entities and we control for these co-morbidities. In trials we do subgroup analyses with prespecified outcomes to see if drugs work better in certain individuals. Big data might help us to identify the people with the right cluster of co-morbidities, if you will, to actually use these drugs in ways in which the trials have hitherto not been very successful in doing.

I see a future where we have to make better use of the limited resources that we have. There are various initiatives around the world to make trial data sets open. In the cardiovascular disease space, which is my disease space, there have been examples of opening up the trial data set to the research and the pharmaceutical communities to do retrospective analyses to inform future trials, and that kind of thing we are seeing much more.

I think both retrospective and prospective observational data are going to be important.

DR. GILLENINE: Other than the lack of data, what are some other hindrances that you see for developing the second medical uses, the repurposing?

DR. CAVALLA: The major one, I think, is the possibility of substitution of a branded product for the secondary use by a generic alternative that was primarily introduced for the first use. That generic substitution, which is liked — and loved, if you like — by the National Health Service (NHS) and increasingly by the American health system, actually prevents us maximizing the efficiency that can be derived from repurposing as a strategy.

DR. GILLENINE: Why do you think pharmaceutical companies looked at the products that had been repurposed? A lot of them were a single enantiomer and could take advantage of the FDA exclusivities that are available.

DR. CAVALLA: Yes, regulatory exclusivities and/or patents can enable this to happen. Thalidomide is an example where there was no patent behind the use. Thalidomide was off-patent as a molecule by the time it was introduced for leprosy. It is a classic example of clinical serendipity, real clinical serendipity.

There was no second medical use patent because the case report was published prior to the development by Celgene. There was extreme nervousness about any product containing thalidomide that engendered huge discomfiture around a thalidomide-containing product. Celgene had the monopoly, and they deployed that when they developed it for multiple myeloma.

DR. GILLENINE: Any questions or comments for the panel?

QUESTION [Dr. Solanki, Intas Pharmaceuticals Ltd. and Accord Healthcare Ltd.]: I am from India. We have European operations with a subsidiary under the name of Accord.

Sir, you were highlighting the effects of zoledronate as a wonderful drug, just once-a-year administration, providing very high convenience. You also highlighted the point of co-administering it with teriparatide, and we see the effect in terms of magnitude in gaining the higher bone mineral density (BMD) for a certain class of patients.

I understand the role of zoledronate acid at the typical anatomical sites, especially the hip and femur, where teriparatide kind of agents are not able to increase BMD. Do the doctors at present feel that zoledronic acid is really meant specifically to increase BMD for preventing hip and femur fractures in a more significant manner than a drug like teriparatide or other bisphosphonates?

The second question is: could we also anticipate a similar kind of synergy by combining with a recent introduction of Denosumab?

PROF. RUSSELL: One of the objectives of the pharma industry has been to develop, not antiresorptive drugs like the bisphosphonates, but to develop what you might call bone anabolic drugs, bone-forming drugs, that will actually make the bone cells, the osteoblasts, make more bone. That was what teriparatide is meant to do.

However, when you look at the trial outcomes for teriparatide, the reduction of fractures is not better than any bisphosphonate, and it is a curiosity that antiresorptive drugs seem to be as good as anything that has ever been tried in terms of reducing fractures. It is almost counterintuitive that the two drugs together would actually have a bigger effect on BMD. They are perhaps working through different bone compartments. The interesting observation is the increase in bone mass. The big question is whether that translates into a better reduction of fractures, and, as I indicated, we are never likely to know the real answer to that.

You asked a question about Denosumab. There is an equivalent study of teriparatide with Denosumab showing a similar result.¹² Giving teriparatide/PTH with estrogen also has a good effect.¹³ So there are drug combinations out there which have been shown in clinical use to have the desired effects on bone, but formally demonstrating that they reduce fractures and whether they do better than the next drug is a big question.

The big problem in our field is also that drugs are never compared one with the other. The trials are independent, one drug is studied at a time, so you do not see trials where, for example, Denosumab and a bisphosphonate are compared, not big studies anyway.

I don't know whether that answers your question.

QUESTIONER [Dr. Solanki]: My second point is rheumatoid arthritis. I have come across a paper where the researchers had highlighted the properties of using the conventional disease-modifying antirheumatic drugs (DMARDs) in combination with methotrexate.¹⁴ In a randomized controlled trial, the efficacy

¹² See L. Idolazzi et al., *Teriparatide and Denosumab Combination Therapy and Skeletal Metabolism*, OSTEOPOROS INT. (Nov. 27, 2016) 3301–07, doi: 10.1007/s00198-016-3647-y. Epub June 1, 2016 <https://www.ncbi.nlm.nih.gov/pubmed/27250971>.

¹³ See V.F. Trevisani et al., *Teriparatide (recombinant human parathyroid hormone 1-34) in Postmenopausal Women with Osteoporosis: Systematic Review*, SAO PAULO MED. J. (Sept. 2008) 126:279–84, available at <https://www.ncbi.nlm.nih.gov/pubmed/19099162>.

¹⁴ See W. Katchamart et al., *Methotrexate Monotherapy Versus Methotrexate Combination Therapy with Non-biologic Disease Modifying Anti-rheumatic Drugs for Rheumatoid Arthritis*, COCHRANE DATABASE SYS. REV. (2010) 4:CD008495, available at [.pmid:20393970PubMedGoogle Scholar](https://pubmed.ncbi.nlm.nih.gov/20393970/); see also Glen S. Hazlewood et al., *Methotrexate Monotherapy and Methotrexate Combination Therapy with Traditional and Biologic Disease Modifying Anti-rheumatic Drugs for Rheumatoid Arthritis: A Network Meta-analysis*, COCHRANE DATABASE SYS. REV. (Aug 29, 2016) (8):CD010227, doi: 10.1002/14651858.CD010227.pub2,

was compared with methotrexate in combination with etanercept. The research group concluded in favor of the old DMARDs because the efficacy was found on par with the methotrexate and biosimilar combination.

There is a very strong message in that particular paper, which was published almost a decade ago, that this work should be carried forward rather than only focusing on developing the biosimilars, which we all know are very expensive medicines for patients to afford and take a long time for the pharma companies to develop. That might even include rituximab and infliximab. The results are expected to be on par.

Any idea or comments on this particular concept, because nothing has been done so far during this ten-year timeframe?

PROF. RUSSELL: I think it is a comparable problem, that if you have those drugs available, particularly with biosimilars coming along, who is going to finance the studies that explore new questions and new uses like that? That is a huge issue. Will the generic companies fund studies, and what is the potential gain for them commercially if you can show a combination works? These are somewhat philosophical questions, but they are central to the theme that we are discussing, aren't they?

DR. GILLENLINE: Any last comments from the panel?

DR. BANERJEE: I would only say to Graham's point about head-to-head comparisons that in the cardiovascular space there are a couple of instances where novel electronic health record trials have been used, using public funds to do those kinds of trials where there is not commercial funding available for that trial at a fraction of the cost.

I am going to be talking later about anticoagulants in the area of atrial fibrillation [see Session 1H]. There are at least four different drugs where there are no head-to-head trials, but there is an ongoing head-to-head study which was publicly funded in Denmark. So again, there may be new ways of trying to find these new tricks.

PROF. RUSSELL: I think the issue of public funding of this sort of research is really important. If the clinical problem is important enough, it should become a priority.

I keep hearing that Kaiser Permanente in California, a big healthcare system, is one of the few healthcare deliverers in the United States that are interested in hip fractures because they see the costs and are prepared to research it, and maybe even conduct studies. Maybe that is a hope for the future.

DR. GILLENLINE: Thank you very much.

[Session Adjourned: 9:38 a.m.]

Second Medical Use: Missed opportunities, clinical successes, and what the data tells us about missed opportunities

Prof. Mondher Toumi
University of Marseille

[Delivered at 1:30 p.m. on Friday, February 9, 2018]

PROF. TOUMI: Good afternoon, everybody.

I have been asked to discuss missed opportunities. It is now a bit late in the program because now you are addressing how to overcome the missed opportunities, but I will bring you back to yesterday.

Agenda

- 1 Patent the cornerstone
- 2 Off label use of generics and biosimilars
- 3 Governmental off label use recommendation
- 4 HTA the major resistance
- 5 Pricing a discouraging step

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One of the big issues for second use is really the patent. Whenever you are facing a product that is covered by a patent, then a third party cannot have access unless you have a deal with the pharma company or it is part of the usual life cycle management of the pharma company. If the product falls off-patent, it is very difficult to avoid the competition from a generic or biosimilar if you do not have a patent, and having a patent may not be enough.

Patent The corner Stone of Second Medical Use Medicine (2/2)

- The return on investment of developing a new medicine is primarily driven by the sales in US.
- In Europe there are large uncertainties on the ability to get access and a relevant price
- So it is important to achieve access in the US
- Data protection and market exclusivity in EU is 10 years, and 3 to 5 years in US, and zero in most developing countries
- Without a patent for second use, data protection in US is too short to permit to recoup the investment and in EU there are too much uncertainty

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If you develop such a product, the return on investment comes primarily from sales in the United States. There is too much uncertainty, with the health technology assessments decisions and the price you may have to consider, that you are going to recoup your investment from sales in Europe. So it is critical to achieve success in the United States.

Data protection is very effective in Europe, but too short for such products in the United States (three to five years), and zero in most of the developing countries. Therefore, without a patent, you are unlikely to recoup your investment in the United States just with data protection.

In our experience — and I have been involved in many dossiers — achieving a second medical use patent was very difficult in the United States.

There were many dossiers where I saw small companies starting the project and finally giving up because they cannot get a patent when they believe they have a good case — at least a good case from a public health perspective, maybe not from a legal perspective. I am not a lawyer.

I would like to show you two cases.

Schizophrenia

- Schizophrenia is a severe condition associated with delusion, hallucination, dissociation and cognitive disturbance
 - Mortality related to schizophrenia is higher than HIV patients 10 years ago
 - 20% of patients are resistant to all available therapies and are treated with clozapine
- Clozapine is associated to major agranulocytosis leading to death.
 - It's use is very limited and most patients do not receive it because of side effects

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The first one is Clopixol®, a product dedicated to schizophrenia. Schizophrenia is a very severe condition. Just to give you an idea, the mortality associated with schizophrenia is higher than HIV mortality ten years ago. To give you an idea of the severity of the condition, 20 percent of the patients are resistant to all available therapies, and the only product that is available for those patients is Clozapine. This

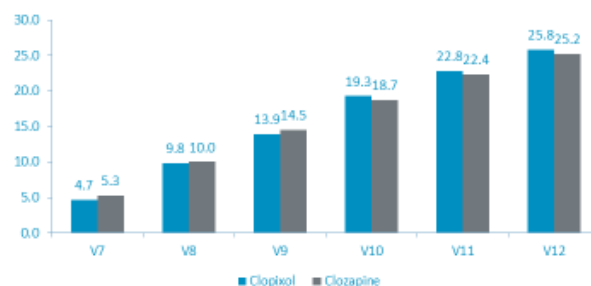
product is associated with major side effects and, because of those major potentially fatal side effects, the product is used in a very limited way and many patients who should be treated are not receiving that product.

Clopixol

	Clopixol	Clozapine
	N=120	N=117
% Reduction, mean(SD)	0.24 (0.10)	0.23 (0.12)
Response rate	62 (51.67%)	56 (47.86%)

ANCOVA adjusted tests : *P<0.05; **P<0.005; ***P<0.0005

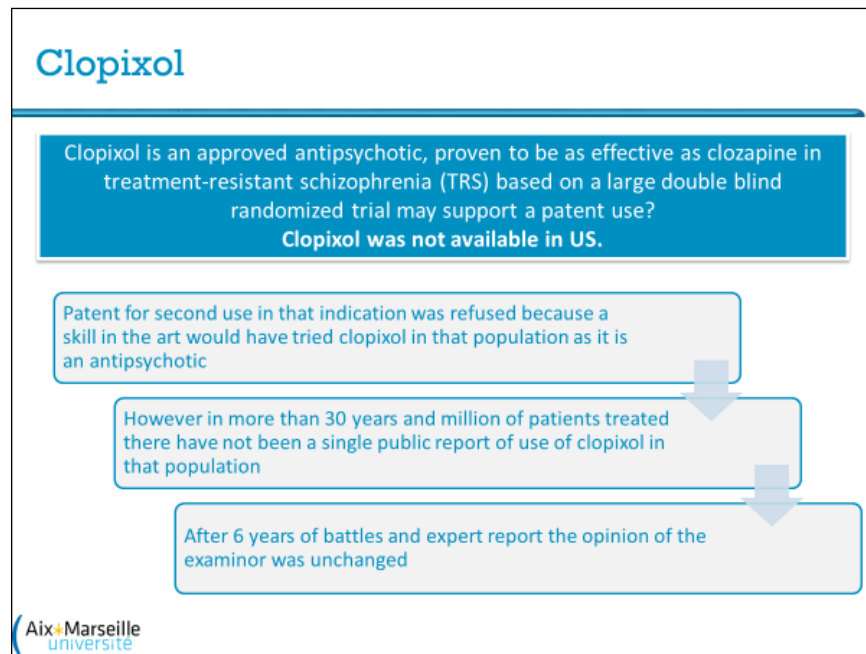
PANSS total score varies from 30 to 210



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A company has identified Clopixol®, for a number of reasons based on preclinical studies and other things, as a potential treatment for patients who are resistant to all schizophrenia treatments. They have done a double-blind random-

ized clinical trial where they show that they reach exactly the same level of efficacy of Clozapine but they were not displaying the same fatal side effects.



But it was impossible to get the patent because, despite all those data, it was stated by the patent examiner that any person skilled in the art would have tried this product because this product is indicated for schizophrenia; therefore, if a patient is resistant, you may try it. So there is no invention behind it.

The product has been on the market for more than thirty years. Millions of patients have been treated, and yet there has never been one single report that this product may be effective to treat these treatment-resistant patients. After six years of battle, the company has decided to abandon the project. We are talking about a lifesaving therapy.

Background

- VLB has been historically developed in Russia within academic institution
- Development was halted following disruption of Soviet Union.
- It was patented only in Russia for the treatment of epilepsy and was then shelved
- The product was later acquired by a western company and was under re-development by Marco Polo Pharmaceuticals (MPP).

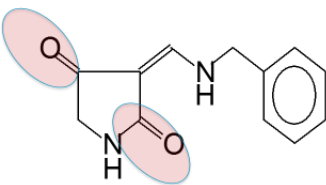
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The other interesting example is VLB-01. This product was historically developed in Russia within an academic institution and was halted following the disruption of the Soviet Union. It was patented only in Russia for epilepsy.

The product was acquired by Marco Polo Pharmaceuticals, a Western company that started developing the product. The company discovered that this product is a pure MT3 receptor, a

melatonin-3 receptor which was totally unknown. To date nobody has ever developed this class of product, and this is a totally new unknown class.

VLB-01 Receptor Profiling



- A large screening has shown that VLB-01 is acting exclusively on the ML2 (MT3/QR2) receptor

There are no example of aproved product or in development product with such mode of action

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I am not going here to talk about pharmacology, but this is to show you that a lot of work has been developed to identify the mode of action of this product, which is totally innovative and totally unknown.

It has potential for other indications, such as a painkiller, antipsychotic, or treatment for bipolar disorder. But it was not possible to get a patent for those indications

because so many epileptics also have other indications similar to that one, painkiller or bipolar disorder, and therefore it was not innovative to say that the product known to be an antiepileptic may also be active in those indications. Here again, the company has given up and the new opportunity for a totally new therapeutic class, totally unknown today, was lost because of the lack of patent.

The other point is the competition with a generic or biosimilar. If you go to market with a product that has a generic or a biosimilar, there is a high risk that they are going to compete and pick up the market because they are going to be cheaper. This will discourage the development.

Example of RANKL Inhibitors

- With a patent use of RANKL inhibitors for their efficacy in the regulation of male fertility (preclinical and clinical evidence)
- NewCo may use the approved therapy Denosumab, a monoclonal antibody RANKL inhibitor
- Because of short term use and high value by avoiding Medically Assisted Procreation, the price will be significantly higher than current Denosumab
- Denosumab patent expiration is planned in 2021 implying the launch and plausible competition from off label use of biosimilars
- This is a possible catch 22 situation unless a smart way to overcome the off label use of the biosimilar

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I would like to show you an example. There is a patented use for receptor activator of nuclear factor kappa- β ligand (RANKL) inhibitor for the regulation of male fertility. The male fertility is poorly treated, and the only treatment that is being used is the *ex vivo* assisted procreation.

There is a product, Denosumab, which is an antibody RANKL inhibitor. This product could have been used, but because of the risk

of competition, because of the difficulty to change the treatment regimen, etc., there may be no option. The company is still investigating opportunities on how to make it, to identify an opportunity to avoid the competition.

Because the therapy is very short with a very high added value, because you prevent very expensive alternative treatment, you are going to deserve a very high price. If you do not get that price, you are not going to recoup your investment because it is a very short therapy. It is not a chronic therapy like for osteoporosis, like Denosumab is used today, where you can recoup your investment because the duration of treatment is very different.

There are other products from the same class which are being developed by other companies, but no company is interested in developing this indication

because if you raise attention that this class of therapy may have an impact on fertility, you may be asked to have a lot of studies from a toxicologic perspective to identify what is the consequence on the future generation of this impact on fertility and to prevent entering into that field, the companies want to keep away from this indication.

You see other opportunities that may be useful for the society that are being wasted.

Lucentis Avastin

Avastin is an EVGF developed for oncology by Roche. Avastin has shown to be effective in Age-Related Macular Degeneration

Roche and Novartis agreed to develop Lucentis (similar to Avastin) for DMLA but much more expensive

In UK Avastin is used in ophthalmology clinics instead of Lucentis

In France the government allowed off label use of avastin instead of Lucentis

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An interesting one is Lucentis Avastin. Avastin is a vascular endothelial growth factor (VEGF) that which was developed for oncology by Roche, and it has been shown by serendipity to be effective on *dégénérescence maculaire liée à l'âge* (age-related macular degeneration) (DMLA).

Roche has decided together with Novartis to develop a biosimilar-like — they say it is not exactly the same, but let's say that these

are two products that are reasonably close — for DMLA. Of course, it is much more expensive because it has a benefit that is different.

In the United Kingdom Avastin is being used in the ophthalmology clinic instead of Lucentis.

**Temporary Recommendation for Use (RTU):
Avastin® for Financial Reason**

Article L. 5121-12-1 of public health code issued from law of December 29, 2011 authorized the French Agency for the Safety of Health Products (ANSM) to elaborate a Temporary Recommendation for Use (RTU) to a drug that already has a marketing authorization (MA) in France, to be used for another indication(s) not conform to its MA.

Avastin Marketing authorization indication

Avastin is a cancer medicine used in combination with other medicines to treat :

- Adult patients with metastatic carcinoma of the colon or rectum
- Metastatic breast cancer
- Unresectable advanced, metastatic or recurrent non-small cell lung cancer
- Advanced and/or metastatic renal cell cancer
- Epithelial ovarian, fallopian tube or primary peritoneal cancer

**RTU indication for Avastin:
The treatment of age-related macular degeneration**

**RTU established in
24/06/2015
and started in 01/09/2015**

RTU is valid for 3 years renewable

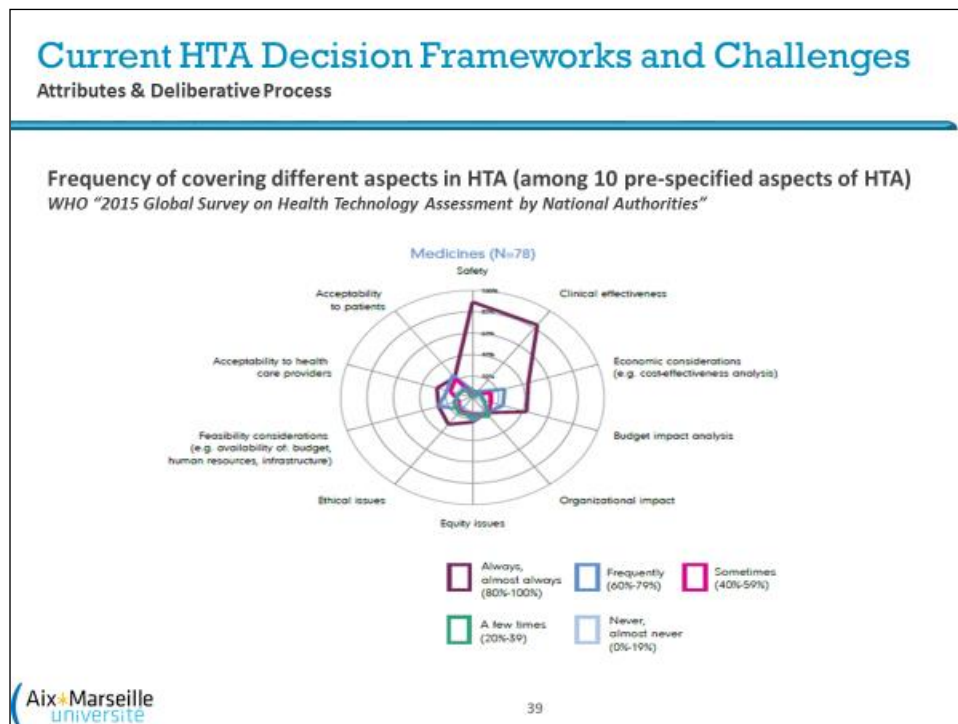
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In France the government has decided to provide a temporary recommendation of use for Avastin, just for financial reasons, because it is cheaper. It was provided in 2015 and is still active today.

This means that there is a lot of uncertainty because if you develop a second medical use and the government decides, against the wishes of the company owning the marketing authorization of the initial product, to give it “marketing authorization lite” — because it is like giving a marketing authorization — then physicians are going to use the much cheaper product.

Roche has stated that Avastin is used for this purpose, etc., but this is totally illegal behavior because the temporary recommendation for use has been designated to allow a safe off-label use of product under specific conditions. But what is the predictability? Not too much.



Probably in Europe — which does not exist today to the same extent in the United States — the Health Technology Assessment (HTA) process is the most critical hurdle for this type of product. HTA uses mainly safety and clinical effectiveness to make their decision, eventually cost-effectiveness, and nothing else, which means all the other dimensions — acceptability of the patient, patient preference, ethical issues, equity, organizational impact — are totally ignored by the HTA organization in practice. In theory, they all say they integrate that, but in practice it is a survey from HTA organizations where they say they do not integrate those elements.

Many of the second-use therapies provide benefit on those dimensions and those are not captured by HTA organization; therefore, they are systematically rejected as having no additional benefit compared to available therapy because they focus only on two main dimensions and ignore the others.

In some countries, second-use medicines are not eligible for HTA. That is the case in Germany, for example, where the Federal Joint Committee (G-BA) does not review products already approved.

In most countries, second-use medicines are not eligible for HTA scientific advice, so HTA organizations say, “We do not recognize your benefit.” But when you want to consult them in advance to understand how you should develop your product to make sure that they analyze your benefit, they say, “We do not consult for lousy product like yours. You are second use; you are not a real product.”

Finally, if you want to go for coverage with evidence development — that means at the time of marketing authorization you get the chance to bring evidence after reaching the market to support the value of your product — second-use medicines usually are not eligible for this type of agreement. That is the case in many countries. I can cite as an example the Netherlands, where they are excluded from all these pricing agreements, such as, for example, differential pricing would not work for these types of therapies.

Finally, pricing is often also a discouraging step in Europe. In Europe price is set in most countries by governmental bodies or by negotiation because you have one single insurer covering 90–100 percent of the population, depending on the country.

Siklos an Interesting Story

- Sickle cell syndrome is a severe hematologic rare condition targeting young children and treated with an oncology product off label Hydrea. The product is an IV formulation while it is used orally by children
- 29th of June 2007 Addmedica is granted a MAA for a new formulation developed for sickle cell syndrome for children named Siklos
- The HTA considered Hydrea as the comparator and concluded at a minor benefit with no comparative evidence
- The pricing committee set the price of Siklos® at €67 (1000 mg) and €13.40, whereas the average EU price was €550 and €110 for the 1000 mg and 100 mg pack, respectively.
- A long court case with multiple procedures in front of various jurisdictions supported the pricing committee decision. Ultimately the product was not made available in France

I want to show you here the example of Siklos. Sickle cell syndrome is a very severe hematologic rare condition that targets young children, who are currently treated with an oncology product called Hydrea. This product is designated to be administered i.v. and is given orally to those kids, some of whom are two, three, four years old, etc.

The company Addmedica decided to file for an orphan designation, which they got, and developed a specific formulation for those patients.

In France the HTA decided that they were of minor benefit, and when you get minor benefit you are not eligible for a premium price. Therefore, in the

pricing committee they were offered €67 and €13 for a different dose and package, while in the rest of Europe the average price was about ten times higher. The rationale is that you do not bring any benefit. The chairman of the pricing committee never tried to give an i.v. formulation orally to three-year-old children; if he had tried, he would realize whether this benefit is appropriate or not.

Addmedica went from court case to court case, through different courts, and ultimately they lost the case.

Conclusion
<ul style="list-style-type: none"> • Current regulation happen to prevent multiple second use medications to reach the market despite a very high potential public health impact • Multiple opportunities exist: orphan designation, new indication extension, pediatric extension, PUMA program etc. • If no options are feasible then public funding should support development of such opportunities • Action is warranted to avoid such society massive loss of opportunities

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To conclude, I would say that the current regulation prevents access to many products that may have a high public health impact and probably at a much lower cost than some of the innovations we see today and not less benefit.

We have been able, especially in Europe, to be very creative — with orphan designation, new indication extension, pediatric extension, pediatric-use marketing authorization (PUMA) program, etc. — to

give a chance for products to get extension of their exclusivity or data protection, but not really in this specific situation.

I can understand that from the legal perspective there are no options, but I do not understand why health authorities do not fund the development of such products and do not fund clinical trials to identify the value and measure the value of such products and allow society to benefit from it, even through the generics that are publicly available.

If we do not want to continue to have such a massive loss of opportunity from a public health perspective and for the society, we should take action.

Thank you for your attention.

MR. CORDERY: Perfect. Thank you. You are wonderful. Great.

Do we have a question or two for Mondher? Yes, we do. Alasdair was first. Robin, you can go second — sorry, I know you are not used to this.

QUESTION [Sir Alasdair Breckenridge, Former Chair of MHRA UK]: Thank you very much for that. Most of what you said I agree with.

Do you believe that there is a case for closer integration of regulation at HTA? The example I cite is in Australia, where when a new product comes up for licensing, both the licensing/regulatory authority and the HTA see the product at the same time; and then, when it comes up to the government for a decision, the government does have both sides of the equation, the regulation and the HTA, to consider.

PROF. TOUMI: I believe this is a political decision. Both decisions, regulatory and HTA, are fundamentally different and call for totally different paradigms. Therefore, they should be handled separately, although synergies exist and relationships should exist.

The decision in Australia is to look at both in parallel in and to say, “If you cannot agree with HTA, you cannot have the license.” Therefore, there is no discussion for a product available for those who can pay and not available for those who cannot pay because it did not get a marketing authorization. If you get the marketing authorization, like in the United Kingdom today and many other countries, and the National Institute for Health and Care Excellence (NICE) says “not recommended,” but people start pushing at the door and say, “It is available, it is approved, it has a good benefit-risk ratio, and we need access to it,” then NICE says, “No, because it is not cost-effective.” The way it operates in Australia avoids this discussion, because to be available you need to be cost-effective and get your license at the same time.

This is more a political discussion. I do not know whether it is going to be used to delay. The Australian system is not very good in terms of time to access. Time to access is dramatically delayed compared to most European countries, so it may be used to delay access to product also from the government perspective.

Frankly speaking, it is a political decision. My opinion is I would prefer that they stay separated, but I have no problem if it is not. Then you have to be vigilant. Sorry.

QUESTIONER: [Sir Alasdair Breckenridge]: If you consider the early access schemes that we have in Europe now, at the same time the people who are giving advice to the companies are the regulators and the HTA together with patients and other bodies. This is an example where most of the exciting new drugs, the biopharmaceuticals, have early access; and there you have an example of regulators and HTA sitting together in the same room with the company. I would put it to you that this is a model to which we should give greater consideration.

PROF. TOUMI: I fully agree. Then you speak about early dialogue that happens before marketing authorization to guide the pharma companies on how they should develop their product to match the expectation from regulators and from HTA bodies. I believe that is a very positive step forward; I fully agree with you. But once it is approved, whether they should work together and give both in parallel or not, I think it is open for discussion.

MR. CORDERY: Thank you.

Robin, did you want to ask a question?

QUESTION [Prof. Robin Jacob, University College London]: I am going to ask you something about what you presented in Seattle. You presented a lot of research on off-label use. Those who have not seen Professor Toumi’s work on that should, and we will somehow get a reference sent out to it all.¹⁵

¹⁵ See Mondher Toumi et al., *Value Added Medicines: What Value Repurposed Medicines Might Bring to Society?*, J MARK ACCESS HEALTH POL’Y 2017; 5(1): 1264717, published online 2016 Dec 23. doi: [10.1080/20016689.2017.1264717](https://doi.org/10.1080/20016689.2017.1264717); Mondher Toumi et al., *Medicines for Europe White Paper, Value Added Medicines Rethink, Reinvent & Optimize Medicines, Improving Patient Health & Access* (May 2016), available at <http://www.medicinesforeurope.com/wp-content/uploads/2016/05/White-Paper-30-May-2016-Toumi-Value-added-medicines-Rehink-reinvent-optimize-medicines-improving-patient-health-access.pdf>.

Could you just give a summary of your overall conclusions of the amount of off-label prescribing and whether it is doing any good, doing any harm, or neither?

PROF. TOUMI: Off-label prescribing remains a major issue from the pharmaceutical perspective. It is continuing to grow, especially with biologics. We see, for example, how the anti-TNF and many other biologics expand their indications, but physicians started to use them in other indications before they get marketing authorization. This is exposing patients to risks and benefits, but the risks and benefits are totally unknown.

We thought, with all those new therapies, this may be going down because they are very targeted, but in reality they are targeting inflammation, which is a very broad concept present in many diseases. That has not diminished. That continues to increase.

My belief is that it is a threat to public health because it often starts without any evidence. People start using it and then they start considering that maybe we should do a trial. Then we do a trial, and then we do a second trial, and then the company may do a well-conducted trial which may have a different conclusion. Sometimes companies do not conduct the trials. Then we stay with clinical trials that are not good clinical practice (GCP) compliant, and therefore they may have biases that lead to false conclusions. I think this is a major issue with off-label use.

QUESTIONER [Prof. Jacob]: Thank you.

PROF. TOUMI: It is not diminishing. Rather, it is increasing.

MR. CORDERY: Thank you very much.

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.
Thursday, February 8, 2018 – 11:25 a.m.*

**Session 1C:
Examples of Success: The Lyrica® Story in Denmark**

Moderator:
Dr. Thomas Hirse
CMS Hasche Sigle, Düsseldorf

Presenter:
Sture Rygaard
Partner, Plesner, Copenhagen

Panelists:
Dr. Ute Kilger
Boehmert & Boehmert, Berlin

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

Dr. Trey Powers
Sterne Kessler Goldstein Fox PLLC, Washington, D.C.

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MR. CORDERY: This session is going to be led by Sture Rygaard, who is with the Plesner law firm in Denmark. Denmark is a small country, but it has been very influential, and I am hoping we will all learn a lesson from Denmark, depending on what Sture has to say.

MR. RYGAARD: I have been asked to speak about the Danish Lyrica® case,¹ which to a wide extent has solved the problems of second medical use (SMU) patents for prescription drugs in Denmark, and then I will also touch upon how this is looked at in tenders for hospital drugs.

The regulatory system in Denmark

Skinny-labelling/carve out

- Generics are allowed to exclude indications still covered by patent when obtaining an MA under the abridged procedure

Indication on the prescription

- In Denmark any prescription must include information about the indication

Substitution did not respect patent rights

- The Danish Medicines Agency ("DKMA") decides which medicinal products can be substituted with each other - in substitution groups
- Patent rights were not taken into consideration
- The pharmacies are under an obligation to dispense the cheapest medicinal product in the same substitution group, unless the doctor has stated "No substitution" on the prescription, or the price difference is below certain limits

PLESNER

First of all, we will start with some basics on the Danish regulatory system. In Denmark, skinny labeling or carve-out is possible, as it is in the whole of the European Union, so the generics can cut out any patented indications in order to try to avoid patent infringement.

Second, there are indications on prescriptions in Denmark, so the doctor always has to put the indication on any prescription that he writes, and then the patient will take the prescription to the pharmacy and the pharmacy will actually print out a label. The label contains both the indication and how the drug is to be taken, so "twice a day," blah, blah, "for pain" or for whatever. This is a good thing in relation to patent infringement, I think, that we have the indication on the label.

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

Further, the Danish Medicines Agency (DKMA) decides in which group different drugs should be categorized, and then at the pharmacy the pharmacist is obliged to substitute with the cheaper drug in that substitution category.

It used to be that patent rights were not taken into account when the Health Agency made these substitution groups. But then the Lyrica® case came along. We will look at the facts. We already heard a little bit about it.

The Lyrica® case: Facts

- Pfizer's second-medical use patent:
"Use of [pregabalin] or a pharmaceutically acceptable salt thereof for the preparation of a pharmaceutical composition for treating pain."
- Pfizer marketed Lyrica® which contains pregabalin approved for three indications:
 - A. epilepsy,
 - B. generalized anxiety disorder and
 - C. neuropathic pain (still patent protection)
- The share of the sale of Lyrica® prescribed for the treatment of pain in Denmark amounted to approximately 50-60% of all sales of Lyrica®
- Krka marketed the generic product Pregabalin "Krka" approved and labelled only for the non-patent protected indications (a and b)

Pfizer had a patent that was still valid, a Swiss-type claim patent: "Use of [pregabalin] or a pharmaceutically acceptable salt thereof for the preparation of a pharmaceutical composition for treating pain."

Pfizer marketed the Lyrica® product which contained pregabalin and it was approved for three indications: epilepsy, generalized anxiety disorder, and neuropathic pain. As we heard, only the pain indication was still under patent protection. The general substance patent had run out about a year before.

The share of the Lyrica® sales that were used for pain was about 50–60 percent in Denmark, and we knew that Krka was coming along with a generic product that was skinny labeled, where the pain indication had been carved out.

The Lyrica® case: The regulatory jeopardy

- Before generic entry, Pfizer contacted the DKMA to try to solve the problem that substitution between Lyrica® and generic pharmaceuticals could constitute patent infringement
- The DKMA asked the DKPTO for a memo about the scope of the second medical use patent in view of the substitution rules. The DKPTO found that:
"When medicinal products are listed as substitutable and the pharmacist for that reason is obliged to hand over the least expensive of the medicinal products, then this will immediately lead directly to an infringement of the patent if the generic medicinal products are sold/put on the market for the use for the patented indication."
- Despite the memo from the DKPTO, the DKMA - after consulting the Ministry - denied to alter the substitution rules at the time
- The DKMA decided to place Lyrica® and Pregabalin "Krka" in the same substitution group
- So, the pharmacies were obliged to dispense Pregabalin "Krka" even if the doctors had prescribed Lyrica® for pain

So what happened? Of course this was going to be a regulatory jeopardy. Pfizer thought it might try to avoid this by contacting the Danish Health Agency (DKMA) and try to persuade them to do something about it and change the substitu-

tion rules in Denmark.

The DKMA listened, and they saw that there might be a problem, and so they said, "Well, we will ask the Danish Patent Office (DKPTO) for an opinion to see whether they believe there is infringement."

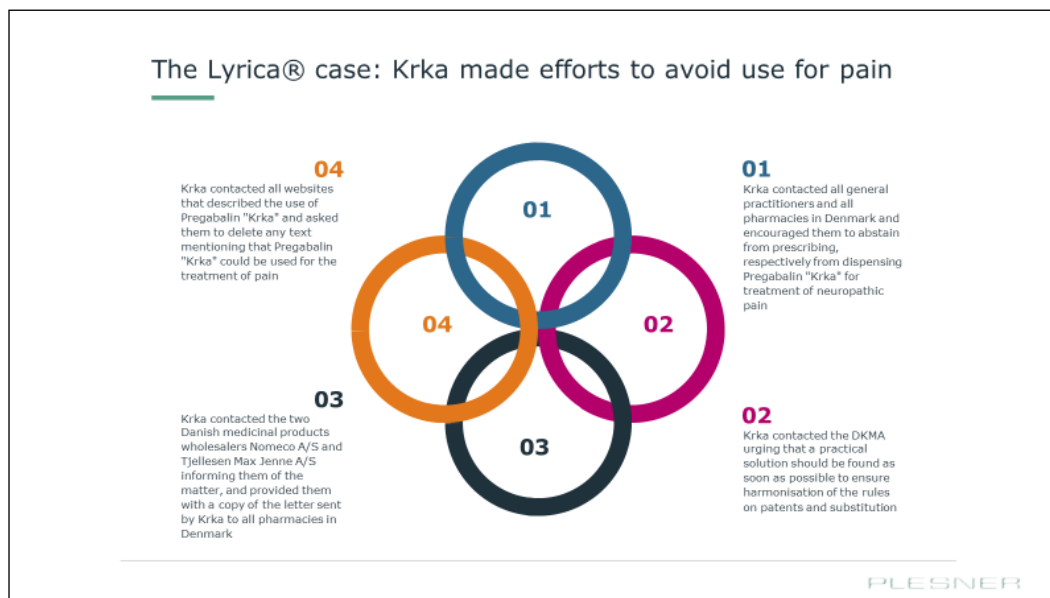
The DKPTO came out with a rather clear opinion: "When medicinal products are listed as substitutable and the pharmacist for that reason is obliged to hand over the least expensive of the medicinal products, then this will immediately lead directly to an infringement of the patent if the generic medicinal

products are sold/put on the market for the use for the patented indication.” They did not specify in detail which patent law provisions were actually infringed by this, but it was a clear opinion that there was an infringement.

Despite this memo from the DKPTO, the DKMA — after consulting the ministry, who really decided this I think — said: “We will not change the rules. We will wait for a ruling and see what happens. So, if you have a problem, you probably have to take it to court.”

The general rules were followed. The Krka pregabalin was put in the same substitution group as Lyrica®, and substitution took place in the pharmacies. Pharmacies, of course, were in a bad situation, between a rock and a hard place, whether to infringe the substitution rules or the patent rules. They also urged the DKMA to try to find a solution to this.

After the trial was started, Krka made quite some efforts to try to avoid patent infringement — and we will come back to the claims later which explains why they did this. Krka contacted the pharmacies and the practitioners and said, “Please do not prescribe or dispense pregabalin Krka for the use for pain.” They also contacted the DKMA and asked them, “Please, can you find a solution to this?”



Further, they contacted the two Danish distributors or wholesalers — there are only two in Denmark — of the drugs and asked them to be aware of this, and sent them the letters they sent to the others. They also contacted some websites saying, “Please do not indicate or say that our product can be used for pain.”

Who then to sue, what to do? In Denmark, I think the real crook here, as I see it, was the ministry because the ministry refused to change the substitution rules as they should. But we cannot get a preliminary injunction in Denmark against a public authority, so it was out of the question to get a preliminary injunction against the ministry or the DKMA. We could have filed a normal lawsuit on the merits, but that would take quite a while in Denmark

PI request against all 219 pharmacies in Denmark and Krka:

- Claims and infringement arguments against the pharmacies:
 - Claim for injunction against dispensing generic pregabalin for treatment of pain (many alternative claim formulations because of regulatory rules)
 - By dispensing Pregabalin "Krka" to patients for treatment of pain and placing a pain indication label on the product, the pharmacies commit a separate and direct patent infringement
- Claims and infringement arguments against Krka:
 - Claim for injunction against sale of Pregabalin "Krka" without ensuring that the product is not distributed and/or dispensed for the treatment of pain as long as the patent is in force
 - Claim for injunction against sale of Pregabalin "Krka" without providing express written instructions to the purchaser that the product must not be distributed and/or dispensed for the treatment of pain as long as the patent is in force
 - Contributory infringement

PLESNER

Instead, Pfizer, represented by my colleague Mikkel Vittrup, decided to make a claim for an injunction against all 219 pharmacies in Denmark. The claim was that they should be enjoined from dispensing generic pregabalin for treatment of pain, and there were some other alternative claims as well.

The argument was that by dispensing pregabalin Krka to patients for treatment of pain, placing the pain indication label on the product, the pharmacies commit a separate and direct patent infringement. That was based both on using the process in the patent claim and also on a product by a patented process. So we tried both.

In relation to Krka, there was a claim for injunction against the sale of pregabalin Krka without ensuring that the product is not distributed and/or dispensed for the treatment of pain as long as the patent is in force. Of course, Krka had done some efforts, but it was still being used and distributed for pain.

There was a second claim for injunction against the sale of pregabalin Krka without providing express written instructions to the purchaser that the product must not be distributed and/or dispensed for the treatment of pain as long as the patent is in force.

These claims against Krka were based on contributory or indirect patent infringement — whatever you want to call it — by delivering essential means to someone else which are suitable and intended for exploiting that patent.

The Lyrica® case: Ruling

- The pharmacies were enjoined from dispensing Pregabalin "Krka" for the treatment of pain as long as Pfizer's patent is in force:

"In consideration of the fact that the Patent in Suit is a second medical use patent with a Swiss-type claim aimed at protecting the use of an already known substance for the treatment of a indication, the court concurs that the pharmacies' dispensing of Pregabalin "Krka" with a label stating that the medicinal product is intended for the patent protected treatment of the indication pain constitutes infringement of the Patent in Suit, see Section 3(1)(iii) of the Danish Patents Act."
- The claim for an injunction against Krka was not allowed
- The primary claim ("ensuring not dispensed for pain") not sufficiently clear to be enforced
- Alternative claim already fulfilled (and PI was awarded against pharmacies)

PLESNER

The ruling: The court came to the conclusion that the pharmacies should be enjoined from dispensing pregabalin Krka for the treatment of pain as long as Pfizer's patent was in force. They said: "In consideration of the fact that the Patent in Suit is a

second medical use patent with a Swiss-type claim aimed at protecting the use of an already known substance for the treatment of a indication, the court concurs that the pharmacies' dispensing of Pregabalin 'Krka' with a label stating that the medicinal product is intended for the patent protected treatment of the indication pain constitutes infringement of the Patent in Suit," and they referred to Section 3(1)(iii), the "product-by-process" provision of the Danish Patents Act.

As against Krka, the claim for an injunction was dismissed. The court found the first claim, that they should “ensure” that its product was not dispensed for pain, not sufficiently clear to be enforced. It was a bit unclear what the enforcement court should do in this respect, i.e. what should be required by Krka. Should they actually go out and put a person in every pharmacy, or what could actually be required for them to “ensure” that this would not happen?

The second claim that the court considered was already fulfilled, that they should contact the customers, and also the court referred to the fact there was an injunction against the pharmacies, so anyway it would not happen.

They changed the law

- Following the PI, the DKMA informed the doctors and pharmacies that the obligatory substitution between Lyrica® and Pregabalin “Krka” was annulled
- Subsequently, the substitution rules were changed and now respect second medical use patent rights, so “***if a prescription for a medicinal product has been issued for the treatment of the patented indication, the pharmacy shall dispense the medicinal product with the patented indication***”
- The DKMA has asked patent holders to inform them of SMU patents and then notifies the pharmacies when a medicinal product has a patented indication
- The provision also applies to a situation where the doctor prescribes a generic product “off-label” under the doctor’s freedom of prescription
- The provision does not apply to hospital pharmacies

The consequences of the ruling were:

- That DKMA immediately informed the doctors and pharmacies that they should not substitute the Krka product for Lyrica®.
- Also, they actually changed the rules: From now on it is like this: if you have a patent for

second medical use, you should inform the DKMA about it; then they will inform the pharmacies of the SMU patents; and the pharmacies when they get the prescription from the doctor will put in the indication and they will find out that for this patented indication they cannot do substitution. In this way the patent for the second medical use is actually protected now for prescription drugs in Denmark.

- This means that even if the doctor has put “pregabalin Krka” on the prescription, it would not be dispensed for pain.
- The provision does not apply to hospital pharmacies.

I think this has solved in Denmark the situation in relation to prescription drugs, but not in relation to hospital drugs.

Hospital products sold through tenders

The tender system in Denmark:

- Amgro is responsible for the procurement of 99% of all medicinal products used at the public hospitals. The procurement is organised through public tenders by Amgro
- Amgro does not organise tenders by indication. Instead, tenders are organised by active ingredient or therapy area, and Amgro does not regulate how the products are subsequently used by the hospitals
- The hospitals’ use of medicinal products is regulated, inter alia, through the issue of various recommendations and guidelines from public advisory boards
- There are no specific rules that govern how Amgro/the regions/the hospitals must deal with second medical use patents
- The Ministry of Health in Denmark has stated that due to regulatory law, public bodies cannot recommend cross-label use when there is an approved drug for the relevant indication

Hospital drugs are sold through a tender system.

Amgro, a public tender party, does all the tenders for all medicinal products used at public hospitals in Denmark. By far, most hospitals are public, and they get the tenders for all the drugs.

Amgros used to do the tenders based on the active ingredient or the therapeutic area and not take patents into account. However, they have changed those rules, so now there is a new model where they make a tender, and if there is a patent-protected indication, they will make sure that there is at least a tender contract that will cover the full label, that has the full label. Then they say that at least they have done their job and they leave it for the hospitals then to decide which products to use.

Hospital products sold through tenders

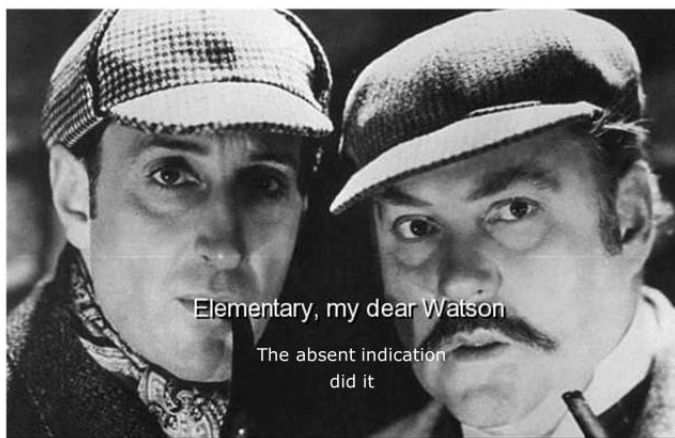
New model adopted by Amgros when SMU and drugs with skinny labels:

- Amgros enters into a number of parallel framework agreements
- One of the framework agreements is reserved for a medicinal product which is approved for the patented indication (full label product)
 - The winner of this framework agreement will normally be the original product (patentee), but can also be a full label generic product
- The tender conditions state that a certain share of sales is estimated to be used for the patented indication
- The hospitals are not obliged to buy the cheapest product if the product is not approved for the patented indication
- As there is no obligation as such for the doctors/hospitals not to use the drugs cross label, it is recommendable to follow up with the hospitals about this

Unfortunately, as things are now, there are no rules that make it mandatory for the hospitals to use the full-label product, so it might be that the doctors at the hospitals have the full-label product on the shelf but they decide to use a carved-out label product for that treatment. Due to

this, right now the recommendation in Denmark is that we make sure that the tender is split up. We make sure that there is actually a contract available for the full label, but then follow up with the hospitals afterward, or the regions that are in control of the hospitals, so that we are sure that they are aware that there is a patent and that they should respect it.

I should mention that this full-label product that Amgros accepts for the tender could be a generic product. In that sense, we are not quite there yet with the Danish rules.



Finally, as I see it, it is not really a mystery what is wrong with the tender system in Denmark. It is rather “Elementary, my dear Watson, the absent indication did it.” I think whenever a hospital or a doctor wants to use a product when the indication is absent from that product, there should be an obligation for the

hospital or the doctor to check on their computer whether there is a patent for that indication; and, if there is a patent indication, the screen should be red and tell him you cannot use that product or you need to use a specific patented version, the Lyrica® product in the pregabalin case.

That should be rather simple, but I think it is important that it is done and it is put into the IT systems, because currently I do not know how the doctors

could actually know. They have no means of knowing whether there is a patent or not. It is not really up to them to spend time on this. It should be there when they want to use it.

Thank you

DR. HIRSE: Thank you, Sture.

We now move on to our panel discussion. I am happy that Ute Kilger from Boehmert & Boehmert, Jane M. Law from Gibson Dunn & Crutcher, and Trey Powers from Sterne Kessler Goldstein Fox are with us.

We had a previous discussion over the phone about how we should structure this. Because there are some other countries where we have had the Lyrica® story as well and the decisions are very variant and have very variant reasonings, it would be good that Ute will say something about the German cases, and then Trey and Jane will say something about the U.S. case, which — to my knowledge — was very straightforward. I will try to give some information, but only a little, because Gareth already touched on it through the UK case, where we have next week the oral hearing before the Supreme Court.²

I would now invite you, Ute, to say something about the German cases.

DR. KILGER: The situation in Germany — patent-wise and market-wise — was similar to Denmark. When generics entered the market, in 2015, the biggest market share was the indication that was still patent-protected, the other indications did not have such a big market share, and the basic compound patent was expired. In Germany, shortly before the expiry date of the use patent in 2017, the patent was invalidated before the German Federal Patent Court.³

I am very happy that Christoph has explained the basics about the German laws and the legal environment, so I can be very brief on that.

Yes, we also have automatic substitution rules in Germany, and, in contrast to Denmark, the doctor would prescribe by name or by API with an indication of strength, dosage, or administration form or packet size, but not with the medical indication.

A branded product is normally prescribed *aut-idem*, which means allowing substitution. The doctor has, in principle, the possibility to invalidate that *aut-idem* sign, but of course doctors are also under budget pressures and would normally not invalidate this sign.

The public health insurances, as Christoph laid out, offer rebate agreements to pharmaceutical companies and offer exclusive agreements via public tenders.

The pharmacists have the obligation to substitute, i.e. they dispense a product for which a rebate agreement is in place or they dispense one of the three

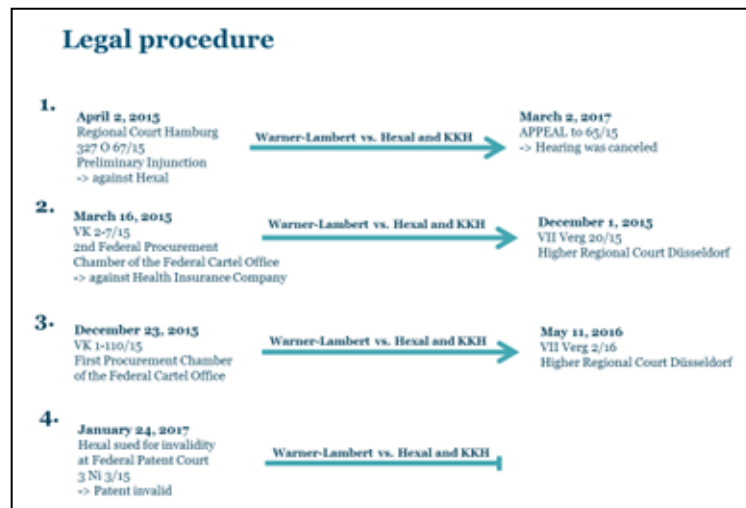
² Warner-Lambert Company LLC (Appellant) v. Generics (UK) Ltd t/a Mylan and another (Respondents), Case ID: UKSC 2016/0197; UK Supreme Court case details and hearings documents available at <https://www.supremecourt.uk/cases/uksc-2016-0197.html>. [Note: Subsequent to this conference, the UK Supreme Court hearings were held February 12–15, 2018. See LifeSciencesIPRReview, Summary from the UK Supreme Court Hearing, available at <https://www.lifesciencesipreview.com/news/warner-lambert-v-actavis-a-summary-from-the-uk-supreme-court-hearing-2723> (Feb. 21, 2018).]

³ Warner-Lambert v. Hexal and KKH, Federal Patent Court, 3 Ni 3/15 (Jan. 24, 2017) (patent invalidated).

cheapest products that meet the requirements. The sanction is quite harsh if they do not do so: 'they do not get any refund from the health insurance.

The pharmacists have software that is fed with all these rebate agreements. Once the pharmacist would look up a certain medicament by brand name or API name, then the software would point to the cheapest substitute because all the rebate agreements are available in the software.

In the Lyrica® case there were quite a lot of proceedings, one of which was already mentioned. In the patent infringement proceeding before the Regional Court in Hamburg, Warner-Lambert was successful in getting a preliminary injunction against Hexal because of indirect patent infringement.⁴



This was a new development in German case law and it was a right step forward, in comparison to former case law in Germany. You may know with respect to infringement of second medical use patents, the German courts have developed the theory of the “manifested arrangement,”

which means a second medical use patent is infringed if this use somehow is manifested into the medicament.

For instance, if you have a new dosage regimen directed to smaller doses and then you produce the medicament too in smaller doses, meaning packaging the pills according to the new regimen, then the new use has manifested into the medicament.

Also, if the use is on the label of the medicament, the label being regarded as belonging to the medicament, then this too would constitute patent infringement because it is in a manifested arrangement. But if you look at carving-out, or skinny labeling, generics could get out of the patent infringement.

The Regional Court in Hamburg was the first court in Germany to say that manifested arrangement is already present by the manufacturing of pregabalin if it can readily be used to treat neuropathic pain.

Therefore, signing the rebate agreement without clarifying that the offered product cannot be sold or prescribed for the patented second medical indication constitutes an indirect patent infringement because the purpose is added by the pharmacist due to automatic substitution and it is obvious that the product offered and supplied under this rebate agreement will be used in the patented indication. This was the first court decision saying that carving-out or skinny labeling does

⁴ Warner-Lambert v. Hexal and KKH, Regional Court Hamburg 327 O 67/15 (Apr. 2, 2015) (preliminary injunction against Hexal); appeal to 65/15 (hearing canceled).

not exclude indirect patent infringement if the rebate agreement is not limited to the non-patented indication; thus, patent law must be respected at all times.

The operational part of this judgment was that the generic company must not enter into a rebate agreement on pregabalin or supply pregabalin in the course of such a rebate agreement if the use of pregabalin for treating pain is not excluded in that rebate agreement without explicitly pointing out to the other party that the offered or supplied pregabalin is not offered for treating pain.

Of course, the question is: Would that be enough, or would the substitution rules still apply? Would the pharmacists still dispense each and every generic product also for pain? Is this really enough? I think we are quite happy with the decision in Hamburg, meaning that at least it has been decided that skinny labeling would not escape from patent infringement.

Further, there were at least two proceedings before the Federal Procurement Chamber of the Federal Cartel Office against the health insurer initiating tender processes including the patented use.⁵

The subject matter of the first proceeding was a tender procedure where pregabalin was tendered per se; thus, it was not a split tender, meaning a patent-free tender and a tender to the patent-protected indication, but it was just a tender for pregabalin per se. It has been decided by the court that the health insurance companies are obliged to start the tender procedure anew, this time respecting patent law, because if a specific indication is patent-protected, the health insurers cannot ignore this and must consider this in the tender procedure in order to prevent an automatic substitution of the original product by generic versions for the protected indication.

Also, it is not sufficient for the health insurer to just pick the least-expensive offer; the bidder must have the necessary suitability, suitability not only in terms of quality. A bidder has to fulfill several requirements. One requirement is — according to this new case law — that the tendered product would not infringe patents. In this case, bidders lacked also the necessary suitability.

Thereafter, the tender process started anew, and this time there were two tender processes, one tender process directed to the patent-free indication and the other directed to the patented indication. But still the patentee, Warner-Lambert, was not satisfied because they argued that patent infringement will be unavoidable; because wide substitution will be the rule, regardless of whether the tender process is split, it was an “impossible offer.” How could one avoid that the pharmacist will substitute?

In addition, the agreements that are limited to an indication are not reported by the association of the health insurers and they are also not listed in the pharmacists’ software. Eventually the tender process was split. But, at the end of the day, the pharmacists will look up the substance, and then the generic product will pop up regardless of whether or not this is prescribed for a patent-free

⁵ Warner-Lambert v. Hexal and KKH, Second Procurement Chamber of the Federal Cartel Office, VK 2-7/15 (Mar. 16, 2015) (against health insurer); VII Verg 29/15, Higher Court of Düsseldorf (Dec. 1, 2015); Warner-Lambert v. Hexal and KKH, First Procurement Chamber of the Federal Cartel Office, VK 1-110/15 (Dec. 23, 2015); VII Verg 2/16 Higher Court of Düsseldorf (May 11, 2016).

indication. Actually, the pharmacist would even not know which indication the medicament is prescribed for because the doctor would not have written the indication on the prescription.

So, is the problem solved in Germany? I think we made progress, we have taken some steps in the right direction. However, as the pharmacist is not obliged to dispense the medicament in conformity with an indication but only in conformity with the active ingredient, it cannot be controlled whether or not the product is dispensed for the patented indication.

The pharmacists' software still points to all generic medicaments independent of patent conformity. However, there are some examples where the pharmacists' software would give the pharmacist a warning if he is in conflict with law. For instance, if you have to dispense a medicament which falls under the narcotics law and the total amount of drug would be too high, then there would be a pop-up by the software warning that the pharmacist should check and determine whether he can substitute each and every one of the generic medicaments available in view of the total amount of narcotics that can be dispensed.

There is also another exemption from the rule that the pharmacist does not know which indication the dispensed item is used for, and this relates to the dispensing of auxiliary means (e.g. inhalators or things like that), because there is an agreement between the pharmacists' association and the health insurers' association that the pharmacist has to put the indication into the system for such devices, and only then would the pharmacist get reimbursed for the inhalator. Thus, in principle, it should be possible that the intended use could be considered when dispensing medicaments. And, still, doctors are not obliged to invalidate *aut-idem* and prescribe the medicament regardless of whether there is patent protection or not.

I think we have to make some more progress in Germany. Maybe also the health insurers should not compensate if a dispense does not conform with patent laws. Maybe the doctors should at least name the indication on the prescription; that would be very helpful, as it is in Denmark. And the software for pharmacists must be adapted to facilitate the dispense that conforms with patent law.

DR. HIRSE: Thank you, Ute.

Jane and Trey, do you want to add something about the U.S. Lyrica® case?

DR. LOVE: Sure. Thank you.

The U.S. Lyrica® case is almost inapplicable to being discussed at this conference because it was an obviousness case. It was a patent that was upheld by the Federal Circuit⁶ and the real issue that was discussed by the courts was obviousness. So I think all of the issues that Ute was discussing really do not apply in the U.S. scenario.

I will just foreshadow that a case I was involved in that involved Novartis does touch on all of these issues, and Dr. Graham Russell was talking about it early today [see Session 1B], the zoledronic acid case.⁷

⁶ Pfizer Inc. et al. v. Teva Pharms. USA et al., No. 2012-1576 (Fed. Cir. 2006).

⁷ Novartis Pharmaceuticals Corp. v. Actavis LLC et al., No. 2:2013cv01028 – Document 259 (D.N.J. Oct. 23, 2013).

Now I will give it back to you for the list of questions.

DR. HIRSE: Okay, thank you.

I now want to move to the UK case. As Gareth and I already mentioned, we will have next week maybe the end of the Lyrica® case in the United Kingdom because of the oral hearing at the Supreme Court.⁸

Lyrica® SMU Patent Case in UK

- 24 June and 12 September 2014: Revocation Claims by Mylan and Actavis
- 8 December 2014: Infringement suit by Warner-Lambert, including application for interim injunction
- **Interim Injunction Proceedings:**
 - 21 January 2015: Arnold J. dismissed application (no arguable infringement case; balance of justice favored refusal)
 - 28 May 2015 CoA dismissed Warner-Lambert's appeal (arguable infringement case, but balance of justice favored refusal and Arnold J. already ordered that NHS Commissioning Board orders that Lyrica® must be prescribed for patented SMU)
- **Main Proceedings:**
 - 10 September 2015: partial revocation for insufficiency and no infringement; 25 November 2015: Arnold J. decided that amendments for claim 3 handed in by Warner-Lambert through conditional application is abuse of the process
 - 13 October 2016: CoA dismissed parties' appeals
 - 12 to 15 February 2018: oral hearing of Warner-Lambert's appeal against CoA decision regarding revocation of patent

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I am not a UK lawyer, but I try to understand the decisions. Therefore, I just put in the information here to summarize it.

It all started, as in many countries, in 2014. Warner-Lambert applied for an interim injunction, and the interim injunction proceedings occurred in 2015.⁹

The Court of Appeal decision¹⁰ said, “Okay, infringement could be arguable here,” but with respect to the balance of justice they refused to grant the preliminary injunction or interim injunction here. They referred also to the fact that Justice Arnold at first instance had already spoken with the NHS

⁸ 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>.

⁹ Warner-Lambert Company, LLC v Actavis Group PTC EHF & Others, [2015] EWHC 485 (Pat) (Mar. 2, 2015) (Arnold, J.), available at <http://www.bailii.org/ew/cases/EWHC/Patents/2015/2548.html>.

¹⁰ 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>.

Commissioning Board and tried to convince them to order that for the patented indication only Lyrica® will be prescribed and dispensed.

The UK Lyrica® case will maybe end next week. The main proceedings are still pending at the Supreme Court. There have been questions of infringement and validity. I think the oral hearing will mostly focus on validity, particularly because the Court of Appeals upheld the first-instance decision that said, “The claims are invalid for insufficiency and the attempt of Warner-Lambert to amend one of the claims in order to bring it into validity is an abuse of process.” The Supreme Court will have to deal with those questions next week. If at the end it turns out that the Supreme Court says the claims are invalid, then certainly we will have no infringement case anymore.

In preparation for our discussion today, I prepared some questions. Certainly, it is open for you as well to raise questions, and we can discuss them here.

Lyrica® SMU Patent Infringement Cases in Selected Countries

- **USA:** U.S. Court of Appeals for the Federal Circuit upheld injunction in February 2014
- **Australia:** 1st decision in May 2014 granted preliminary injunction in appeal; latest decisions in February 2017 regarding PBS listing being no infringement
- **Germany:** 1st instance (LG Hamburg) granted preliminary injunction in April 2015; patent invalidated in 2017
- **Denmark:** 1st instance decision in June 2015 (no infringement by Krka, but by pharmacies)
- **Spain:** 1st instance decision in June 2015 (no preliminary injunction granted); July 2016 preliminary injunction granted on the grounds of indirect infringement in appeal
- **France:** 1st instance decisions in October 2015 and December 2016 (no infringement); July 2016 patent not invalid due to lack of sufficiency
- **Netherlands:** 1st instance decision in action against Dutch state in January 2016 (no infringement)
- **Sweden:** 1st instance decision regarding validity in August 2016
- **UK:** no interim injunction in 1st instance and appeal in 2015 (invalidity suit pending in Supreme Court; hearing 12 to 15 February 2018)

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What was very interesting for me — and this is now a question for you — is that the cases are very differently decided by the national courts. We had the discussion of direct infringement, particularly in Germany “*sinnfälliges Herrichten*” [manifest arrangement]; and then it turned to a lengthy discussion of indirect or contributory infringement in the Court of Appeals’ decision in the United Kingdom, but it was not relevant for the decision at the end.

What is coming around for me is how we could harmonize it a little bit, because in the end all pharmaceutical companies are globally acting and certainly want to know what could happen in the various countries. I think it would be particularly very helpful if those decisions would be harmonized.

Lessons learned from Lyrica® SMU Patent Cases

- Why are there so different decisions regarding infringement?
 - Direct infringement of SMU patents?
 - Indirect/ contributory infringement of SMU patents?
 - What could be expected from the manufacturer of the generic product?
- Are SMU patents – as such – more difficult to obtain and to defend?
- What changes are required for substitution rules for pharmacies?
- What changes are required in public tenders?
- What about doctor's freedom on prescription?
- Putting information regarding disease on prescription?

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Also — and this already came up in the previous session — what do we expect that the manufacturer of the generic product could do in order to avoid any infringement?

Any answers to those questions?

DR. KILGER: As regards what can be expected from the generic manufacturer, at the end of the day if he tenders or if he is a bidder only for a patent-free indication, if he is not promoting it, and, and, and, then I think it is more the substitution rules, then it is more the other stakeholders, the health insurers, and, and, and, which are now required to take further steps to make sure that regardless of the patents there is no substitution.

I have the feeling that the courts, including the German courts, have done a good job with respect to enforcing second medical use patents going forward. But I think it is now the time to bring the other stakeholders to the table — like the legislators, for instance — to amend the substitution rules, like we have heard was done in Denmark, or to think about whether it would be not helpful or required that the doctor put the indication on the prescription form.

For me, it is not clear why this should not be done. I have the impression that we cannot push much further what the generic company should do at this point to ensure that there is no substitution.

DR. HIRSE: Sture?

MR. RYGAARD: Indirect or contributory patent infringement is a very difficult problem. Do you really want to give the whole market to the patent holder if there is substitution in the pharmacies — “Sorry, generic, your product is actually being substituted, you know that; so, hey, you have to go off the market” — or do you want to neglect the patent holder and just give it all to the generic? That is a very difficult question to answer.

I think the only fair answer requires that the rules, as you say, are tailored so that they actually provide for the indications. I think it is pretty simple: you have to have the indications if you issue patents for second medical indications. If you want patents for second medical indications — with, of course, all the money and exploration and research going into it before you get those patents — then of course the systems will have to respect the indications as well.

I don't know. In some countries, it might be that it is thought that indications are private or whatever. I find that to be a strange argument, considering that most products, drugs, are only there for one indication, so whenever you are

going to pick up any drug you would normally just have one indication and the pharmacist would know this is for whatever sickness.

So it is only in these quite few situations where the drug has more than one indication that with the indication on the prescription the pharmacist would have some information that he is not “supposed” to have about whether you use it for A or B. That seems ridiculous to me. It is simply not an argument that I find has any bearing.

I think at the worldwide level you have to put the indications in the system if you want the system to respect second medical use patents and you want to encourage more research in them.

DR. POWERS: Forgive me if you said this, but in Denmark can a physician prescribe a medicine for a nonapproved use?

MR. RYGAARD: Yes, they are allowed to do that. They have this freedom of prescription.

But again, I think the system at the pharmacies whenever it is handed out should catch that. There should be a database where the pharmacist then could tell — or at the hospital if it is at the hospital — where it says: “Well, red light, you cannot use this product. If you want to use it for that indication, you have to hand out this product.” Simple.

Of course, then if the generic says the patent is invalid, that is a question on whether should the generic product start in or out, and who needs to do the litigation first before you have it in the database or not. There is an issue there, but that can be dealt with.

DR. HIRSE: I would be interested in the American view on that, because this seems a purely European discussion we have here.

DR. POWERS: Yes, it is true that in this country we have sort of a sacrosanct relationship between a doctor and a patent, such that oftentimes medicines are prescribed off-label. That is why I asked the question.

I guess then it means a complicated database would need to be used in order to determine what indication something is being prescribed for and then whether or not that is on-patent. Administering that would be a challenge, but I agree with you that as a policy consideration it makes a lot of sense. I am sure the patent lawyers here would like that. It would give us a lot of clarity.

DR. LOVE: I agree, I think there is a different relationship in the United States than in other countries, and that is the U.S. government is less willing to be involved in the patent issues. I am not an FDA lawyer — I am sure many people in the room will know much more about this than I — but here is one difference. Although the FDA proctors the Orange Book, which is a public list of the patents that cover an approved product, the FDA itself has not gotten into the business of helping administer or adjudicate the patent rights as they exist in connection with product candidates or approved products. This situation is somewhat problematic.

What is more problematic in the United States is the extensive and very complicated private relationships between the insurance companies and the hospitals and the manufacturers of medicines and all of the stakeholders in between. The ability, from a litigation perspective, to obtain the information

necessary to prove infringement, or inducement, for example, becomes exceedingly complicated.

I agree with my co-panelists that I assume that the data is available. I use the word “available” to mean that there is likely electronic data available that will link a prescription to a particular individual and that individual to a particular diagnosis or disease indication. Drawing that line would simplify inducement claims and may give back some force to the second medical use patents in the United States.

Insurance companies are in the business of paying for doctors’ visits based on what the diagnosis is. For example, insurance companies will authorize payment for appropriate materials used in a hospital or the products administered in a hospital based on what the diagnosis is for a particular patient. Therefore, the physicians are very focused on making sure the diagnosis is correctly recorded and is available to the insurance company. If that is all true, then the electronic data is likely available to draw the line I just described.

I can imagine a world in which that data is made anonymous in terms of proof for an infringement proceeding so that you can show an indication is linked to a prescription. You do not need to know exactly “who” was diagnosed in order to preserve anonymity. This data could serve the purpose of an evidentiary showing of infringement and maybe inducement. Of course, each case will be very fact-specific, but this information would give a window into the relationship between diagnosis and indication as compared to which medicines are prescribed. All very useful for the patent analysis.

DR. POWERS: I think if you want to talk about the American perspective, if you want to protect second medical uses, our system works.

DR. HIRSE: We have a question from the floor.

QUESTION: I have one point to make, and that is that indication runs through our medical system, right from the point that things are discovered and the efficacy is measured through to when they are regulated, and it seems really odd that by the time it gets to the pharmacist that person does not know what the indication is.

One other point that we have not really touched upon is the relationship between the physician and the patient. The patient, from the perspective of informed consent, needs to know what the indication is. There are a number of situations where a patient who is prescribed initially Drug A can go home, look it up on Google, and then say: “But doctor, I’m not depressed. Why are you prescribing for me something for depression? I came to you with an issue of pain.”

I think for all these reasons the indication should be much more prominent in the relationship between the end of the process when something is prescribed.

PARTICIPANT [Prof. Robin Jacob, University College London]: There are a whole lot of reasons why you should put the indication on the prescription, not least, nothing to do with the problem we are talking about, but in the future data miners will be able to know what it was prescribed for and see what happened.

There are those who argue that you should not put it on the prescription because you are now telling the pharmacist what this guy has got. Most times you

are doing that when it has just only got one indication anyway. That seems to me to be taking privacy laws to a ridiculous extent. A bit of anonymization should do the trick.

Finally, I just want to put all this discussion in perspective. This is all presupposing you have a patent for a second medical use in some way or other. One of the troubles with the topic we are discussing is that in many cases you cannot, and you cannot because the thing that led to the work on the second medical use was a publication by some doctor saying: "Look, I found this new use. It seems to be happening." It is a bit difficult to say that the patent is not obvious after that.

Then you get the problem of conducting clinical trials, and sometimes in the course of conducting the clinical trials where you find out the second medical use works you are disclosing it to the patients, and then somebody is going to say, "Well, that was a disclosure, wasn't it?"

So even if we can fix the patent law for second medical use and fix the enforcement of it, you still have a big unsolved problem there.

One final point. Some doctors, particularly in countries where people have to pay for the medicines themselves, may fiddle it. They say, "Well, I can write the prescription for the old indication but I'll tell the patient to take it for the new, and he pays one-tenth of what he would have to pay if he was actually using it for the condition he actually has got." I mean, if I was a doctor and I had a poor patient, I would be tempted to do that.

I am just giving you a host of other things. This panel has been brilliant, but if we had the Danish solution it would not be enough.

DR. KILGER: Don't make it even harder.

DR. HIRSE: You already touched on my second question. But that is true, and that is what I am also coming around to when I reviewed the decisions. We have the UK court decisions that say it is lacking sufficiency, but the German Federal Patent Court said it is invalid because of lack of inventive step. That is also a problem that second medical use patents face, that you cannot get a patent granted and defend it because somebody will find one publication once the API is out in the world.

DR. POWERS: So maybe in this case the American system works to protect second medical uses. But this case here was litigated pre-[America Invents Act](#), which means that *inter partes* reviews were not available. I think it has gotten even tougher just a few years after this litigation. Now it remains to be seen how that pendulum might swing back, especially given what the Supreme Court might do, but it is worth pointing out that although the system worked then, it is even tougher now for patent owners.

DR. HIRSE: Any questions from the floor?

QUESTION [Stefano Marino, Head of Legal, European Medicines Agency]: How is the Danish national competent agency behaving with respect to the indications? In other words, does it do like the Dutch, which includes the new indications, even against the will sometimes of the generic applicant?

MR. RYGAARD: You are allowed to carve out. If the generic asks for a Summary of Product Characteristics (SmPC) or marketing approval for a drug,

you are allowed to carve it out. That is in Article 11 of the Directive.¹¹

QUESTIONER [Mr. Marino]: And would the Danish agency ask the generic applicant to submit an additional form of listing as to why the carve-out was given?

MR. RYGAARD: No, there are no extra statements like in Holland.

By the way, the disbursement system in Denmark also has different levels for different indications, like in the pregabalin case there were different levels of reimbursement for the individual indications. So it is in that sense rather flexible.

QUESTIONER [Mr. Marino]: I am asking how the situation is because last year there was a [reference to the Court of Justice](#) from the Netherlands¹² concerning the scope of Article 11 of the Directive, whether it is appropriate, it is legitimate, it is allowed, that a national competent authority, despite the will of the applicant, forces the applicant to include the patented indication. The Court must respond.

PARTICIPANT [The Hon. Rian Kalden, Senior Judge, Court of Appeal, The Hague]: It was actually a reference by my court. It is still pending so I cannot say too much about it.

The situation is that the Medicinal Board takes the view that the marketing authorization that is applied for by the generics, because they refer to the originator file, includes the patented indication. The position of the Medicinal Board is that the marketing authorization that they get includes that specific indication as well.

Despite the carve-out — they say the carve-out is just sort of an external thing between the originator and the generic company but does not prevent that indication from being within the marketing authorization, and that being the case, they feel obliged to inform the public exactly for the reasons that were just mentioned — if some patient looks up on the Internet why I am prescribed pregabalin because I do not see pain on the leaflet because it is carved out, then the online version of the SmPC that is published by the Medicinal Board includes the patented indication that is carved out by the generics so that the patient can actually see that it is also to help cure pain. That is the position.

Now, the position by the originators is “if we apply for a carve-out, that precludes the indication from being within the marketing authorization, it is entirely unclear what is the case.” That is question one.

Question two is: If it is indeed within the marketing authorization despite the request for a carve-out, is it still legitimate for the Medicinal Board to publish the full text of the SmPC?

The text that is required to put in the carve-out leaflet is that they have to refer the patient within the leaflet to the website of the Medicinal Board, and if

¹¹ Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community Code Relating to Medicinal Products for Human Use (as amended), OJ (L) 311, 28/11/2004 at 67–128, *available at* https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-1/dir_2001_83_cons2009/2001_83_cons2009_en.pdf.

¹² C-423/17, Warner-Lambert Company. Please note that the case is still pending; the Advocate General’s Opinion has not been published either. The public summary of the request for the preliminary ruling is available at <http://curia.europa.eu/juris/document/document.jsf?text=&docid=194930&pageIndex=0&doclang=en&mode=lst&dir=&occ=first&part=1&cid=459051#1>.

they then follow that suggestion, they will find the full version of the SmPC. That is the situation. So they are not obliged to, despite the carve-out, state the indication, but they have to make a reference to the website, and on the website they find the full text. Those are the facts.

DR. HIRSE: Thank you very much.

[Session Adjourned: 12:26 p.m.]

APPENDIX A
TRANSCRIPT OF THE
RECORD OF JUDGMENTS FOR
THE MARITIME AND COMMERCIAL HIGH COURT
(TRANSLATION)

DECISION

Rendered on 25 June 2015

A-6-15

- 1) Warner-Lambert Company LLC
 - 2) Pfizer ApS
- (both represented by Mikkel Vittrup, Attorney-at-Law)

vs

- 1) Krka, d.d., Novo mesto
 - 2) Krka Sverige AB
- (both represented by Klaus Ewald Madsen, Attorney-at-Law)

and

The Danish Association of Pharmacies representing
3) - 222) [names of Danish pharmacies]
(represented by Attorney Ole Spiermann and Attorney Jakob
Lentz)

Non-party intervener: The Danish Health and Medicines
Authority
(Attorney Henrik Nedergaard Thomsen representing the Legal
Advisor to the Danish Government)

Introduction

The issue of this case is whether a so-called second medical use patent for the medicinal product pregabalin for the treatment of the indication pain is infringed by Krka, d.d., Novo mesto's and Krka Sverige AB's sales of the generic product Pregabalin "Krka" in Denmark and by the pharmacies' dispensing of this medicinal product for the treatment of the indication pain under the rules on substitution of medicinal products. A further issue of this case is whether the conditions for granting a preliminary injunction against the producer of the medicinal products and the pharmacies under Part 40 of the Danish Administration of Justice Act are fulfilled.

Claims and pleas

Warner-Lambert Company LLC and Pfizer ApS have submitted the following final claims and pleas:

1 Primarily

Krka, d.d., Novo mesto and Krka Sverige AB are to be enjoined from selling the medicinal product Pregabalin "Krka" in Denmark without ensuring, at the same time, that the product is not distributed and/or dispensed for the treatment of the indication pain as long as Danish patent DK/EP 0 934 061 T6 is in force.

In the alternative

Krka, d.d., Novo mesto and Krka Sverige AB are to be enjoined from selling the medicinal product Pregabalin "Krka" to Danish wholesalers, pharmacies and branches of pharmacies without providing, at the same time, express written instructions that the product Pregabalin "Krka" must not be distributed and/or dispensed for the treatment of the indication pain as long as Danish patent DK/EP 0 934 061 T6 is in force.

2 Primarily

Defendants 3-222 are to be enjoined from dispensing the medicinal product Pregabalin "Krka" for the treatment of the indication pain as long as Danish patent DK/EP 0 934 061 T6 is in force.

Irrespective of the rules on substitution of medicinal products, Defendants 3-222 are to be enjoined from dispensing the medicinal product Pregabalin "Krka" for the treatment of the indication pain as long as Danish patent DK/EP 0 934 061 T6 is in force.

In the alternative

- (A) Defendants 3-222 are to be enjoined from dispensing the medicinal product Pregabalin "Krka" for the treatment of the indication pain as long as Danish patent DK/EP 0 934 061 T6 is in force, except for the filling of prescriptions where the issuer of the prescription has expressly written on the prescription that the pharmacy is to dispense the medicinal product Pregabalin "Krka" for the treatment of the indication pain and that the medicinal product may not be substituted, for example by adding "Ej S" ("No substitution").

Defendants 3-222 are, without taking into consideration the rules on substitution of medicinal products, to be enjoined from dispensing the medicinal product Pregabalin "Krka" for the treatment of the indication pain as long as Danish patent DK/EP 0 934 061 T6 is in force, except for the filling of prescriptions where the issuer of the prescription has expressly written on the prescription that the pharmacy is to dispense the medicinal product Pregabalin "Krka" for the treatment of the indication pain and that the medicinal product may not be substituted, for example by adding "Ej S" ("No substitution").

In the second alternative

- (A) Defendants 3-222 are to be enjoined from dispensing the medicinal product Pregabalin "Krka" for the treatment of the indication pain as long as Danish patent DK/EP 0 934 061 T6 is in force, except for the filling of prescriptions where the issuer of the prescription has expressly written on the prescription that the pharmacy is to dispense the medicinal product Pregabalin "Krka" for the treatment of the indication pain.

- (B) Defendants 3-222 are, without taking into consideration the rules on substitution of medicinal products, to be enjoined from dispensing the medicinal product Pregabalin "Krka" for the treatment of the indication pain as long as Danish patent DK/EP 0 934 061 T6 is in force, except for the filling of prescriptions where the issuer of the prescription has expressly written on the prescription that the pharmacy is to dispense the medicinal product Pregabalin "Krka" for the treatment of the indication pain.

In the last alternative:

- (A) Defendants 3-222 are to be enjoined from dispensing the medicinal product Pregabalin "Orion" when filling prescriptions where the issuer of the prescriptions

has prescribed the medicinal product Lyrica for the treatment of the indication pain as long as Danish patent DK/EP 0 934 061 T6 is in force.

- (B) Defendants 3-222 are, without taking into consideration the rules on substitution of medicinal products, to be enjoined from dispensing the medicinal product Pregabalin "Krka" when filling prescriptions where the issuer of the prescriptions has prescribed the medicinal product Lyrica for the treatment of the indication pain as long as Danish patent DK/EP 0 934 061 T6 is in force.

Krka, d.d., Novo mesto and Krka Sverige AB have claimed judgment in favour of the defendants.

The Association of Danish Pharmacists acting for defendants 3-222 has primarily claimed dismissal, in the alternative judgment in favour of the defendants.

The Danish Health and Medicines Authority has made statements in support of the Danish Health and Medicines Authority's alternative claim for judgment in favour of the defendants.

The information provided in the case

Warner-Lambert Company LLC and Pfizer ApS

Warner-Lambert Company LLC is part of the Pfizer group that is among the world's largest producers of medicinal products. In Denmark, the Danish subsidiary Pfizer ApS markets the prescription-only product Lyrica® containing the active ingredient pregabalin. Lyrica is approved for the treatment of three different indications: A) epilepsy, b) generalised anxiety disorder and C) neuropathic pain.

Warner-Lambert Company LLC holds Danish patent DK/EP 0 934 0 61 T6 (the "Patent in Suit"). The patent in suit, which is in force until 16 July 2017, is a so-called second medical use patent, ie a patent for a new use of a known substance.

Claims 1 and 3 of the patent in suit are as follows:

- "1. "Use of (S)-3-(aminomethyl)-5-methylhexanoic acid or a pharmaceutically acceptable salt thereof for the preparation of a pharmaceutical composition for treating pain.
3. Use according to Claim 1 wherein the pain is neuropathic pain."

The compound "(S)-3-(aminomethyl)-5-methylhexanoic acid" is the active ingredient "pregabalin". Pregabalin is no longer protected by a patent in terms of the treatment of the indications epilepsy and generalised anxiety disorder and can therefore freely be used in medicinal products for the treatment of these disorders.

Lyrica is Warner-Lambert Company LLC's and Pfizer ApS' (in the following collectively referred to as "Pfizer") best selling medicinal product. At present Lyrica is sold in Denmark in the following dosages: 25 mg, 75 mg, 150 mg, 225 mg and 300 mg. Based on figures from Statistics Denmark Pfizer has prepared market statistics from which it can be seen, for instance, that in 2009 Lyrica was prescribed for the treatment of pain in 74% of the cases. In 2013 the figure was 53%.

Krka

Krka. d.d., Novo mesto is domiciled in Slovenia and primarily manufactures and sells generic products. In Denmark Krka, d.d., Novo mesto markets medicinal products through Krka Sverige AB. In the following they are collectively referred to as "Krka".

On application Krka was granted, on 3 February 2015, a marketing authorisation by the Danish Health and Medicines Authority to market in Denmark the medicinal product Pregabalin "Krka", a generic version of the medicinal product Lyrica, for the treatment of the indications epilepsy and generalised anxiety disorder. Under section 11 of Order No 1239 of 12 December 2005 on marketing authorisation for medicinal products (the Marketing Order) the indication "neuropathic pain" is not included in the summary of product characteristics for Pregabalin "Krka" due to the patent in suit, and therefore the indication is not covered by the marketing authorisation.

On Monday, 2 March 2015, Krka started marketing Pregabalin "Krka" in Denmark. At present Pregabalin "Krka" is sold in Denmark in the following dosages: 25 mg, 75 mg and 150 mg. According to market statistics from DLI Pharma for the period 1 - 3 March 2015 Pregabalin "Krka" immediately took over on 2 March 2015 approximately 70% of the market for the sale of medicinal products containing pregabalin.

The application for an injunction was received by the Danish Maritime and Commercial Court on 4 March 2015.

The pharmacies and the rules on substitution

At present, there are 220 pharmacies in Denmark with associated supplementing units and pharmacy branches. A pharmacy is operated by a pharmacist under a license granted by the Danish Health and Medicines Authority and is to fill in prescriptions, among other things. Prescriptions must indicate the indication for which a medicinal

product is prescribed, and the indication must appear from the label that the pharmacist affixes to the medicinal product when dispensing it to the patient.

In order not to put the patient to unnecessary expense the pharmacy is to dispense the cheapest medicinal product in the group of equivalent medicinal products which the prescribed medicinal product forms part of. This is referred to as substitution. The rules on substitution appear from Order No 167 of 12 December 2013 on prescriptions (the "Prescription Order") that was issued under the provisions of section 61 of the Danish Medicines Act (Consolidated Act No 506 of 20 April 2013).

The following is stated in section 61(2) and (3) of the Danish Medicines Act:

"(2) The Danish Health and Medicines Authority shall lay down rules on the medicinal products to be dispensed subject to a prescription, and on the division of medicinal products into dispensing groups.

(3) The Danish Health and Medicines Authority shall lay down rules on the wording of prescriptions, etc. and on dispensing and substitution of prescription-only medicinal products and non-prescription medicinal products. The Danish Health and Medicines Authority shall furthermore lay down rules on the dispensing of medicinal products in special cases without guarantee for payment."

The following is, among other things, stated in section 38 and 43 of the Prescription Order:

"Section 38.

(1) A pharmacy's filling of a prescription shall be carried out on the basis of the cheapest medicinal product in the group of pharmacy-restricted medicinal products, see section 60(1) of the Danish Medicines Act, and of vaccines which according to Appendix 1 or Appendix 2 can replace the medicinal product prescribed (substitution). The pharmacy shall dispense the cheapest medicinal products of the medicinal products referred to in the first sentence, but see subsection (4).

...

(3) The provision in subsection (1) is not applicable if the prescribing doctor has expressly indicated on the prescription that substitution may not be carried out, see section 43(1).

...

43.

(1) If the prescribing doctor has indicated on the prescription: 'No S', the pharmacy and the holder of the license referred to in section 1(1) must not substitute the prescribed medicinal product with another medicinal product.

..."

Violation of section 38(1) and section 43(1) of the Prescription Order is punishable by a fine, see section 72 of the Order.

Under the Danish Medicines Act the Danish Health and Medicines Authority divides medicinal products into substitution groups based on an assessment of whether such medicinal products are substitutable. The substitution groups appear from appendices 1 and 2 to the Prescription Order. The Danish Health and Medicines Agency classifies Lyrica and Pregabalin "Krka" in the same substitution group.

When Pregabalin "Krka" is the cheapest medicinal product in the relevant substitution group the pharmacies are obliged to dispense Pregabalin "Krka" to the patient when the doctor has prescribed Lyrica for the patient, unless the doctor has indicated "Ej S" ("No substitution") on the prescription). This also applies when the doctor has prescribed Lyrica for the treatment of the indication pain. The pharmacies' profit is the same regardless of whether they sell Lyrica or Pregabalin "Krka".

Correspondence between Pfizer and the Danish Health and Medicines Authority prior to the institution of legal proceedings

Following the expiry of Pfizer's product patent for Lyrica (pregabalin) on 6 July 2014 Pfizer approached the Danish Health and Medicines Authority by a letter of 18 September 2014 and briefly explained that the Danish rules on substitution apparently do not take into account second medical use patents and that the rules consequently imply possible patent infringements. Pfizer requested a meeting with the Danish Health and Medicines Authority for the purpose of explaining this in more detail and for the purpose of discussing an adaptation of the rules. Pfizer further pointed out in the letter that Pfizer expected generic versions of Lyrica to be introduced on the market during the first six months of 2015.

By a letter of 9 October 2014 to the Danish Health and Medicines Authority Pfizer elaborated on the issue relating to the Danish rules on substitution in relation to second medical use patents and requested a meeting as soon as possible.

On 6 November 2014 Pfizer sent a reminder to the Danish Health and Medicines Authority and on 10 November 2014 the Authority replied that, based on internal discussions, it had asked the Danish Patent and Trademark Office for input regarding the rules concerning the intellectual property rights. In an email of 10 November 2014 Pfizer repeated that time was of the essence.

On 8 December 2014 the Danish Health and Medicines Authority advised Pfizer by email that on 5 December 2014 the Authority had had a meeting with the Danish Patent and Trademark Office and that it had been indicated during the meeting that it could not be ruled out that the situation described by Pfizer in the letter of 9 October 2014 implied a patent infringement and that it had therefore been agreed at the meeting that the Patent and Trademark Office as soon as possible would prepare a memorandum about that. In the email the Danish Health and Medicines Authority requested that Pfizer advised when Pfizer expected the generic products to be marketed.

By an email of 9 December 2014 Pfizer replied that it was not unlikely that generic products could be on the Danish market at the end of January 2015 or at the beginning of February 2015.

On 10 December 2014 the Danish Health and Medicines Authority replied by email that if the Patent and Trademark Office's assessment gave rise to any changes in current practice, such changes would be implemented without delay.

The Patent and Trademark Office's memorandum on the issue was available on 26 January 2015. The following was written in the memorandum:

"Memo regarding patent protection and substitution of pharmaceuticals

BACKGROUND

The Danish Patent and Trademark Office has become aware of a potential problem regarding patent protection and substitution of pharmaceuticals.

The purpose of the memo is to explain what is meant by patent right to be able to solve this problem. The problem arises when indications (the use) of an original pharmaceutical product and a generic pharmaceutical product are different and this difference is a result of the fact that some of the indications are protected through a patent, and where the pharmacist as a consequence of the generic pharmaceutical product and the original pharmaceutical product are stated as substitutable, is obligated to hand over generics for the patent protected indication.

The patent right, including what a patent is and what the protection covers, is explained below.

Applicable law

The Danish Patents Act¹ [Note 1: deleted] comprises provisions on protection, registration, enforcement etc. of patents.

Intellectual Properties, including patents, are also governed in the Agreement on Trade-Related Aspects of Intellectual Property Rights (TRIPS agreement), according to which Denmark, as a member of WTO, shall commit to the provision of the TRIPS agreement. The TRIPS agreement sets out minimum standards for protection of IPR, which countries, who are members of WTO, are obligated to meet. The provisions of the TRIPS agreement regarding patents were executed by the amendment of the Patents Act in 1995.² [Note 2: deleted]

What is a patent?

A patent protects inventions which have a technical solution. A patent may be protection of a product, a process or a use. It is for example possible to protect mechanics, electronics and pharmaceuticals. A patent may only be registered if the invention meets the following three criteria:

1. The invention can be used industrially meaning that it should be possible to manufacture and sell it.
2. It has to be new compared to prior art, and
3. it has to involve an inventive step meaning that it should differ significantly from prior art.

The patent right stimulates innovation by giving the proprietor of a patent exclusive rights to the invention for a period of 20 years and accordingly giving the proprietor of the patent the opportunity to recoup the costs in connection with the invention.

The contents of the protection

Section 1 of the Danish Patents Act states that the inventor has the right, after applying, to take out a patent of the invention thereby acquiring exclusive rights to use this invention for commercial purposes. The exclusive right in the form of a patent is a negative right. It provides the proprietor with the right to exclude others to use the invention commercially, but it does not necessarily provide the proprietor with the right to use the invention as other legislation may prevent this.

What is to be understood by commercial use is regulated in section 3 of the

Danish Patents Act. It appears hereof that the exclusive right imply that others besides the proprietor of a patent may not, without permission, use the invention in terms of making, providing, offering for sale or using a product which is secured by a patent³. [Note 3: In section 3(3) of the Danish Patents Act exceptions to the exclusive right are listed, hereinafter the exclusive right shall not extend to: *"(i) acts done for non-commercial purposes, (ii) acts concerning products put on the market in this country or in another country within the European Economic Area (EEA) by the proprietor of the patent or with his consent, (iii) acts done for experimental purposes relating to the subject-matter of the patented invention, (iv) acts delimited to the subject-matter of the patented invention which are necessary for obtaining a marketing authorisation for a medicinal product for humans or animals in the EU, in an EU member state or in other countries, or (v) the preparation in a pharmacy of a medicinal product according to a medical prescription for individual cases or acts concerning the medicinal product so prepared."* However, none of the exceptions are relevant for the situation stated in this memo".]

The contents of the protection are also regulated in the TRIPS agreement Article 28(1), which to a large extent are similar to section 3(1) of the Danish Patents Act. The TRIPS agreement requires Denmark to have rules regarding patent protection among other things, which at the very least should correspond to the protection according to the TRIPS agreement. Accordingly, national rules should be amended in such a way that they do not undermine the provisions of the TRIPS agreement and in such a way that a situation in which someone, as a consequence of the national rules, happens to infringe Denmark's international commitment, does not occur.

The problem

The problem may be illustrated by an example:

An original pharmaceutical product A with the active ingredient X is patented for treatment of pain and inflammation (patent 1). After a number of years it is discovered that X may also be used for treatment of depression. Subsequently, a patent for the new use is applied for (patent 2). After patent 1 has expired manufactures of generic pharmaceuticals may legally, that is without infringing patent 1, manufacture the pharmaceutical product with the active ingredient X. The generic pharmaceuticals (B, C, D etc.) may only be approved for treatment of pain and inflammation as the second medical use patent "ingredient X for treatment of depression" is still protected by patent 2. Thus the proprietor still has

a patent for the use of X for treatment of depression and can forbid others to produce and sell the pharmaceutical product for treatment of depression. If generics are sold or put on the market for treatment of depression it will involve an infringement of patent 2.

This is illustrated below:

	Patent 1	Patent 2
Protection	Product claim: Ingredient X Claim: ingredient X for treatment of pain and inflammation	Claim: ingredient X for treatment of depression
Validity	Expired	In force
Generics	Upon expiry of patent and data protection: Generic pharmaceuticals	X for treatment of depression is still protected by patent
New situation on the market	Generic pharmaceuticals B, C, D... with the active ingredient X for treatment of pain and inflammation	Original pharmaceutical product A with the active ingredient X for treatment of pain, inflammation and depression

How a similar problem was handled in Norway

A similar problem has been handled in Norway where the Ministry of Health and Care Services (Helse- og omsorgsdepartementet) in 2011 asked the Norwegian Medicines Agency (Statens Legemiddelverk, NOMA) to clarify the relations between the substitution list and the rules on document, marketing and patent protection. Against this background, NOMA presented a report in 2013 which deals with the problem regarding two pharmaceuticals - the original pharmaceutical product and the generic pharmaceutical product - which appear substitutable, but have differences in the approved indications as a consequence of patent protection.⁴ [Note 4: deleted].

The report indicates that in NOMA's estimation of whether two pharmaceuticals are substitutable, patent protection of indications for substitutable pharmaceuticals are to be considered in case of:

1. the suppliers of generics and original pharmaceuticals agrees that the indications are protected by patent

or

2. a judicial decision exists which proves that the indication is patent protected.

In a follow-up memo, the Ministry of Health and Care Services point out that in their opinion NOMA should go further than what is stated in the report. Particularly, since it is quite simple to determine whether or not an indication is protected by a use patent. This will clearly appear from the patent which will be publicly available. Furthermore, it is their opinion that NOMA in all circumstances shall assume that an announced patent is valid until a decision states otherwise. Therefore, a patent should not automatically be ignored just because a company which offers a generic pharmaceutical product claims that the patent is invalid⁵ [Note 5: deleted]

The arrangement which is handled in the report and the following memo from the Ministry of Health and Care Services has now been completed, and it appears now from NOMA's website that they take differences in protected indications into account when accepting a pharmaceutical product on the substitution list. It is the pharmaceutical company who must inform NOMA of whether or not an indication is protected and enclose all relevant information.⁶ [Note 6: deleted]

Summary

As explained above, the problem arises in situations in which two pharmaceuticals - the original pharmaceutical product and the generic pharmaceutical product - appear to be substitutable and are listed as such on the substitution list, but still have differences in the approved indications as a consequence of patent protection.

When the pharmaceuticals are listed as substitutable and the pharmacist for that reason is obligated to hand over the least expensive of the two pharmaceuticals, then this would lead to an infringement of the patent if the generics are sold/put on the market for the use for the second indication (the use) which is protected by a patent."

Pfizer informed the Danish Health and Medicines Authority as follows by a letter of 18 February 2015:

"Substitution between Lyrica and generics

By letters of 18 September and 9 October 2014 Pfizer informed the Danish Health and Medicines Authority that substitution between Lyrica and generic versions of it may give rise to patent infringement.

According to the information provided this is because one of the three indications for which Lyrica is approved for treatment is protected by a patent and the Danish rules on prescriptions and substitution do not allow for this, which implies that the patent may be infringed if generic products are dispensed on the basis of the protected indication.

Accordingly, Pfizer expects questions to arise as to whether the patent protection of pregabalin for the treatment of pain is respected. This applies *ia* when the prescription is made by the doctor and also when it is filled at the pharmacy.

However, it is the opinion of the Danish Health and Medicines Authority that it will be in accordance with the applicable rules on substitution that Lyrica and any generic versions of it are placed in the same substitution group and that the question concerning a potential infringement of a patent right may be settled by a civil action.

In this connection the Danish Health and Medicines Authority refers to section 150(2) of the Danish Health Act. It is stated in the provision that the Danish Health and Medicines Authority can divide various medicinal products that are used for the same indication and have comparable effect in terms of therapeutic benefits into reimbursement groups for the purpose of fixing the same reimbursement price for the products in question.

The primary purpose of the provision is to ensure that only the cheapest of several "similar" medicinal products can be substituted. The provision does not include an absolute requirement that the medicinal products must have the same indications, merely that they are used for the same indications. In this connection it is noted that it follows from the comments to the Danish Health Act that the provision is an unchanged transfer of section 7d(1)-(4) of the Danish National Health Insurance Act.

The following is stated in the comments to section 7d(2) of the Danish National Health Insurance Act:

"The Danish Medicines Authority can divide various medicinal products that are used for the same indication and have comparable effect in terms of therapeutic benefits into reimbursement groups for the purpose of fixing the same reimbursement price

for the groups in question. In this context the Government has regard to continuation of the present criteria for grouping of medicinal products into reimbursement groups with existing synonymous medicinal products with the same active ingredient ."

The following is stated in Report No 144[4] on "Reimbursement and correct use of medicinal products":

"Synonymous medicinal products are characterised by being medicinal products with the same active ingredient in the same strength and, usually, in the same pharmaceutical form. The prices of synonymous medicinal products can vary significantly. However, such price differences do not indicate any difference in the therapeutic benefits of the medicinal products."

..."

Correspondence between the Association of Danish Pharmacists and the Danish Health and Medicines Authority

Following a request from Pfizer the Association of Danish Pharmacists contacted the Danish Health and Medicines Authority by an email of 4 February 2015 and requested that the Authority took steps to solve the situation in which the pharmacies were placed due to the conflict between the rules on substitution and the Danish Patents Act.

On 18 February 2015 the Danish Health and Medicines Authority advised that on the same day it had informed Pfizer that the Danish Health and Medicines Authority found that it would be in accordance with the applicable rules on substitution that Lyrica and any generic version of it be placed in the same substitution group and that the question regarding possible infringement of patent rights may be settled by a civil action.

The Association of Danish Pharmacists informed the Danish Health and Medicines Authority by an email of 27 February 2015 that the pharmacies were placed in an untenable and completely unacceptable dilemma because they risked infringing Pfizer's patent due to the rules on substitution. The Association of Danish Pharmacists offered to contribute to an exchange of ideas in respect of a technical solution to ensure that substitution did not take place if Lyrica had been prescribed for the indication pain.

On 3 March 2015 the Danish Health and Medicines Authority informed the Association of Danish Pharmacists as follows by email:

"Further to your email I can confirm that the generic versions of Lyrica will be placed in the same dispensing group as precisely Lyrica. This classification is a direct consequence of the current rules in the area of medicinal products and the classification implies, in the opinion of the Danish Health and Medicines Authority, that when filling prescriptions for Lyrica (or generic versions of it) with the indication pain the cheapest medicinal product in the group is generally to be dispensed. The Danish Health and Medicines Authority is unable to assess the risk of such dispensing actually constituting infringement of the relevant patent and, if so, who would be responsible for such infringement, but we recommend that the prescriptions in question be filled in accordance with the current rules in this area."

By an email sent later the same day the Association of Danish Pharmacists asked for a clear and unambiguous reply, following which the Danish Health and Medicines

Authority replied as follows by email later the same day:

"I am sorry that the answer is not clear. The Health and Medicines Authority assesses that the pharmacies must comply with the rules on substitution applicable in connection with the processing of prescriptions for Lyrica or generic versions thereof."

Correspondence following the institution of legal proceedings

On 11 March 2015 Krka sent a letter by email to all pharmacies with the following text:

"Instructions regarding dispensing of Pregabalin Krka

As you might know, we have recently launched the product "Pregabalin Krka" in Denmark.

As the name suggests, our product "Pregabalin Krka" contains pregabalin as the active ingredient and is a generic version of the product Lyrica® marketed in Denmark by Pfizer ApS. "Pregabalin Krka" is approved for treatment of General Anxiety Disorder and Epilepsy.

In that connection we would like to draw your attention to the fact that although pregabalin is no longer protected as an active ingredient, Pfizer holds a patent which protects use of pregabalin for treatment of pain, in particular neuropathic pain, until 16 July 2017.

For the same reason, our product "Pregabalin Krka" is only approved for the indications which are not covered by the patent, i.e. treatment of General Anxiety Disorder and Epilepsy.

We would like to inform you that prescribing and dispensing "Pregabalin Krka" for treatment of neuropathic pain would infringe Pfizer's patent rights. "Pregabalin Krka" should therefore only be dispensed for treatment of General Anxiety Disorder and Epilepsy.

"Pregabalin Krka" is substitutable with Lyrica®, and under the applicable substitution rules of the Executive Order on Prescriptions the pharmacy must always dispense the cheapest substitutable product. However, in this case, the cheapest substitutable product cannot legally be dispensed for treatment of neuropathic pain, and we therefore recommend that whenever

Lyrica® is prescribed for treatment of neuropathic pain, Lyrica® should not be substituted with "Pregabalin Krka", even if the prescription does not explicitly describe the product as not substitutable ("Ej S") ("No substitution").

If you have any questions regarding this letter or our product 'Pregabalin Krka', please do not hesitate to contact us."

On 13 March 2015 Krka's attorney contacted the Danish Health and Medicines Authority by email in respect of the case.

On 18 March 2015 Krka sent out a letter by email to all general practitioners in Denmark with a text that is essentially similar to that in Krka's letter of 11 March 2015 to the pharmacies.

Further to a telephone conversation on 18 March 2015 between Krka's attorney and the Danish Health and Medicines Authority Krka's attorney wrote on 19 March 2015, among other things, the following to the Danish Health and Medicines Authority:

"As I mentioned yesterday, Pfizer has applied to the Danish Maritime and Commercial High Court for a preliminary injunction to be granted against my client Krka as well as all Danish pharmacies for the purpose of preventing that Pfizer's product Lyrica® is substituted with my clients product Pregabalin "Krka", also when it is prescribed for the indication "pain".

I do not know to which intent that might actually be the case but my client has no intentions at all of infringing Pfizer's patent rights and have therefore precisely exempted the patented indication in the marketing authorisation for its product Pregabalin "Krka". In other words, my client's product cannot be sold for the treatment of pain.

However, due to the current rules on substitution, and in accordance with the Danish Health and Medicines Authority's direct statements, the pharmacies have to substitute the two medicinal products regardless of the indication for which they are prescribed; and without taking into account whether it implies so-called off-label use (use outside approved indications) and furthermore without taking into account existing patent protection.

It is a fact that Pfizer has a patent that covers the indication pain and

therefore in principle has an exclusive right to market and sell pregabalin products for this indication.

On this background it also seems quite clear that there is a clash between, on one hand, the patent rules and, on the other hand, the regulatory rules on substitution of medicinal products.

As far as I know, this is the first time this question has arisen in Denmark but, on the other hand, it is probably not the last time. It is therefore crucial to solve this problem, not only for the sake of the present proceedings, but also for the sake of future product launches.

As mentioned during our telephone conversation yesterday it is my opinion that the problem might be solved administratively, for example by maintaining the existing dispensing group for Lyrica®, where substitution is made when prescriptions are made for the treatment of generalised anxiety disorder and epilepsy, and then introduce a separate dispensing group for Lyrica® when it is prescribed for the treatment of neuropathic pain, where no substitution is to be made.

I understood from you that such a solution might be implemented but that it will probably require certain changes to the system. I do of course understand that it may take time to implement changes to the system, but if the Danish Health and Medicines Authority acknowledged the problem and initiated this work it might be possible to find a manual solution until it is possible for the systems solution to be in place.

I suggested that a meeting be held between the Association of Danish Pharmacists and the parties involved (Pfizer, the Association of Danish Pharmacists and Krka) as soon as possible in order to discuss possible solutions to the problem, but you indicated that the Danish Health and Medicines Authority found a meeting to be premature as long as the court had not made any decision. I do not agree with that and suggested that the Danish Health and Medicines Authority contacted the Legal Advisor to the Danish Government to obtain an assessment of the matter. I do not know whether the Danish Health and Medicines Authority intends to do so but in any case I ask the Danish Health and Medicines Authority to reconsider.

It would be extremely expedient if a practical solution to this problem could be found instead of all pharmacies and Krka having to be taken to court and having to spend time and costs defending themselves against a claim for an injunction that is exclusively due to disharmony between the rules of patents law and the Danish Health and Medicines Authority's administration of the regulatory rules on medicinal products.

If the Danish Health and Medicines Authority adheres to its point of view not to do anything at present, I urge the Authority to intervene as a non-party in the current proceedings in support of the defendants."

By letters of 13 April 2015 Krka's attorney informed the two Danish pharmaceutical wholesalers Nomeco A/S and Tjellesen Max Jenne A/S about the matter and about Krka's letter of 11 March 2015 to all Danish pharmacies.

In a Reply of 24 April 2015 Pfizer pointed out that it appears from the websites "www.pro.medicin.dk", "www.min.medicin.dk", "www.apoteket.dk" and "www.apotekets-webshop.dk" that Pregabalin "Krka" can also be used for the indication neuropathic pain.

On 30 April 2015 Krka's attorney sent a letter by email to Dansk Lægemiddelinformation A/S that is behind the websites "www.pro.medicin.dk" and "www.min.medicin.dk" with the following contents:

"Pregabalin "Krka"

We approach you on behalf of our clients KRKA, d.d., Novo mesto and KRKA Sverige AB because it has come to our attention that your websites pro.medicin.dk og min.medicin.dk include information about our client's product Pregabalin "Krka" that should be corrected.

It is stated on the websites that the product is a remedy that may be used for treating pain.

We note that, as indicated by the name, our client's product Pregabalin "Krka" includes the active ingredient pregabalin and is a generic version of the product Lyrica that is marketed in Denmark by Pfizer. Pregabalin "Krka" is approved for the treatment of generalised anxiety disorder and epilepsy.

In that connection we would like to draw your attention to the fact that although the active ingredient pregabalin is no longer subject to patent protection Pfizer holds a patent which protects the use of pregabalin for the treatment neuropathic pain until 16 July 2017.

For the same reason, our client's product "Pregabalin Krka" is only approved for the indications which are not covered by the patent in question, *ie* the treatment of general anxiety disorder and epilepsy.

We therefore request that you immediately remove any references on your websites to the effect that Pregabalin "Krka" can be used for treating pain.

If you have any question concerning this letter, please let us know."

Other

By a letter of 24 September 2014 to the Danish Health and Medicines Authority Pfizer requested access to the files concerning marketing authorisations for generic products containing the active ingredient pregabalin filed by Actavis, Krka, Orion Corporation, Ratiopharm and Sigillata that according to the letter have all applied for marketing authorisations in Denmark by using the decentralised procedure with different reference member states.

The parties have also produced several foreign decisions concerning corresponding issues.

Witness statements

Lene Juncker-Jensen, Per Suhr, Viktor Kozjan and Anne Kahns have given evidence during the proceedings.

Lene Juncker-Jensen stated *ia* that she is a doctor by profession and that she has been employed with Pfizer ApS for 10 years where she is a medical director.

The annual turnover for Lyrica in Denmark amounts to approximately DKK 130m. This figure is based on the pharmacy purchase prices, *ie* the wholesalers' sales.

The market statistics produced were prepared by a healthcare economist with Pfizer based on data from Statistics Denmark and concern the sale of Lyrica. The five bar charts on page 6 show the number of packages sold with one of the three indications. It appears from this that 74% of the total number of packages sold in 2009 concerned

the indication pain. In 2013 the figure was 53%. Approximately 20% of the packages were sold without any specification of indication. Accordingly, these figures indicate their most conservative estimate. In 2014 Pfizer exclusively focused their marketing on the indication pain. There has been considerable growth in sales of Lyrica of more than 10% from 2013 to 2014. They assume that more pain patients are being treated with the product in Denmark. She therefore estimates that today at least 60% of the total number of packages sold are used for the indication pain.

She assumes that Krka is also aware of this information. Market analyses and statistics can be purchased and it would be natural to investigate the size of a market before entering it.

Krka's sale of Pregabalin "Krka" has increased steadily since Krka's introduction of it. Krka now has a market share of more than 70% and it looks as if the market share is increasing. Normally, several generic producers enter the market when a product patent expires, which exerts downward pressure on prices, and in a very short time, normally within three months, the original producer will have 5% left of the market. Pfizer knows that Orion has also been granted a marketing authorisation for a generic product of Lyrica and that two positive "opinions" have been provided in respect of Mylan and Sandoz.

Pfizer has been in contact with the suppliers of the IT systems that help to support the Danish Health and Medicines Authority's substitution system. The suppliers have advised that a technical solution is possible. They have not been in contact with the Danish Health and Medicines Authority about an IT solution.

They approached the Danish Health and Medicines Authority because they wanted to discuss a solution. She did not decide not to institute legal proceedings against the Danish Health and Medicines Authority.

She had a meeting with the Association of Danish Pharmacists before Krka came on the market. It was at the beginning of February.

Peter Suhr stated *ia* that his career as a pharmacist started at Svane-apoteket in Åbenrå in 1965. Since then he has been working at "Glostrup Apotek" and "Ordrup Apotek". In 1983 he was granted a pharmacy license at "Helsingør Apotek". [Note: "Apotek" is Danish for "Pharmacy"] He retired in 2007. He also worked with medicines information in the Danish Medical Association. In that connection he attended courses in pharmacology, medicinal products and statistics. He also learned how to programme at university extension courses.

When medicinal products are dispensed in accordance with a prescription the pharmacist always affixes a label to the product stating both indication and dosage.

He was involved in developing the pharmacies' IT system "C2". It is possible to solve everything by means of computer technology. It is his guess that [finding] a solution to the problem in this case would be an average job. He cannot say how long it might take.

The pharmacy's computer system does not prevent the pharmacists selecting Lyrica instead of the generic product and thus from complying with any injunctions. In principle you could also place a post-it on your computer screen stating that you should remember that Lyrica must not be substituted by other products in case of the indication pain.

Victor Kozian stated *ia* that he has been working at Krka for 16 years. He has been working at Krka's headquarters in Slovenia for the last five years. He is responsible for the Scandinavian market, among others. Krka Sverige AB is responsible for sales in Denmark. Krka sells its products in Denmark through the wholesalers Nomeco A/S and Tjellesen Max Jenne A/S.

Krka did not apply for marketing authorisation for the indication pain because that indication is still patented. It is the intention that Pregabalin "Krka" is only sold for use for the two other indications. When the patent for the indication pain expires in 2017 Krka will add the indication pain. Krka has done something similar in relation to two or three other Krka products and the procedure is normal.

Krka has an IP department that always examines the market and products etc for the purpose of avoiding infringement of other parties' patents.

He is familiar with the Danish rules on substitution and knows that due to these rules Pregabalin "Krka" is also being dispensed for the indication pain. Krka cannot do anything about it, including for example by including clauses about it in their contracts with the wholesalers. If Krka was to do anything to completely avoid the problem Krka would have to remove Pregabalin "Krka" completely from the market.

Krka has sent a letter to the wholesalers and to the pharmacies that they must only sell Pregabalin "Krka" for the two other indications.

Krka's contribution ratio from the sale of Pregabalin "Krka" is far more than 50%. At

present Krka has a market share of approximately 70% for the two other non-patented indications. He expects this market share to reach 90% within one or two months after Pregabalin "Krka" was introduced on the market. They expect competition from other producers of generic products at least before the end of the year, which will imply price drops. If there are several competitors the price will drop by more than 50%. If there is only one other competitor the price will drop by 20-30%. He has seen on a Danish website that Orion was granted a marketing authorisation at the beginning of March 2015 but that Orion has not launched a product yet. There may also be marketing authorisations covering the EU, and thus Denmark, but he has not looked into that. There is no saying when competing products will be launched.

Krka receives IMS-data from Denmark, Sweden and Norway on a monthly basis but these are very simple data that do not show Krka's market shares distributed on the different indications.

Anne Kahns stated *ia* that she has been a pharmacist for seven years and is the chairman of the Association of Danish Pharmacists.

The pharmacies sell around 58m packages of prescription-only medicinal product annually. In her pharmacy, which is a medium-sized pharmacy, they sell approximately 350,000 packages annually. The pharmacies are subject to a gross profit agreement and are consequently not affected by the prices of medicinal products.

Today the majority of prescriptions are electronic. National Health Data and Information Communication Technology (in Danish: *Nationalt Sundhedsdokumentation og -it*) under the auspices of Statens Seruminstitut that is responsible for the system on behalf of the Ministry of Health. When the patient comes into the pharmacy the pharmacist locks into the system by using the patient's personal identity number. The pharmacy then gets access to a screen view showing an overview in relation to the customer where it is possible to see which prescriptions are open and what has been prescribed to the patients on previous occasions. There is a line for each product the doctor has determined that the patient is to be treated with. It is possible to see the product designation under which the medicinal product is registered. The product designation is attached to a six-figure product number. It is also possible to see the dosage of the medicinal product, the package size and whether there are several types of packages. The pharmacist then selects the products that are to be supplied to the customer by highlighting the line. This is followed by a picture showing information about the patient and the doctor. If the doctor has not added "Ej S" ("No S"), meaning "no substitution", the pharmacist continues to an overview of product

substitution prepared in accordance with the substitution groups which the Danish Health and Medicines Authority has divided the medicinal products into. The substitution overview comes from "medicinpriser.dk" that is updated by the Danish Health and Medicines Authority on a regular basis. If the prescription says "Lyrica", you go to the overview of product substitution and the pharmacist is obliged to advise the patient about the cheapest medicinal product. The pharmacist does not discover the indication for which the medicinal product is to be used till he or she, at a late stage, is about to print the label that is to be affixed to the package. The pharmacist may open a screen picture at an earlier stage by using a keyboard short cut; this will show the entire head of the prescription, including the indication.

If the indication has not been filled in on the prescription the pharmacist always contacts the doctor, if it is clinically relevant. If the patient has been supplied with the medicinal product before or is familiar with it, they do not contact the doctor.

The Association of Danish Pharmacists' website "www.apoteket.dk" links to the website "www.min.medicin.dk". The information about Pregabalin "Krka" that is available at "www.apoteket.dk" comes from "www.min.medicin.dk".

She has received Krka's letter of 11 March 2015 about the matter that was sent to all pharmacies in Denmark. However, the pharmacies have to address the rules of the Danish Health and Medicines Authority. The pharmacists cannot omit dispensing Pregabalin "Krka" if the doctor has added "Ej S" ("No substitution"), as stated in Krka's letter. It is not for the pharmacy to take any position on the doctor's choice of medicinal product. If the doctor has added "Ej S" ("No substitution") the pharmacist cannot do anything about it.

It is not a workable solution to place a post-it note on the pharmacists' computer screens or make a pop-up picture on the screen pointing out that Lyrica must not be substituted when it is prescribed for the indication pain. It would prolong the processing time and create uncertainty about the filling of prescriptions.

The pharmacies will be able to comply with a possible injunction in this case but it will require a large number of practical changes to the system.

This case places the pharmacists in a completely unreasonable situation. If an injunction is issued against the pharmacies, she has a strong presumption that the Danish Health and Medicines Authority will solve the problem for them. If an injunction is issued they will contact the Danish Health and Medicines Authority as the rules then ought to be amended. She cannot say whether, in case of an injunction, they will comply with the

injunction or with the Danish Health and Medicines Authority's rules on substitution.

The parties' points of view

Pfizer has in particular stated that the conditions for granting an injunction against Krka as well as the pharmacies are fulfilled.

No matter that the pharmacies are subject to public law regulation, the pharmacies are not a public authority and the pharmacies do not exercise public authority. However, due to its dispensing and sales of medicinal products the pharmacies are to be considered parties to private legal relationships and are therefore not subject to section 411 of the Danish Administration of Justice Act.

Pfizer holds the right that may be sought protected by the granting of an injunction,
see section
413(i) of the Danish Administration of Justice Act.

As far as Krka is concerned, Krka infringes the Patent in Suit under section 3(2) of the Danish Patents Act on indirect patent infringements. The rule is to be interpreted in accordance with the general rules of Danish law on contributory liability that are very wide. Objectively Pregabalin "Krka" is suitable to be used for the treatment of pain. Krka sells Pregabalin "Krka" to pharmacies knowing that the medicinal product is dispensed for the treatment of the indication pain. Krka has indisputably no intention for Pregabalin "Krka" to be used for the treatment of the indication pain, but it is sufficient that Krka knows that it is done. Accordingly, Krka supplies "means" to the pharmacies so they can exploit the "invention" in Denmark without being entitled to do so. Accordingly, the means are "intended" to be used in connection with the exploitation of the invention and therefore this constitutes infringement under section 3(2) of the Danish Patents Act.

The fact that Krka has been granted a marketing authorisation for marketing of Pregabalin "Krka" is not tantamount to such marketing not being able to continue infringing other parties' patent rights. Krka only took steps for the purpose of complying with the alternative claim submitted by Pfizer after the filing of the application for an injunction. In the future it will also be relevant that Krka draws attention to Pfizer's rights under the Patent in Suit, including when it comes to new pharmacies, and therefore the alternative claim is not fulfilled in terms of the future.

Pfizer has no objections to the prescription of genetic pregabalin for the non-patented indications and the claim submitted against Krka is clear, precise and takes this into

account. If the Court should find that the claim implies that Krka has to completely withdraw Pregabalin "Krka" from the market it cannot in itself prevent the granting of an injunction in accordance with the text of the claim but should instead be included in the Court's balancing of proportionality.

As far as the pharmacies are concerned, Pfizer's right has been rendered probable already by the memorandum prepared by the Danish Patent and Trademarks Office according to which the dispensing of Pregabalin "Krka" amounts to an infringement of the Patent in Suit. The Patent and Trademark Office's conclusion is supported by Krka having stated clearly in its letters and emails to the pharmaceutical wholesalers and the general practitioners that it is also Krka's opinion that the pharmacies' sale and dispensing of Pregabalin "Krka" imply an infringement of the Patent in Suit.

It is not important to the case that the Patent in Suit is a Swiss-type claim. The EPO Board of Appeal recognised this type of claims in 1983 by decision G-5/83 (EISAI Co. Ltd.). EPO's practice in respect of Swiss-type claims was established and known when Denmark joined the Patent Convention (EPC) as of 1 January 1990. Thus, Danish legislation on the granting of second medical use patents is earlier than the Danish rules on substitution. Furthermore, the reason given for the patent protection of a second medical use patent is the new use of an otherwise known substance. The protection has in reality nothing to do with manufacturing and accordingly it is legal fiction created in case law that the text of the patent claim is formulated as a method claim. As use of the substance is crucial, the Patent in Suit should be understood and interpreted on the basis of the purpose of the invention. This is supported by the fact that it appears from the legislative history of the amendment of EPC in 2000 that there was no wish to change the scope of protection by a second medical use claim. There was a wish to formalise the protection of second medical use claims, which was obtained by abandoning the previous formulation of Swiss type claims for the EPC 2000 claim formulation: "use of a substance for the treatment of a specific disease". Denmark ratified EPC 2000 in 2006. Today, the Danish Patent and Trademarks Office accepts both types of claims. Interpretation of the Patent in Suit on the basis of the purpose of the invention is further supported by the fact that the patent would in reality be worthless if you were only to focus on whether a medicinal product is manufactured for the treatment of a specific indication, as it would never be possible to prove that such manufacture is only made for a specific indication. It cannot be crucial which intentions Krka originally had when manufacturing the product. The Patent in Suit should also provide protection against subsequent purchasers of the product that will infringe the Patent in Suit under section 3(1)(iii) of the Danish Patents Act. In the alternative, it is claimed that the pharmacies' actions amount to manufacture, see

section 3(1)(ii) of the Danish Patents Act, as the pharmacists determine that Pregabalin "Krka" is to be dispensed for pain and thus carry out the last stage of the manufacture of the product by adding a label.

Both Krka's and the pharmacies' actions are carried out "without permission" under section 3 of the Danish Patents Act. Pfizer has not consented to Pregabalin "Krka" being sold or dispensed for the indication pain and no exemptions to Pfizer's exclusive right are expressly permitted under the Danish Patents Act. The defendants' understanding of the term "without permission" is not supported by the legislative history, case law or in legal literature and such an understanding would also infringe Denmark's obligations under TRIPS, article 28. To this should be added that neither medicines legislation nor the legislative history of medicines legislation states that medicines legislation takes precedence of the Danish Patents Act or that the Danish Health and Medicines Authority can issue an order that cuts across the Patents Act, and in a conflict situation it is clear that the Danish Patents Act must take precedence over an order. If it was the intention that the Danish Health and Medicines Authority should be able to determine rules by imposing orders it would require clear statutory authority in the enabling act. Such statutory authority does not exist. However, it is clear from the legislative history of the Danish reimbursement rules that patents and their influence on the National Health Service's expenses for medicinal products have been known. Medicines legislation also provides scope for restricting a marketing authorisation for a generic product to concern only the non-protected indications as in this case. The principle of *lex specialis* is not relevant as the two legislations have widely different focus and if the principle was relevant the Danish Patents Act should be considered far more "detail regulated" than medicines legislation. There is a presumption against the Danish Parliament having wanted to come into conflict with international conventions such as TRIPS, the Paris Convention from 1883 and the Enforcement Directive when creating the Danish rules on substitution. It is not claimed that the rules on substitution are invalid but it is claimed that they do not include statutory authority to infringe the Patent in Suit. Accordingly, the possible conflict of rules does not prevent the granting of an injunction.

As there is an ongoing infringement of the Patent in Suit the granting of an injunction is necessary and therefore the condition in section 413(ii) of the Danish Administration of Justice Act is fulfilled. Nor are there any such special circumstances that the conditions in section 413(iii) of the Danish Administration of Justice Act are not fulfilled. This condition is as a general rule always fulfilled in cases concerning patent infringement and Pfizer will in the specific situation suffer a significant and irrevocable loss if Pfizer has to await a full trial. Besides Pfizer has not been acquiescent as the application for an

injunction was filed a few days after Pregabalin "Krka" was brought on the market in Denmark. The general rules on compensation in Danish law do not provide adequate protection of Pfizer, see section 414(1) of the Danish Administration of Justice Act.

In practice section 414(2) of the Danish Administration of Justice Act on proportionality is not used in patent proceedings and the granting of a preliminary injunction in the present case will not inflict any damage or inconvenience on Krka or the pharmacies that is clearly disproportionate to Pfizer's interest in the injunction being granted. If an injunction is not granted, the adverse effect is far more serious for Pfizer as Pfizer will suffer a significant and irrevocable loss. Krka has acknowledged that there will soon be generic competition in the market and furthermore it will be more relevant for Krka to bear any loss as Pfizer's rights are infringed. Also, it is of no real importance to the pharmacies whether they sell and dispense Lyrica or Pregabalin "Krka". The fact that compliance with the injunction should allegedly involve practical difficulties is not sufficient to refuse granting an injunction.

It is contested that the question of any conflict of rules should exclusively be decided in an ordinary legal proceedings instituted against the Danish Health and Medicines Authority. Firstly, Krka and the pharmacies are carrying out the patent infringing actions, not the Danish Health and Medicines Authority. Secondly, it is not possible to have a preliminary injunction granted against the Danish Health and Medicines Authority in the present situation. Civil proceedings against the Danish Health and Medicines Authority will furthermore take several years and will not protect Pfizer in any way in terms of the current infringement of the Patent in Suit. If Pfizer was only to be able to institute legal proceedings against the Danish Health and Medicines Authority in the present situation, the whole injunction remedy would be illusory. Thirdly, the fact that this is a leading and legally complex case does not imply that the case cannot be decided within the framework of a case on a preliminary injunction before the Danish Maritime and Commercial High Court that in the present case is presided over by three judges. Also, the Maritime and Commercial Court's position does not imply any production of evidence outside the scope of an injunction case.

Krka has not produced any documentation for the submitted claim for security or for Krka's contribution margin and the claim is far higher than dictated by practice in patent proceedings.

Finally, Pfizer is to be awarded legal costs if an injunction is granted.

Krka has in particular stated that Pfizer's primary claim is too unclear to be adjudicated; *ie*

what does it mean "to ensure". It will be completely impossible for the judge to enforce an injunction granted in accordance with the primary claim.

Krka has no influence on or knowledge about the indications for which the individual products are dispensed in the pharmacy and has furthermore, through its letter to all the pharmacies and doctors' surgeries in Denmark and the the Danish Health and Medicines Authority, taken all reasonable steps for the purpose of avoiding that Pregabalin "Krka" be dispensed for the treatment of the indication "neuropathic pain". If Pregabalin "Krka" is nevertheless dispensed for the treatment of the indication "neuropathic pain" due to the current rules on substitution it is not within Krka's power to "ensure" that this is not done. The primary claim can therefore only be complied with if Krka completely removes Pregabalin "Krka" from the market, which *de facto* will imply that an indisputably lawful activity is prohibited. The market for sale of Pregabalin "Krka" for the two non-patented indications amounts to approximately DKK 65m annually. If Pfizer's rights to prohibit the sale of Pregabalin "Krka" for the indication pain are protected, Krka's rights to sell Pregabalin "Krka" for the two non-patented indications will be infringed at the same time.

As far as Pfizer's alternative claim 1 is concerned, it is claimed that Krka has already fulfilled the condition in it. Pfizer has not explained what else Krka is to do. Therefore there is no basis for complying with the alternative claim.

It is stated in section 3(2) of the Danish Patents Act that no one except the proprietor of the patent may "without permission" exploit the invention. It is not stated anywhere that the rules of the Danish Patents Act cannot be restricted by other legislation and it is not abnormal that one type of legislation restricts another type of legislation. In this case there is clear statutory authority in the Danish Medicines Act and the Prescription Order for the pharmacies to dispense the cheapest product in the same dispensing/substitution group irrespective of any patent protection. The pharmacies are obliged to dispense the cheapest substitutable medicinal product. The rules on substitution have been in force for many years and violation of the rules on substitution is punishable and may inflict consequences in terms of the pharmacist's license. The granting of a preliminary injunction implies that the rules on substitution do not comply with statutory rules and regulations. However, there must be a presumption that the rules comply with statutory rules and regulations until the opposite has been established by a final judicial decision.

Pfizer's patent is furthermore a so-called Swiss-type claim, ie a purpose related method claim aimed at the use of a substance for manufacturing a medical product for a specific medicinal use. Already because the pharmacies do not use pregabalin to manufacture a

pharmaceutical composition for the treatment of pain the pharmacies do not exercise the invention and therefore section 3(2) of the Danish Patents Act is not applicable to the case. The pharmacists' printing of a label has nothing to do with working the invention. Section 3(2) envisages a completely different situation. Furthermore, Pregabalin "Krka" is not "intended" for any patent infringing use as described in section 3(2) of the Danish Patents Act. Pregabalin "Krka" is only intended to be used for the two non-patented indications. Infringement under section 3(2) implies a subjective intention with the manufacturer, which is not the case. Anything else will result in a completely untenable legal situation. It is not sufficient that Krka knows that Pregabalin "Krka" is also dispensed for the treatment of pain. Krka does not supply any "means" for anything forming part of a patent infringing process as Krka manufactures and supplies a finished product. Accordingly, no "means" are supplied for someone to "work the invention", ie manufacture a pregabalin product for the treatment of pain.

The memorandum prepared by the Danish Patent and Trademark Office is not sufficient to establish infringement. The Danish Patent and Trademark Office has for example used an EPC 2000 claim, not a Swiss-type claim, in the example referred to and it is further only stated that it will constitute "direct" infringement. Nor does the Danish Patent and Trademark Office appear to have considered the restriction inherent in the work "without permission" and the Office has not attributed the infringement to Krka or the pharmacies.

Accordingly, it has not been substantiated or rendered probable that Pfizer holds the right that is sought protected by the injunction, see section 413(i) of the Danish Administration of Justice Act. At any rate there is such uncertainty as to Pfizer's alleged right that, also for that reason, a preliminary injunction cannot be granted.

Krka's behaviour does not necessitate the granting of an injunction. Krka only markets and sells a product in compliance with statutory rules and regulations and in accordance with the marketing authorisation granted by the Danish Health and Medicines Authority where the indication pain is intentionally exempted. Krka complies with all rules and has acted correctly in all respects. As mentioned, Krka has also taken all reasonable steps for the purpose of avoiding that Pregabalin "Krka" is dispensed for the treatment of neuropathic pain and Krka has gone much further than Krka is obliged to do. This has all been done to avoid this case. Therefore nothing in Krka's behaviour justifies or necessitates the granting of an injunction against Krka. Accordingly, the condition in section 413(2) of the Danish Administration of Justice Act is not fulfilled.

Furthermore, the principal question about the compatibility of the Danish Patents Act and the Danish Health and Medicines Authority's interpretation of the regulatory rules on

substitution of medicinal products should not be decided in connection with legal proceedings case concerning a preliminary injunction but during legal proceedings between the actual parties to such a dispute, *ie* Pfizer and the Danish Health and Medicines Authority. During the present legal proceedings the Court neither can nor should consider the compatibility of the regulatory rules on medicinal products and the Danish Patents Act. This will necessitate a production of evidence that is completely outside the scope of this case concerning a preliminary injunction, see section 417(1) of the Danish Administration of Justice Act. Instead of instituting these legal proceedings concerning a preliminary injunction Pfizer could and ought to have issued a writ of summons against the Danish Health and Medicines Authority already in the autumn of 2014.

Finally, it would be obviously unfair if Krka was to be liable for/assume the risk of the construction/management of the Danish rules on substitution. If Pfizer believes that the Danish Health and Medicines Authority's interpretation of the rules on substitution does not comply with statutory rules and regulations it will be most relevant if Pfizer is to bear the risk. Accordingly, injunctive relief should be denied also for reasons of proportionality, see section 414(2) of the Danish Administration of Justice Act.

Should the Maritime and Commercial Court find that a preliminary injunction can and must be granted, such injunction must necessarily be directed against the pharmacies and not against Krka as the pharmacies know for which indication the individual product is dispensed, and the pharmacies make the decision of whether to substitute medicinal products.

Taking into consideration that an injunction granted in accordance with Pfizer's primary claim can in reality only be complied with if Krka completely refrains from selling "Pregabalin Krka", an injunction should be conditional on Pfizer providing security for the loss that Krka would indisputably suffer, see section 415 of the Danish Administration of Justice Act. Security in an amount of less than DKK 25m will not be reasonable.

If an injunction is not granted, Krka claims to be awarded full legal costs.

The Association of Danish Pharmacists has in particular stated in support of the claim for dismissal that an injunction cannot be issued against the pharmacies, see section 411(1) of the Danish Administration of Justice Act, as the pharmacies in reality act as representatives of the authorities. The Danish Health and Medicines Authority has determined and prepared the rules on substitution and ordered the pharmacies to carry out such substitution. Accordingly, the pharmacies' actions indisputably amount to

exercise of authority and the application for an injunction has been made due to the Danish Health and Medicines Authority's exercise of authority. The Court's review of the application for an injunction further requires a review of the validity of the rules on substitution. A case based on such points of view should be instituted against the relevant authority. Pfizer cannot obtain a result contrary to section 411 merely by choosing, instead of the Danish Health and Medicines Authority, the pharmacies which are subject to the regulation of the Danish Health and Medicines Authority. It will fundamentally be incompatible with section 411 of the Danish Administration of Justice Act to set aside applicable public law regulation.

Furthermore, the pharmacies are not in a situation where there is any certainty that an injunction can be complied with. An injunction will not have any force of law against the Danish Health and Medicines Authority and will therefore not apply to the relationship between the Danish Health and Medicines Authority and the pharmacies. The pharmacies' obligation to carry out generic substitution will therefore still exist. An injunction will present the pharmacies with an absurd choice between being punished for violating the injunction or for violating the rules on substitution. The pharmacies are taken hostage in an attempt to obtain amendment of the rules on substitution.

The above allegations are also submitted in support of the claim for a judgment in favour of the defendants.

Furthermore, the claims are not formulated clearly and are not suitable to be used as basis for an injunction, in particular the words "dispense ... for the treatment of the indication pain".

Also, the conditions in section 413(1) of the Danish Administration of Justice Act are not fulfilled. Pfizer has not substantiated or rendered probable that it has the right it asserts, including that the pharmacies' dispensing of Pregabalin "Krka" would imply infringement of Pfizer's Swiss-type patent.

In order to be an infringement, the pharmacies' dispensing has to be contrary to the claims of the Patent in Suit and the pharmacies do not "manufacture" a pharmaceutical composition by affixing a label to the package, see section 3(1)(ii) of the Danish Patents Act. Infringement of section 3(1)(iii) of the Danish Patents Act further requires the existence of a product that has been manufactured by a process that infringes a patent, but Pfizer does not claim that Krka infringes the Patent in Suit by manufacturing a medicinal product for the treatment of pain. Therefore the provision is not applicable in terms of the pharmacies when a Swiss-type patent is involved. As for the memorandum prepared by the Danish Patent and Trademark Office, reference is made to Krka's

comments in that respect. There is no necessary conflict between medicines legislation and patents legislation. Section 3(1) of the Danish Patents Act and the words "without permission" can be interpreted in accordance with the medicines legislation and there is no doubt that the pharmacies' dispensing of Pregabalin "Krka" is permitted. According to Danish law, the Danish Patents Act is to be harmonised with other legislation. Anyhow, acknowledgement of Pfizer's points of view implies an amendment not only of the Prescription Order but also of the Danish Medicines Act and in such a situation the granting of an injunction is out of the question due to considerable legal uncertainty.

Nor is the condition in section 413(ii) of the Danish Administration of Justice Act fulfilled. The Danish Medicines Act, or at least the Prescription Order, orders the pharmacies to dispense the cheapest product in the substitution group (in this case, Pregabalin "Krka"), irrespective of indication. The pharmacies cannot lawfully decide to change its conduct and the pharmacies neither could nor should have acted differently. Accordingly, the pharmacies conduct does not "necessitate the granting of an injunction".

The condition in section 413(iii) is not fulfilled either as the provision is based on the premise that the question that is the subject of the disagreement between the parties in injunction proceedings may be decided conclusively in a civil action between the same parties, see section 425 of the Danish Administration of Justice Act. That is not the situation in this case where it cannot be decided which rules take precedence. It requires legal proceedings against the Danish Health and Medicines Authority.

Also, the condition in section 414(1) of the Danish Administration of Justice Act is not fulfilled. In this case where the pharmacies' dispensing of Pregabalin "Krka" indisputably follows from current law Pfizer is protected adequately by general Danish rules of damages.

Finally, the condition in section 414(2) of the Danish Administration of Justice Act is not fulfilled. The granting of an injunction against the pharmacies will be completely disproportionate. Compliance with Pfizer's application will imply the consequence that the pharmacies must also expect in the future to be involved as parties in conflicts in which they have no share. It is of significant importance, also in terms of future cases, that it is determined that legal proceedings have to be instituted against the actual opponent and that the injunction remedy cannot be used contrary to the general principles of Danish administration of justice.

Furthermore, in practice it will not be possible for the pharmacies to comply with an injunction almost immediately as the current systems are tied up with the substitution

and reimbursement groups determined by the Danish Health and Medicines Authority.

The Association of Danish Pharmacies claims to be awarded legal costs. If the Danish Maritime and Commercial High Court should uphold Pfizer's application, the Danish Health and Medicines Authority should be ordered to compensate such legal costs of the Association of Danish Pharmacists (and the pharmacies) as the court might award to Pfizer, see section 420(2) and section 252(4) of the Danish Administration of Justice Act.

The Danish Health and Medicines Authority has in particular stated that the Court may take into account that the two medicinal products are synonymous and, accordingly, substitutable. The Danish Health and Medicines Authority has therefore correctly classified Lyrica and Pregabalin "Krka" in the same substitution group and, accordingly, also in the same reimbursement group. The Danish Health and Medicines Authority does not have any competence in relation to patents legislation. Nor is it indicated in the legislative history of the medicines legislation or the patent legislation that the Danish Health and Medicines Authority is to consider patent issues in addition to its professional assessment of the medicinal products.

Patent law is not absolute. It is stated in section 3(1) of the Danish Patents Act that the exclusive right conferred by a patent shall imply that no one except the proprietor of the patent may "without permission" exploit the invention by various means. Article 28 of the TRIPS agreement is consistent with this. Accordingly, the patent right can be restricted if there is statutory authority to do so. Pfizer has acknowledged that the doctor's free right of prescription, for example, takes precedence over the Danish Patents Act. The rules on generic substitution of synonymous medicinal products authorise dispensing of the cheapest medicinal product in the same substitution group without having to take into consideration any patent rights. The Prescription Order that includes the rules on generic substitution is not contrary to the statutory authority on the basis of which it has been issued and is therefore in compliance with statutory rules and regulations. Furthermore, the possibility of patenting medicinal products has arisen gradually. That also applies to second medical use patents. At some point the expanded patent rules collide with other rules and the patent rules have to accept that. The rules on substitution have been in force since 1991 and were amended in 1997. By Act No 399 of 30 April 2007 with effect from 1 July 2007 second medical use patents with EPC 2000 claims were allowed, see section 2(5) of the Danish Patents Act. The legislative history does not include any information that the Bill referred to the rules on substitution of medicinal products. Nor do the consultation responses include anything to that effect. If the rules on the new second medical use patents were to amend the current rules on substitution under medicines legislation that have been in force since 1991, a clear statutory provision to that effect would be expected

and failing that the rules on substitution have not been amended. This also conforms with the fact that the Bill is not expected to have any socio-economic consequences. It also conforms with *lex specialis* considerations that there is no conflict between the relevant rules of medicines legislation and patents legislation, in the alternative that the medicines rules take precedence over the patents rules. In case of any conflict between the two bodies of rules the principle of *lex posterior* applies according to which a recent statutory rule prevails over an earlier rule, and the principle of *lex specialis* which has as its basis that the rule which specifically concerns the area which the legal result aims at should be applied. The medicines rules are earlier than the rules on second medical use patents from 2007 and are specifically aimed at the dispensing of a medicinal product, as in this case, while the patent rules have a more general aim. Therefore the rules on substitution of medicinal products take precedence of the patent rules.

Accordingly, there is no basis for prohibiting the pharmacies' dispensing of Pregabalin "Krka" instead of Lyrica for the treatment of neuropathic pain as long as these two medicinal products are actually substitutable and Pregabalin "Krka" is the cheapest medicinal product. Pfizer in fact requests that the Maritime and Commercial High Court disregards the rules on substitution. That is Pfizer's actual purpose of the case. An injunction would furthermore, depending on the text of such an injunction, also affect the system. It cannot be decided within the scope of patent injunction proceedings whether the rules on substitution comply with statutory rules and regulations or not. It must imply that the Danish Health and Medicines Authority is a party.

The High Court's reasoning and ruling

Krka

The substance of the primary claim according to which Krka is to be enjoined from selling Pregabalin "Krka" without "ensuring", at the same time, that the product is not distributed and/or dispensed for the treatment of the indication pain is not clear enough to be enforced by the Enforcement Court pursuant to section 424 of the Danish Administration of Justice Act or to provide the basis for sanctions pursuant to section 430 of the Danish Administration of Justice Act. Consequently, the claim cannot serve as basis for the granting of a preliminary injunction.

Krka has already performed the actions that are mentioned in the alternative claim. Accordingly, and as a preliminary injunction against the pharmacies is granted at the same time by this decision, see below, it has not been rendered probable that Krka's conduct necessitates the granting of a preliminary injunction; see section 413(ii), of the Danish Administration of Justice Act.

Consequently, the Court finds in favour of Krka in relation to the claims for an injunction.

The pharmacies

The pharmacies are independent businesses and not public authorities; not even when they fill in prescriptions. Therefore, section 411(1) of the Danish Administration of Justice Act does not prevent the granting of an injunction against the pharmacies.

Pfizer is the holder of a valid patent, DK/EP 0 934 061 T6, that is a so-called second medical use patent with a Swiss-type claim. The Patent in Suit concerns a new use of the already known drug pregabalin which Pfizer sells in Denmark as the medicinal product Lyrica. According to claim 1, the Patent in Suit comprises use of pregabalin for manufacturing a medicinal product for the treatment of pain.

Krka legally manufactures and markets Pregabalin "Krka" in Denmark for the treatment of the indications epilepsy and generalised anxiety disorder. The Danish Health and Medicines Authority considers Pregabalin "Krka" and Pfizer's Lyrica to be substitutable, and when Pregabalin "Krka" is the cheapest of the two medicinal products the pharmacies must, due to the rules on substitution, dispense Pregabalin "Krka" if the doctors have prescribed Lyrica, including when the medicinal product has been prescribed for the treatment of the indication pain. The question is whether this dispensing infringes Pfizer's rights according to the Patent in Suit.

In its memorandum of 26 January 2015, prepared at the request of the Danish Health and Medicines Authority, the Danish Patent and Trademark Office reaches the following conclusion:

"When medicinal products are listed as substitutable, and the pharmacies are thus obliged to dispense the least expensive of the two products, this would constitute a patent infringement if the generic product is sold/brought into circulation for use for the second indication (the use) that is protected by a patent."

In consideration of the fact that the Patent in Suit is a second medical use patent with a Swiss-type claim aimed at protecting the use of an already known substance for the treatment of a new indication, the court concurs that the pharmacies' dispensing of Pregabalin "Krka" with a label stating that the medicinal product is intended for the patent protected treatment of the indication pain constitutes infringement of the Patent in Suit, see section 3(1)(iii) of the Danish Patents Act.

Neither section 61 of the Danish Medicines Act, nor the legislative history of this provision, nor the Prescription Order seem to introduce a clear and limited exception to the exclusive rights which belong to Pfizer as the patent holder pursuant to the Danish Patents Act, so that others might, without Pfizer's consent, exploit the Patent in Suit commercially. This understanding is also supported by the TRIPS Agreement, Annex 1C, Articles 28 and 30. Consequently, the Court finds that it has been rendered probable that Pfizer holds the right that is sought protected by the application for an injunction, see section 413(i) of the Danish Administration of Justice Act, and that the pharmacies' conduct necessitates an injunction, see section 413(ii) of the Danish Administration of Justice Act.

Based on the evidence, the Court finds that it has been proved that it would be possible for the pharmacies to comply with an injunction. The pharmacies' practical difficulties in that respect are not found to be clearly disproportionate to Pfizer's interest in the granting of a preliminary injunction.

On this basis, and as the other injunction requirements are fulfilled, the Court finds in favour of Pfizer in relation to the primary claim (A) of claim 2.

On the basis of the evidence, the Court takes into account that the granting of a preliminary injunction will not impact the pharmacies' earnings; and for this reason alone there is no basis for conditioning an injunction on the provision of security, which the pharmacies have not asked for either.

Legal costs

Due to the outcome of the case, Pfizer is to pay legal costs to Krka. Based on the value, nature, course and extent of the case, including the fact that the trial hearing lasted three days, the amount is fixed to DKK 500,000 in total, including VAT, which covers payment of Krka's reasonable expenses in relation to legal assistance.

In view of the special nature of the case and its general public importance the court finds that none of the other parties, including the non-party intervenor, should be awarded legal costs.

It is ordered that:

The Court finds in favour of Krka, d.d., Novo mesto and Krka Sverige AB.

Defendants 3 - 222 are enjoined from dispensing the medicinal product Pregabalin "Krka" for the treatment of the indication pain for as long as Danish patent DK/EP 0 934 061 T6

is in force.

Warner-Lambert Company LLC and Pfizer ApS must jointly pay within 14 days legal costs in the amount of DKK 500,000, including VAT, to Krka d.d., Novo mesto and Krka Sverige AB.

None of the other parties are awarded any legal costs, including the Danish Health and Medicines Authority.

The legal costs will incur interest pursuant to section 8a of the Danish Interest Act.

Lise Krüger Andersen

Henrik Rothe

Mette Skov Larsen

(Signature)

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This is certified to be a true copy.

The Danish Maritime and Commercial High Court

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.
Thursday, February 8, 2018 – 9:35 a.m.*

**Session 1D:
The Regulator's Perspective**

Moderator:
Brian Cordery
Bristows LLP, London

Panelists:
Prof. Sir Alasdair Breckenridge, CBE
Former Chair of MHRA, UK

Stefano Marino
Head of Legal, European Medicines Agency, London

Daniel Kracov
Arnold & Porter, Washington, D.C.

* * *

MR. CORDERY: This is the second session, which is looking at matters from the regulator's perspective. I am Brian Cordery. I am standing in today for Wolfgang Rehm, who was snowed under — not with the white stuff, but with work — and so he was not able to come from Munich to be here today.

I think everyone in this room realizes that this is a multidisciplinary issue. It is not something that can be solved — it certainly cannot be solved by patent law; it probably cannot be solved by regulatory law alone — but it requires a multifactorial approach, which is why we have gathered experts from many disciplines here in the room today.

Clearly, an important aspect is the perspective of the regulators. Of course, the regulator's main mission — at least as I understand it, and I am not a regulatory lawyer, I will confess at the start — is to guarantee public safety as far as possible, to control the medicines that are given to patients, and to ensure that

their safety is maintained.

With that brief introduction, I would like to introduce our three panelists very briefly.

First, from the United Kingdom we have Sir Alasdair Breckenridge, who trained as a pharmacologist and spent many years in that area, then became the Chairman of the newly formed Medicines and Healthcare Products Regulatory Agency (MHRA), which is roughly the equivalent of the Food and Drug Administration (FDA), when it was formed in 2003.

Stefano Marino, who is a law graduate like myself, spent the first part of his career in private practice before changing tack in 2013 to become Head of Legal Services at the European Medicines Agency (EMA). These days Stefano has a number of challenges to deal with, not least the relocation of EMA to a beautiful city near the sea — not Dublin, not Belfast, not Edinburgh, but Amsterdam. Nice to have you here, Stefano.

Last but not least, Daniel Kracov, who is a Partner with Arnold & Porter based in Washington and, as I understand it, he has his career helping clients with issues relating to the FDA.

With that introduction, Sir Alasdair is going to start with some observations. Thank you.

PROF. BRECKENRIDGE: Thank you very much, and thank you for inviting me to this meeting. The mix with the law is always a challenge.

What I propose to do, quite briefly, is to discuss four essential principles of drug regulation that are referable to the topic of this meeting, which explain why repurposing is not necessarily a short process and why it may be expensive.

Issues

- Market access is determined by regulation and health technology assessment
- Benefit risk of the same medicine will vary in different indications
- Dose response relation of a medicine will vary when the responses differ
- Regulatory science moves on. Previous standards (e.g. in preclinical studies) may not be acceptable in a repurposed indication

These are the four issues, and I will deal with each of them separately:

- market access;
- benefit-risk;
- dose-response;
- the advance of regulatory science.

Let's start with market access.

Market access

- Market access is determined by regulation and health technology assessment
- Medicines regulation is determined by considerations of safety, quality and efficacy
- Health technology assessment comprises considerations of comparative clinical efficacy and cost effectiveness

Market access to a medicine is determined not only by the regulator. The regulator will consider issues of safety, quality, and efficacy; but also there is the

consideration of health technology assessment, the considerations of comparative clinical efficacy and cost-effectiveness.

There is no point in a medicine being approved by the regulator if the payor will not buy it. In the United Kingdom we have an organization, called the National Institute for Health and Care Excellence (NICE), whose role is to look at medicines which have been approved by the regulator and to decide whether or not they are appropriate for our National Health Service (NHS).

Health technology assessment is more widely developed in Europe than it is in the United States, but even in the United States there are now serious considerations of this. So market access is my first issue.

Benefit risk balance

- Marketing authorisation of a medicine is determined by its benefit risk balance.
- Benefit risk balance will vary when the same drug is used in different indications.
e.g. Herceptin in advanced and early breast cancer

The second issue I want to talk about is benefit-risk assessment. The balance between benefit and risk is the essence of medicine's regulation. The benefit-risk balance

will differ when a medicine is used for different purposes, i.e., when it is repurposed.

One of the best examples of this I know is the drug Herceptin, which is used to treat breast cancer. Herceptin is remarkably effective for advanced breast cancer, for which it was licensed. Even though the toxicology and the clinical toxicity of Herceptin is pretty horrendous — it causes cardiomyopathy and heart failure — regulators worldwide have decided that the benefits conferred by Herceptin give it a positive benefit-risk balance.

When this became available in the United Kingdom, there was a strong movement in which ladies said: "Well, it is effective in advanced breast cancer; we want it for early breast cancer," and they paraded up and down Whitehall wearing very attractive pink dresses and tried to push the regulators.

What they did not realize was that when it was used in early breast cancer the cardiomyopathy was still caused, patients still developed heart failure, but its efficacy was less than in advanced breast cancer. So here was a drug used in two indications where the benefit-risk balance was quite different, and in fact the drug

was not licensed for that indication.

The benefit-risk balance then must be ascertained for all indications, and, as we heard in the last session, the repurposing may not entail further clinical trials. We are more and more interested in using real-world data to make into real-world evidence. The day of the clinical trial is certainly not over, but the real-world data to real-world evidence is being increasingly used in order to ascertain benefit-risk balance.

Dose response relationships

- Dosage is critical to obtain an optimal therapeutic response
- In different indications, since the responses differ, so will the dose response relationship
- Assessment of dose is important in repurposing

The third point is dose-response relationships. Clearly, the dose of a medicine is crucial to obtaining an optimal therapeutic response, but in different indications, since the

responses differ, since the medicine will be acting on different receptors, so will the dose-response relationship.

Examples of this can be seen especially in cancer where, as we have heard already, a large number of drugs which were not invented for anticancer drugs — drugs like the macrolide antibiotics, cimetidine, Metformin — are now being used to treat cancer, in some cases quite successfully. This has implications for preclinical testing as well because in these indications there has to be a reassessment of the preclinical assessment.

Standards in regulatory science

- Regulatory science has progressed over time
- Previous standards may no longer be acceptable
- Previous preclinical data may no longer be acceptable in a repurposed situation
e.g. 5-HT₂ agonist in anxiety and drug resistant depression

The fourth one is what I have called standards in regulatory science. Regulatory science has progressed, obviously, over time, and what was acceptable previously may no

longer be acceptable now. Here I am thinking about preclinical data.

A good example of this is I am involved with a group now that is looking at a 5-HT₂ agonist, which was previously licensed for the treatment of anxiety, for the treatment of drug-resistant depression. When we looked at the preclinical data which had been obtained before, it became immediately apparent that this was totally inappropriate for what we now wanted, and so we have had to embark on quite a lengthy and expensive process of preclinical pharmacology.

These four reasons, I believe, contribute to the cost and length of repurposing.

Now, before I sit down, there is one thing I do want to say. As many of you will know, there is an unfortunate movement at the present time that the

United Kingdom is going to leave the Europe Union. Whatever political ramifications this has, it has obviously got medicines regulatory implications as well.

At the present time, the UK medicines regulations are those of the European Union. When we joined Europe in 1973, we abrogated our medicines regulation to the European Union. When we leave in March 2019, the chances are very strong that we will no longer be able to march with our European colleagues, and what will happen is that the United Kingdom is going to be faced with setting up a whole new armamentarium of regulations, some of which I have discussed already. As somebody has said, we hope for the best but we fear the worst.

MR. CORDERY: Thank you very much, Alasdair.

We will not take questions at this point because I want to get through some observations from all of our panelists, but there was plenty of food for thought in there.

Stefano, let's go straight on to you.

MR. MARINO: Thank you very much, Brian.

Thanks very much, first of all, to UCL and to Georgetown University for having invited me. I have to say I was at the Seattle conference in December 2015, and today, as in Seattle, I am here not exactly on a personal basis, but almost, in the sense that EMA does not have an official position on repurposing (yet). We are trying to make some progress, and I will explain how, together with the European Commission, but today my role here is to mainly update you on what has been the pace of the discussions in Europe about this subject in the last three years.

Just being here on a personal basis, I am very flattered that UCL has invited me again. I have no slides, but I will try to follow a logical order.

First, I would like to mention the regulatory environment that we have in front of us, the role of the [Commission Expert Group on Safe and Timely Access to Medicines for Patients \(STAMP\)](#), and I will tell you (a) what STAMP is; (b) the four types of repurposing identified by STAMP; (c) the lessons from STAMP so far; (d) and then I will try to draw some conclusions.

The regulatory environment: Europe is a difficult environment. As Sir Alasdair was saying, it will be even more difficult after March 30, 2019. It is difficult because there are twenty-eight — and then, unfortunately, twenty-seven — Member States.

We have the European Commission, which is really the licensing authority. We have EMA, which is the centralized agency providing scientific opinions and technical recommendations to the Commission. Then we have in twenty-seven Member States healthcare payors that are not necessarily aligned among themselves; and then we have doctors, doctors' associations, and pharmacists; and each Member State has its own system for pricing reimbursement because pricing reimbursement is a national competence.

This makes everything very complicated. Amongst other things, that is why in 2015 the Commission decided to form the STAMP.

What is the purpose of STAMP? It is to provide advice and expertise to

the Commission's services on how to improve implementation of the pharmaceutical legislation, and also to speed up access to innovative and affordable medicines. It is a forum to facilitate information among Member States trying to harmonize their practices, to create best practices, and examine some national initiatives.

In this context, STAMP in 2015 initiated a discussion on repurposing of established or off-patent medicines and different uses of active substances with representatives of a number of associations, including patients' associations. I will come back to the role of the patients' associations in a few minutes. Also, industry is well represented, in the sense that they are often invited. There are representatives for Medicines from Europe but also from the European Federation of Pharmaceutical Industries Association (EFPIA). So the voice of industry is well heard.

STAMP, in the last eight meetings in two and a half years, identified four different types of repurposing activities: (1) new therapeutic indications for an authorized drug; (2) new administration rules for the same indication; (3) new combinations of medicines previously used as separate products, i.e. monocomponents; and (4) new drug and medical device combinations.

After a couple of meetings, however, the Expert Group decided to concentrate on new indications for well-established and off-patent medicines in areas of unmet medical needs that could lead to faster development times and reduce the cost of developments whilst offering additional therapeutic options to patients.

Already, just conceptually, with the four types that were identified, it was impossible to address them at the same time, and there was a pragmatic decision to concentrate only on the new indications for well-established uses, which is one of the main subjects of this conference.

The lessons that came out of these eight meetings are as follows, at least this is my understanding of what has come out so far.

- First — and I think Sir Alasdair made very good hints to this subject — there is a common fear among EU Member States of lowering the requirements for the safety and efficacy of drugs. This is because the more we go ahead, the more we are pressed by independent scientists, patients' associations, and doctors' associations, we need to make sure that when EMA and the Commission approve new drugs they do not do that just for the sake of pleasing industry or just creating alternative therapeutic aids, even if it is done in order to stimulate competition. It is not that. There is a very strong common sense of duty that we should only approve medicines that are safe, efficacious, and of good quality, and nobody in Europe wants to deviate from those rules.

Therefore, when it comes to, for example, lowering the need for providing scientific evidence contained in a regulatory dossier, the immediate reaction is a sort of skepticism by a wide range of observers. One has to be very careful when dealing with this subject. We are used to those comments and to that sort of criticism because EMA launched three years ago now the [Adaptive Pathways in Europe and the Priority Medicines \(PRIME\)](#) project, and there was a rain of concerned comments on these initiatives taken by EMA. I think we are doing

very well and, so far so good, the first results of these two initiatives have been quite rewarding.

- The second lesson that came out from STAMP is that there is a fear of rewarding a very modest innovation. There have been suggestions that perhaps we might need to identify new criteria to identify what is really innovative. I think that David Cavalla hinted at that some minutes ago (see Session 1B).

- The third lesson from STAMP — and I am disappointed about this — is a pretty wide skepticism about brand-prescribing models, which was one of the suggestions that the Seattle conference came out with; brand-prescribing models in the sense that R&D efforts on new indications of existing medicinal products might be rewarded if the EU Member States could introduce for that particular indication a sort of mandatory prescription by brand name.

Now, this would certainly not work if it were not assisted in turn by a very robust administrative system for monitoring prescriptions and monitoring abuses. So far, only one Member State, Belgium, by a royal decree of 2001, is reimbursing new indications for drugs by way of categorizing medicinal products in category 1, category 2, etc. Category 1 would cover all indications except the patented one/s; while category 2 would cover only that particular drug, that particular indication, where, for example, a company invested some dozens of millions of euros to develop such a new indication. But so far Belgium is the only case in Europe.

I remember one very old example in France in 1991, but then the French law was aborted, was changed, and therefore this system did not fly.

- The fourth lesson from STAMP is that there is a, perceived at least, lack of information in the public domain about possible uses of new drugs. Several mitigating factors were mentioned. For example, it was suggested to use more the system provided by [Article 5.3 of Regulation 726/2004](#) establishing the EMA.¹ This Article refers to an opinion by the [Committee for Medicinal Products for Human Use \(CHMP\)](#), the main Committee providing recommendations to the Commission, whereby upon request of the Executive Director of the Agency, by Member States, or by the Commission, the Committee could provide some ideas for new uses of existing drugs and, thus, stimulate industries and academia to look into it. My personal idea is that, yes, it could be a nice way to go ahead; however, it would possibly encourage more off-label uses than new indications of drugs.

The other comment I would like to make about this is that, in my opinion,

¹ Regulation (EC) No 726/2004 of the European Parliament and of the Council of 31 March 2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency OJ (L) 136, 30.4 at 1 (2004), available at https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-1/reg_2004_726/reg_2004_726_en.pdf

Article 5.3: “At the request of the Executive Director of the Agency or the Commission representative, the Committee for Medicinal Products for Human Use shall also draw up an opinion on any scientific matter concerning the evaluation of medicinal products for human use. The Committee shall take due account of any requests by Member States for an opinion. The Committee shall also formulate an opinion whenever there is disagreement in the evaluation of medicinal products through the mutual recognition procedure. The opinion of the Committee shall be made publicly accessible.”

it is actually only a perceived lack of information. If you think about access to documents and the way that this has developed in Europe after 2001, and particularly in the last five years, and if you take a look at the three landmark rulings that were rendered by the General Court just a few days ago in favor of the European Medicines Agency and in support of the widest transparency of the documents that we hold,² I think you may realize that this is a false problem. I do not think there is really a lack of information in the public domain.

Finally, EMA also can give scientific advice to companies and whoever else wants to come. There are incentives in terms of fee waivers for small and medium-sized enterprises and academia, for example, who want to develop a new indication.

The final lesson coming from STAMP was a long discussion about financial incentives. Are the regulatory incentives for new indications enough in Europe? I do not want to go into details because I do not have the time and the clock is ticking, but in particular two of these were discussed.

- Fee waivers: for those who want to develop new indications, Europe might consider a fee waiver, so not asking the company or the applicant to pay any fee or to pay a nominal fee.
- The second one — this is more complicated to adopt and implement— is a system very much resembling the [FDA priority review voucher](#). This is something that we have been discussing in the last twenty years in Europe and we have not come to a conclusion yet. Perhaps this last point gives the possibility to see what is really practicable and what is not yet mature in Europe for a policy discussion on these new incentives.

In that regard, the first consideration I would like to make is that although STAMP has made a lot of progress, and I think the European Commission should be praised for that, the discussions actually concentrated more on these possible financial incentives — as I say, the FDA-like voucher or fee waivers — or perhaps on the other element, which I have already said is a false problem, i.e., a lack of information on possible new uses of drugs.

Quite strangely, the STAMP attendees seem to have taken some

² On February 6, 2018, the General Court delivered three landmark judgments relating to transparency of clinical trial data in the European Union. The long-awaited rulings clarify the scope of commercial confidentiality with regard to data pertaining to centrally approved medicinal products and included in the MA application dossier. The three rulings uphold the European Medicines Agency (EMA)'s decisions to release documents requested in accordance with the so-called "[Transparency Regulation](#)" and EMA's 2010 policy [0043 on access to documents](#).

The judgments concern [Case T-235/15, *Pari Pharma v EMA*](#), regarding the disclosure of CHMP similarity and superiority reports on an orphan medicine; [Case T-718/15, *PTC Therapeutics International v EMA*](#), on the disclosure of a clinical study report; and [Case T-729/15, *MSD Animal Health Innovation and Intervet international*](#), concerning five toxicology study reports for a veterinary medicine.

According to an [EMA press release](#), the General Court noted that the companies failed to give any concrete evidence of how the release of the contested documents would undermine their commercial interests, and therefore rejected their claims. This is the first time in which the General Court pronounced itself on the merits with respect to the Transparency Regulation and EMA's Policy 0043. Available at http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2018/02/news_detail_002899.jsp&mid=WC0b01ac0858004d5c1

distance from the other three main “elephants in the room.”

- The most important one is the fact that without a robust revision of the administrative system on prescribing, dispensing at the level of the pharmacist, and reimbursing, there will be no real progress in this area. It was said before that without a strong connection with the healthcare payors, whatever we can discuss here or at the STAMP will be of scarce utility. EMA tried hard to move the discussion and to push the audience toward those arguments, but so far we were not very successful apparently.

- The second thing is perhaps, yes, there may be a need of fine-tuning a little bit the criteria for innovation. This is something that EMA could certainly try to do. Europe’s best scientists sit in our committees. Member States’ scientists can certainly help us be more clear when we say what is innovative, what is innovation, what do the regulators expect from the researchers outside.

I think, as Sir Alasdair was saying before, Brexit brings many bad things, but maybe one good thing is that it stimulates our brains to think outside the box. There will be competition in London very soon on who attracts more development efforts to register a new product. Perhaps, together also with the MHRA, we might try to identify new criteria to reward innovation in the long run.

- The third conclusion I would submit to your attention is that we should probably listen more to patients and patients’ associations. The voice of the patients’ associations is very important for EMA. They should be the real driver for the regulators and for industry to identify what new uses or new indications may be worthwhile exploring.

The final thing I would like to say — sorry, I am a lawyer; I cannot resist saying this — is there have been a couple of judicial developments just in the last two or three weeks. I have already mentioned the three General Court judgments³

³ EMA, Press Release, General Court confirms EMA approach to transparency (Feb. 6, 2018), available at http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2018/02/news_detail_002899.jsp&mid=WC0b01ac058004d5c1:

Three rulings clarify the scope of commercial confidentiality with regard to authorised medicines

The General Court delivered today three landmark rulings for the European Medicines Agency (EMA), upholding EMA’s decisions to release documents requested in accordance with [Regulation \(EC\) No 1049/2001](#), the so-called “Transparency Regulation”.

This is the first time that the [Court of Justice of the European Union](#) has had the opportunity to pronounce itself on the application of the Transparency Regulation to documents held by EMA. “We are very pleased that the General Court affirmed that the information contained in these documents cannot be considered commercially confidential in its entirety”, explained Stefano Marino, EMA’s Head of Legal Department. “We understand that with these rulings the General Court endorses our implementation of the Transparency Regulation that focuses on the interest of patients and public health”.

The judgments concern [Case T-235/15, *Pari Pharma v EMA*](#), in relation to the disclosure of similarity and superiority reports on an orphan medicine, prepared by the Committee for Medicinal Products for Human use (CHMP); [Case T-718/15, *PTC Therapeutics International v EMA*](#), on the disclosure of a clinical study report; and [Case T-729/15, *MSD Animal Health Innovation and Intervet international*](#), regarding five toxicology study reports for a veterinary medicine. In all three cases, the

on access-to-documents. Have a look at those judgments. I think they are really landmark rulings in terms of wider circulation of scientific information.

The second development is a judgment that I do not think it has been yet commented on — maybe Brian may correct me on that — i.e. the [Avastin judgment by the Court of Justice](#) further to a preliminary reference from Italy.⁴ Now, there are many things that the Court said in that judgment, but one in particular could be a problem for the repurposing of existing drugs. The Court seems to encourage in some way a concept of increasing substitutability among medicinal products, including those products that have not yet received an approved indication; that have not received, in other words, a marketing authorization. By putting on the same level one authorized drug and one non-authorized drug used by doctors in the same indication for the same purpose, the Court seems to endorse the “evergreening” concept of substitutability, which, if you think about it, might be an issue for the repurposing of drugs and for the rewarding of innovation.

Thank you very much.

MR. CORDERY: Stefano, that’s great.

Dan, could I ask you to make some observations because, obviously, we are here today in the United States and it is the most important country for many people?

MR. KRACOV: I should start by saying I am an imposter here today. I am not a regulator. We did not have an FDA speaker, so I was asked, as a thirty-year observer of FDA, to say a few words about where FDA is going in this area.

Whatever you think about the Trump Administration — obviously, a very controversial administration in many ways — we are actually extremely lucky from the perspective of bringing new therapies to patients, given what is happening in this administration, because the Secretary of Health, Alex Azar, and Human Services and a FDA Commissioner, Dr. Scott Gottlieb, actually know what it takes to bring a drug to market and the difficulties associated with that. While they have been subject to criticism for their associations with industry, I think at the end of the day the current priorities of the FDA Commissioner, are

pharmaceutical companies challenged EMA’s decision to release the concerned documents in accordance with the Transparency Regulation and [EMA’s 2010 policy on access to documents](#) (Policy 0043).

The General Court noted that the companies failed to give any concrete evidence of how the release of the contested documents would undermine their commercial interests, and therefore it rejected their claims.

Based on the guidance issued today by the General Court, the Agency will continue to diligently assess each individual request for access to documents submitted under the Transparency Regulation and in accordance with its policy on access to documents.

⁴ Court of Justice of the European Union, Press Release No 06/18 Luxembourg (23 January 2018), Judgment in Case C-179/16, F. Hoffmann-La Roche Ltd and Others v Autorità Garante della Concorrenza e del Mercato, available at <https://curia.europa.eu/jcms/upload/docs/application/pdf/2018-01/cp180006en.pdf>; full judgment available at <http://curia.europa.eu/juris/document/document.jsf?text=&docid=198644&pageIndex=0&doclang=EN&mode=req&dir=&occ=first&part=1&cid=728186>

very complementary in terms of the interests of patients and the interests of the industry.

I will just talk about a few of the things that FDA is really focused on. There is really a handful of things that I would emphasize.

This administration is very focused on breaking down unnecessary barriers to innovation, at least in the FDA space, without necessarily compromising, obviously, benefit-risk, but Commissioner Gottlieb right out of the box has been very, very focused on using both existing tools and new tools at his disposal as a result of recent legislation, most notably the [21st Century Cures Act](#), which was passed in December 2016, and the [FDA Reauthorization Act](#), which was passed in 2017, both of which were focused on optimizing the drug-development process.

How is FDA going about that? There are a number of different initiatives.

FDA has initiated a [Strategic Policy Roadmap](#) that is focused on things like looking at alternative approaches to clinical development; how do you bring down drug development costs by breaking down the traditional Phase I through Phase III approach; and using adaptive trials, computational modeling, and other approaches to try to expedite the development of information necessary to achieve approval? That is an area where there are a lot of different things going on.

There is also a particular focus on the patient experience, real-world evidence, and big data, and how that can be used in the drug development and approval process. This is exactly where we should really be going, and this could have very significant implications for second medical uses in terms of the wall that needs to be climbed to get to market.

The other thing that FDA is very, very focused on right now is drug pricing, but not directly — not direct policy with respect to drug pricing, but breaking down barriers to competition. FDA is very focused on the regulatory science associated with making that happen, as well as the process issues associated with generic drug approval.

As part of the [Generic Drug User Fee Amendments](#) there are some new incentives for generic drug development that were put in place.

FDA has also embarked on significant efforts to focus on what kind of guidance and regulatory science needs to be developed in order to approve nonbiologic complex drugs. That is really the challenge in the drug side for FDA over the next twenty years: how do you take some of these more complex drug products and safely allow competition for those without making the barriers insurmountable?

The other obvious issue for FDA is opioids. We have an opioid epidemic in the United States. If you listened to the 2017 confirmation hearings in this area, they are very much focused on opioids and dealing with the opioid crisis. That also has implications for second medical uses because of the need for different types of pain medications as well as abuse-resistant or deterrent forms of opioids. There are a lot of very interesting initiatives within FDA right now in those areas, all of which have implications for different types of second medical uses.

But FDA also has some limitations.

FDA does not control market access. Frankly, in the United States there is a lot that FDA could do, but there is a lot more that can be done from a payment system perspective to try to foster an environment for second medical uses. If I had to rank the issues, I would say the regulatory barriers are certainly important; but the market access barriers are even more important because right now in many situations you can bring that product to market for the second medical use, but if the original product is generic, there is a free-rider problem: the payor does not want to pay for the second medical use, and that is really the fundamental problem we deal with.

The second issue that FDA cannot deal with is creating new incentives, such as new exclusivities. That requires statutory change, and statutory change is very complicated right now, both because of the politics that we are dealing with in the United States as well as the fact that new exclusivities are “scored” as costing money. In order to adopt a new exclusivity, typically what needs to happen is you have to find something to cut to pay for that new exclusivity, and that can be an extreme challenge, to have that sort of zero-sum budget environment.

Finally, FDA needs resources. Many of these resources are given to FDA through user fees, but sometimes these new mandates, these new incentives, are not accompanied by new resources, and that is a real challenge for the agency.

So, just a few high-level remarks on the issues in the United States.

MR. CORDERY: That is really interesting, Dan, and thank you.

We have a few minutes left before the coffee break, which I will not hold you from, I promise. I have some questions of my own, but I do not want to dominate, so I am going to ask if anyone in the audience has a question for any of our speakers.

QUESTION [Chris Loh, Fitzpatrick Cella]: I want to follow up on one point that Dave brought up. I am curious if there are any similar initiatives in the MHRA or in the EMA to use big data or data mines with retrospective analysis as a way of lowering the Phase I to Phase III cost.

PROF. BRECKENRIDGE: Last week we had a meeting at our Academy of Medical Sciences, which is equivalent to your National Academy of Medicine, at which we had representatives from the FDA, from the EMA, and from the MHRA. The one thing which came out, to me anyway — and don't take this badly — was that the FDA is considerably in advance of the EMA in doing this. I think that the FDA is to be congratulated for the innovative way in which they are using big data, not just for safety — we are all using it for safety — but for efficacy as well. I do not know whether you would agree.

MR. MARINO: I do agree, absolutely. Why is EMA in arrears? Because in Europe the legislation does not allow us to have access immediately to the so-called raw data, to the individual patient data. They may be requested from the companies applying for a new marketing authorization, but only in exceptions, and there must be a reason to do so, and the privacy laws are extremely strict and are now becoming even stricter. So there is a fundamental difference between the EU and the U.S. legal environments about this.

That said, in the last eighteen months EMA has also — shyly at first but

now very steadily — been trying to open the debate on big data. We also had two major conferences in London at our premises. Indeed, the trend is to have a further look at this and try to see how to make the best use of big data, particularly in an effort to sustain industry's efforts toward innovation.

MR. CORDERY: Thank you.

I think we have time for one further question.

QUESTION [Bruce Bloom, Cures Within Reach]: Alasdair mentioned how when you look at a different indication you need to look at the safety. I wonder how regulators use real-world evidence, such as the number of patients who have taken a drug for the first indication and all the safety data that is gathered around that, plus all the off-label use that is already occurring when physicians prescribe the drug for the new indication that has not yet been approved. How do regulators use those data to help satisfy some of the safety issues that might come up which are different for the second use or third use of a drug?

PROF. BRECKENRIDGE: That is really a catch-all question. What the regulators try to do is to make the best use of whatever evidence there is from whatever source it comes, be it electronic medical records, our own databases, or whatever.

The critical thing, in my view, is the indication that the drug is being used for. For example, if you had a drug which was a cough suppressant which is found to have the potential to treat cancer, then the safety data for the cough suppressant may be entirely irrelevant for the other use, so you really have got to take into account the different indications for which the drug is being used.

Dosage is important as well, because the dose that is being used for one indication may be ten, twenty, or thirty times more than the other, and, as we well know, if you look at dose-response curves for safety, these are really very important.

So we will use whatever we can, but we will rely on fundamental pharmacological principles to make our final judgment.

MR. CORDERY: Thank you. We will have one more question and then we are going to break. Amitava?

QUESTION [Dr. Amitava Banerjee, UCL Farr Institute of Health Informatics]: We have traditionally looked at pharmaceuticals differently from devices, and increasingly in all markets now we are seeing apps and digital applications and data applications that also have medical uses which are new types of devices. Do the panel see any new form of regulatory framework where you have an overlap — for example, new uses of anticoagulants which are guided by apps, where you have a kind of combined regulatory framework across pharmaceuticals and devices with them? Thanks.

MR. CORDERY: Briefly, does anyone want to respond?

MR. MARINO: In Europe we have a new [Medical Device Regulation](#).⁵ EMA has limited competence in that area. However, it is an important piece of legislation and it responds to what the Parliament and the Council saw as an increasing trend of developing medical devices in association with drugs.

STAMP, as I mentioned, initially tried to have a look at new uses of indication, repurposing, also making use of medical devices. So far, the discussion on that particular subject has not evolved, due to lack of time, but this is one of the things that indeed could be examined in the future.

I guess, in any event, the general principles will have to be respected, so the prerequisites of safety, efficacy, and quality will remain, because otherwise the legislation should be changed again, and there is no particular appetite for that.

PROF. BRECKENRIDGE: Can I just add one thing? We are struggling with this question that you raise. You are obviously very aware of it as well.

When does an app become the province of the regulator? The wording that has been used is “when it has a therapeutic implication,” but that is as long as it is broad, and we are trying to deal with it at the MHRA on a case-by-case basis. It is not easy because you have very clever guys who are trying to change the wording in a way in which it will not come under the aegis of a regulatory authority whereas in fact it probably should.

MR. KRACOV: There has been a lot of policy development and legislation in that area in the United States.

Essentially, what has happened is a lot of these apps that do not have direct medical implications, that are transparent to the physician — in terms of, for example, algorithms used for clinical decision making, etc. — have been taken off the table in terms of regulation. They are either unregulated now, other than the claims that are made for them, or they are subject to enforcement discretion. So, FDA is really focused on those that have a direct link to either a medical device or are embodied in drug labeling or whatever it might be. It is a lot more complex than that, but there is a lot that is going on here to kind of clear the ground for the development of those technologies.

MR. CORDERY: Thank you very much. We will come back to these topics during the course of the next two days. If you have a question you did not get answered, you will get another opportunity.

The final thing is to ask you to thank our panelists for their very interesting discussion. Thank you.

[Session Adjourned: 10:38 a.m.]

⁵ Regulation (EU) 2017/745 of the European Parliament and of the Council of 5 April 2017 on medical devices, amending Directive 2001/83/EC, Regulation (EC) No 178/2002 and Regulation (EC) No 1223/2009 and repealing Council Directives 90/385/EEC and 93/42/EEC, available at <http://eur-lex.europa.eu/legal-content/ENG/TXT/PDF/?uri=CELEX:32017R0745&from=EN>.

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.
Thursday, February 8, 2018 – 10:45 a.m.*

**Session 1E:
A Critical Review of the Current Landscape — Presentations**

Presenters:

Christoph de Coster
Taylor Wessing LLP, Munich

Elaine Herrmann Blais
Goodwin Procter LLP, Boston

Daniel Kracov
Arnold & Porter LLP, Washington, D.C.

Gareth Morgan
CMS Cameron McKenna Nabarro Olswang LLP, London

* * *

MR. CORDERY: This session has no moderator, but it does have four outstanding lawyers who are going to tell you about basically how the landscape for second medical use is operating in their country, the idea being we know it varies a lot from country to country, so we need to look at some of the most important countries.

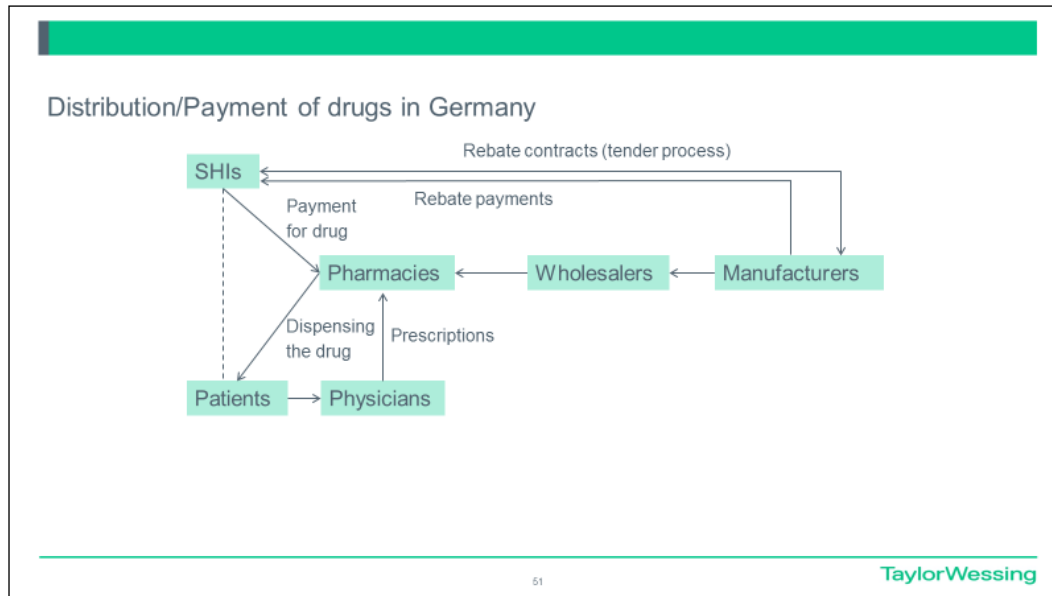
We are not going to bother with introductions. I will ask each of the speakers just to introduce themselves by name and a couple of words and then get onto the meat of their presentation.

Christoph, I will hand it over to you.

MR. de COSTER: Thank you, Brian.

My name is Christoph de Coster. I am a Munich-based patent litigator from Taylor Wessing, and my task here is to give you a very brief overview about enforcement of second medical use patents in Germany and the problems that we face in view of the regulatory environment.

I will use two slides to explain how the distribution of drugs in Germany is handled; what the rules are, especially the substitution rules; and will then show you two slides on German case law and what we already have as guidance from the German courts as regards enforcement of second medical use patents. The last slide is dedicated to some conclusions for later discussion.



How are drugs distributed in Germany? Very basic, and probably very similar to other countries: the patient sees a physician; the physician writes a prescription; the patient gets the prescription, goes to the pharmacy; and the pharmacy dispenses the prescribed drug.

There are two special characteristics in the German system that I should mention:

First, most of the patients, 90 percent, are insured via the public system, the social healthcare insurance companies (SHIs), and these pay for the drug if the patient who is insured gets it from the pharmacy. The payment, of course, is highly regulated in Germany, and the pharmacies only get compensation if they follow the rules, especially the substitution rules; otherwise, they have to pay themselves. Therefore, there is high pressure on the pharmacies to follow the rules.

The second feature, which is a little bit specific to Germany, are rebate contracts. As soon as the active pharmaceutical ingredient (API) market becomes generic, the SHIs — and it is not a central authority; there are 120 different social healthcare insurance companies in Germany — at that moment invite all the manufacturers on the market, the generics and the innovators, to offer rebates on products that they pay for. That is a public tender process, and the manufacturer/distributor that offers the highest rebate as a rule gets the rebate contract with a certain social healthcare insurance company.

Why do distributors offer rebates? Because they get an exclusive slot with this company they concluded the rebate contract with. That means that their product is the only one that is substitutable for the patients of this insurer, and that is the incentive for the rebates. The rebates are massive; very often, they are about 60 percent of the listing price.

Substitution in Germany		
General rule: Substitution is possible, if <ul style="list-style-type: none"> a physician allows it and products are substitutable (same API and one identical indication) 		
	Information	Obligations/Incentives
Physician	<ul style="list-style-type: none"> Patient and indication Available products (software) 	<ul style="list-style-type: none"> Under control and budget pressure of the SHIs
85 % of the prescriptions allow substitution		
Pharmacist	<ul style="list-style-type: none"> Prescription Patient/SHI but no indication Substitutable products (software) Rebate contracts of SHIs 	<ul style="list-style-type: none"> Obligation to dispense the substitutable product which is <ul style="list-style-type: none"> under a rebate contract with SHI otherwise one of the three cheapest on the market
Conclusion: Regulatory system promotes wild substitution (cross-label)		

How does substitution now work in Germany? As a general rule, there are two conditions. The first condition is that the physician allows substitution, and the second condition is that the product or the products must be eligible for substitution.

There are different requirements, but the main requirements are: (1) it must be the same API; and (2) only one indication must be identical — not all, only one. That means that “skinny label” products, which carve out certain indications because of patent protection, are substitutable for products with a full label.

What drives substitution? First of all, the physicians are, in principle, free to prescribe the product they prefer. It is in their discretion to allow substitution or to exclude substitution. However, they are under strong pressure from the social healthcare insurance companies to allow substitutions because of budget reasons. They all have budgets that are controlled by the healthcare insurance companies, and if they do not follow the rules, there are sanctions. They have to compensate the social healthcare insurance companies if they do not act cost-efficiently. That means that 85 percent of the prescriptions allow substitutions.

Then, at the pharmacy level, substitution is almost automatic because the pharmacist, under of data protection rules in Germany, does not know the indication. He just sees the prescription that allows substitution, and then he has to follow the rules. The rules are: (1) if there is a rebate contract in place, they have to substitute by the rebated product; (2) if there is no rebate contract in place, they have to dispense one of the three cheapest products on the market, usually

generic products. That, as a conclusion, of course promotes wild substitution, i.e. cross-label substitution.

German case law

- > Pregabalin (Rebate tenders)
 - DC Hamburg (2015: Patent Chamber): Gx have to indicate limitations of their tender offer (not for protected indication)
 - CoA Dusseldorf (2016: Procurement Division): SHIs have to split tender for APIs into a tender for the protected indications and a tender for the non-protected indications; *Social security law does not have priority to patent protection*
- > Fulvestrant (Liability of Gx despite skinny label)
 - CoA Dusseldorf (2017: Patent Division): Direct infringement is possible, if
 - > product is suitable for infringing use
 - > Gx knows or should know that wild (and infringing) substitution occurs in practice to a relevant extent

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TaylorWessing

What is the German case law in view of these problems?

There was a pregabalin (Lyrica®) case in Germany. I know that a colleague of mine in the next session will describe the case in more detail (see Session 1F). The scenario was that for pregabalin the API was already off-patent, but there was one very important indication, pain, that was still patent-protected.

As soon as generic products with a skinny label — i.e. a label that carved out the still-protected indications — came on the market in Germany, the social healthcare insurance companies started the tender process and invited offers for pregabalin. This tender process was not indication-specific but API-specific.

All the generics with the skinny-label product could participate, and did so. That, of course, would have led to wild substitution because we know that the company that wins the tender process and the rebate contract with a certain SHI is then entitled to exclusive substitution, even if it is a skinny-label product.

That was the reason for Pfizer to take two actions.

The first one was against the generics that participated in such tenders without indicating that they were only able to provide products for the protected use. The District Court in Hamburg (decision dated April 2, 2015 315 O 24/15) said in the 2015 preliminary injunction (PI) proceedings: “That is not allowed as it is promoting wild substitution.” Therefore, the Hamburg court found these activities of the generics qualify as indirect patent infringement because, by participating in such tenders, generics would promote wild substitution.

Pfizer also attacked the social healthcare insurance companies. The argument was that they cannot offer unrestricted tenders if there is still protected use because this (1) promotes patent infringement by the end-users and (2) thus also violates procurement law. The Düsseldorf Court (Procurement Division decision dated December 1, 2015 VII Verg 20/15) agreed that, yes, that is against procurement law and the social healthcare insurance companies have to split tenders in protected indications and unprotected indications. The court

specifically emphasized that social security law does not have priority to patent protection. That is a clear case, because here we have active promotion of patent-infringing use by the social healthcare insurance companies and by the generics.

But what happens if the generics have a skinny-label product and do not show any activities that actively promote the wild substitution of this product, but just realize that the product is also used for protected use? Because of the substitution rules, it happens, but the generics do not have influence. So are they liable for this?

There is a recent decision from last year of the Court of Appeals in Düsseldorf (decision dated May 5, 2017 I-2 W 6/17 – *Östrogenblocker*). It was also a patent infringement case and it was rejected for other reasons. The court stated, “Yes, not only active behavior causes liability of generics but also passive behavior.” So if the generic has a skinny label but realizes that wild substitution happens to a substantial extent in the market, then the generic cannot just sit there and wait and see, but has to take possible measures against such use.

Guidelines and remaining problems	
<p>1. Rebate Tender</p> <ul style="list-style-type: none"> SHIs have to split tender offer Gx cannot participate with skinny label products in an unrestricted tender <p><u>Problem:</u> Even if different rebate contracts for the same API but different indications exist, pharmacist still does not know which one applies to a certain prescription.</p>	<p>2. Wild Substitution</p> <ul style="list-style-type: none"> Gx are potentially liable for wild substitution as soon as it becomes relevant and obvious <p><u>Problem:</u> Which measures have to be taken and who is responsible?</p> <ul style="list-style-type: none"> Limited measures available since the Gx have limited influence on behaviour of SHIs/physicians Still unclear who (the patentee or the Gx) is responsible for identifying reasonable measures

What is the situation at the moment?

With regard to tenders, it is very clear. Tenders have to be split. If they are not split, then the generics cannot participate; they cannot actively promote wild substitution.

What if there is no tender, if the generics are just aware of wild substitution in the market without having any influence on it? Then they have to act if the infringing use, the wild substitution, is relevant and obvious. The problem is — and that is not yet solved in Germany — what are the measures that need to be taken by the generics because they do not really have influence on what happens in the marketplace; it is driven by the system?

Therefore, there are very limited measures generics can take to solve the problem. They can just write physicians and social healthcare insurance companies telling them to be compliant and not to substitute if there is still protected use. But that will not really help.

Conclusions

- The regulatory framework in Germany promotes cross-label (wild) substitution
- German courts cannot solve but just mitigate the dilemma
- Within the current regulatory framework the problem can be mitigated, if physicians do not allow substitution in case
 - the prescription is for a still protected indication of the API and
 - the other available products have carved out this indication
- But:
 - SHIs have to promote such practice under their cost efficiency control and
 - physicians need sufficient information
- Proposal: Agreement between Association of SHIs and the Association of physicians providing an up-to-date list of products for which substitution should be excluded for certain (still protected) indications plus software implementation

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TaylorWessing

Very quickly, the conclusions.

The regulatory framework in Germany creates the mess and the dilemma (wild substitution), and the German courts, at least the patent courts, cannot really solve this, and also not the parties to such proceedings, the innovators and the generics. Within the current German regulatory system, the physicians can avoid wild substitution if they do not allow substitution for still-protected uses, and the social healthcare insurance companies can help to solve the problem by not applying cost-efficiency pressure on the physicians who do not allow substitution for protected use.

So it is still a dilemma, and certainly not to be solved by the courts, but probably only by the legislator by clearly splitting the market between protected and non-protected uses and prohibiting the substitution if there is protected use.

Thank you very much.

MS. BLAIS: Hello. I am Elaine Blais from Goodwin Procter. I am a patent litigator who is actually seeing a lot of these cases lately. It is interesting that we talk about there not being incentive to come up with second medical uses. Despite there being some truth in that concept, we are certainly seeing a lot of litigation about second medical uses and a lot of patents on second medical uses.

Dan is going cover the regulatory exclusivities, so I am going to skip that part and just talk about method-of-use (MOU) patents.

In our system, a company that wants to make a generic version of a drug has to tell the Food and Drug Administration (FDA) how they want to treat patents that are listed in the Orange Book. We can say, "We are going to wait for the patent to expire" (you might have heard of Paragraph III); or we can say, "We are going to challenge the patent; we either do not infringe it or it is invalid" (that is Paragraph IV); and in the case of method-of-use patents, if there are multiple uses on the brand's label, we can ask to carve out a patented use (we refer to that as a Section viii carve-out).

Overview: Protection for Additional Uses

- Regulatory exclusivities – Dan Kracov’s presentation
- Method-of-Use Patents
 - Companies manufacturing generic versions of drugs can either:
 - Wait for the patent to expire (“Paragraph III” or “PIII”),
 - Challenge the patent (“Paragraph IV” or “PIV”), or
 - Carve-out the patented use (“Section viii carve-out”)
 - Carve-out means: not seeking FDA approval on the patented use
 - The patented use will be “carved-out” from the generic label; the resulting label will be a “skinny label” omitting information about the patented use

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I am focusing largely on small molecule patent litigation in this presentation. The biosimilars arena is slightly different, and I think it is going to be very interesting to see how each of the things we talk about here may be different when we start seeing more biosimilar competition and as we are beginning to see it.

A carve-out means essentially that you tell FDA, “We are not seeking FDA approval on a particular patented use.” The reason for a carve-out being a possibility, of course, is to incentivize the marketing of products for nonpatented uses, so we want to allow generics to be available for the nonpatented uses while still carving out the protected use.

I think, similar to what we have said about the European Union, the problem we are facing here is inherent in our system. We have seen in some of the current litigations that the system is on trial in some of our cases.

And to emphasize how hot an issue this is, as I was sitting listening to the other speeches, I got a message from a reporter who wanted to speak to me about why a biosimilar applicant had removed two uses from its label. She was just puzzled — why would that happen? So today in the news someone is writing a story about this issue. We might think it is interesting, but apparently the public thinks it is interesting as well.

Overview: Method-of-Use Patents

- Method-of-use patents (“MOU” patents) cover new indications/uses for a drug
- No direct infringement
 - Drug manufacturers are not treating patients or practicing the patented method
- Indirect infringement
 - Contributory infringement
 - defeated if there is a substantial noninfringing use, which the remaining labeled (first) use often is
 - Induced infringement
 - requires showing specific intent and active steps taken to cause direct infringement

Method-of-use patents cover new indications or uses for a drug. These patents present a challenge in patent litigation for the brand to prove infringement, and that is because the generic drug manufacturer does not directly infringe those patents. Of course, generic drug companies are not administering drugs or treating diseases. So we end up litigating about indirect infringement. There are two flavors of indirect infringement, and obviously this is the high-level, very short version of this lesson.

Contributory infringement is particularly hard to show with regard to a second medical use because a claim for contributory infringement can be defeated if there is a substantial noninfringing use for the product. Many times the first medical use is off-patent by the time we are litigating patents on second medical uses.

So we end up fighting about induced infringement. The law of inducement in the United States is pretty complicated. There is a lot of law here, and I am not going to go through a bunch of cases today. In a nutshell, it requires a showing that there was specific intent and active steps taken to cause direct infringement. It is very important that intent alone is not enough; active steps are very, very important to the finding of inducement; and we are starting to see more and more litigation about causation as well.

I am not going to spend a lot of time on prescribing, dispensing, and reimbursement because this afternoon there are entire panels that are going to talk about those issues.

But, just for context, our system is similar to what we talked about in Europe. Here doctors are free to practice medicine and they can prescribe medications for whatever they want to prescribe them for, regardless of the uses for which a drug is approved. They can prescribe either by brand name or by generic name, by the molecule name, and they can optionally further specify “dispense as written.” So it is possible for a doctor to limit the drug that is administered in response to a prescription. If they write the brand’s name and they write “dispense as written,” it will not be substituted with the generic.

Overview: Prescribing, Dispensing, Reimbursement

- Doctors **prescribe** drugs
 - Doctors can prescribe either by brand name or active ingredient, and can optionally further specify to “dispense as written”
- Pharmacies **dispense** drugs
 - Automatic substitution laws: unless doctor specifies “dispense as written,” a generic will be automatically substituted for the brand drug
 - Indications play no role in generic dispensing
 - Pharmacies dispense AB-rated generics for all uses regardless of label carve-outs
 - Pharmacies typically do not know (a) what indications are in a generic label, and/or (b) which condition the product was prescribed to treat
- Insurers determine **costs** of drugs
 - Prescription filled with an AB-rated generic: low copay
 - Prescription filled with brand drug, when an AB-rated generic version is available: higher copay, or no coverage at all

Pharmacies then dispense the drugs, and largely the pharmacies have no idea what the drug is being used for. The prescription does not say “dispense

Drug A for patented use” or “dispense Drug A for nonpatented use”; it says, “dispense Drug A” and the pharmacies do that. Unless the doctor specifies “dispense as written,” a generic will be automatically substituted in most cases. Now, there is variation among states, but I am assuming the afternoon panel will cover those details.

Insurers then determine the cost of drugs and they decide how much patients are going to pay for drugs. The system is set up so that, in general, patients pay less for generics, and so they are incentivized to ask their doctor to write the generic; or, if they standing at the pharmacy and the price is a lot, to say, “Wait a minute, can’t I get the generic?” That is how the system works absent any action from the generic company taking active steps to encourage doctors to prescribe, pharmacies to dispense, or insurers to pay in any particular fashion.

Especially when we focus on the direct infringer in these cases, it is the doctor. There is largely no communication between the generic company and the doctors. The product becomes available, the doctor writes the prescription, and then we go through this system that I have just laid out.

It is worth noting here that this is again in the small molecule context. For biosimilars it is going to be interesting to see how it plays out because there will not be automatic substitution unless a product is determined to be “interchangeable” and state law provides for automatic substitution..

In the absence of an interchangeability determination, there may be more interaction between the biosimilar manufacturers and the physicians because the lack of auto-substitution is going to require some marketing. It will be interesting to see how this evolves as we move to a new area of drugs with different rules in place.

Implications for Patent Litigation

- Inducement infringement requires specific intent and active steps taken to cause direct infringement
- Doctors prescribe drugs – practice of medicine
- Pharmacies dispense drugs – automatic substitution laws
- Insurers determine costs of drugs – copay schedule depends on availability of generic

How do these legal and practical contexts inform induced-infringement cases?

- Is mere knowledge of how a generic might be dispensed and/or used for a patented method enough to show inducement?
- What factors should be considered in demonstrating specific intent and active steps taken to induce infringement?
 - pre-launch: inducement based on label only
 - post-launch: other activities (e.g. marketing) may come into play
- What factors should be considered in attributing causation?
 - What influences doctors to make their prescribing decisions? Medical journals? Practice guidelines? Brand promotional activity? Generic promotional activity?

The top of this slides is just a summary of what I just talked about.

There are a number of questions that are often raised in these cases. Often the brand will argue: “Well, you knew that your product would be dispensed for infringing uses.” Is that enough? Generally, the courts say: “No, it’s not. There have to be active steps. Mere knowledge under the case law is not enough to find inducement.” So we end up looking at facts, and the facts can differ depending

on whether we are talking about a product that is not yet in the market or a product that has been launched into the market.

If we are talking about prelaunch, then the courts tend to focus on the label, and they ask the question of whether there is a possibility of inducement with what is left in your label. So you might carve out an indication, and there might be an argument that what remains there — safety information, for example — the indication is gone, but you could not take other things out, and that there might still be inducement. We litigate about that.

Post-launch it becomes really interesting because then we are talking about not just what is in the label, but did anything happen in the marketplace to induce.

Just a quick anecdote. I am litigating a case — it is public; I will not name it, but you can go find it if you want to — in which we litigated prelaunch and the court decided that our carve-out was appropriate and dismissed the brand's case. It went up on appeal. The Federal Circuit said: "Yes, that's right. This is an appropriate carve-out. There is no inducement based on this label." Actually, it was in the preliminary injunction context, so it got remanded for the court to deal with it.

The court was ready to dismiss, and then the plaintiffs asked: "Well, can we file an amended complaint? Now that the product has launched we have new information in the marketplace that some of the salespeople are out there saying things to doctors that would induce infringement."

Of course, our client said, "What are you talking about?"

The court said, "Well, okay, if these facts are true, then we get to go forward."

Now we are litigating a case where the patented use was appropriately carved out of the label and the only evidence of inducement is one doctor who said that one third-party contract salesperson said, "Oh, you can use it for anything the brand is approved for. Oh, sure, you can use it for this patented use." We have yet to see how these witnesses hold up and how credible the story is, but that is the story we that are litigating. So you can see that these cases can become very fact-intensive.

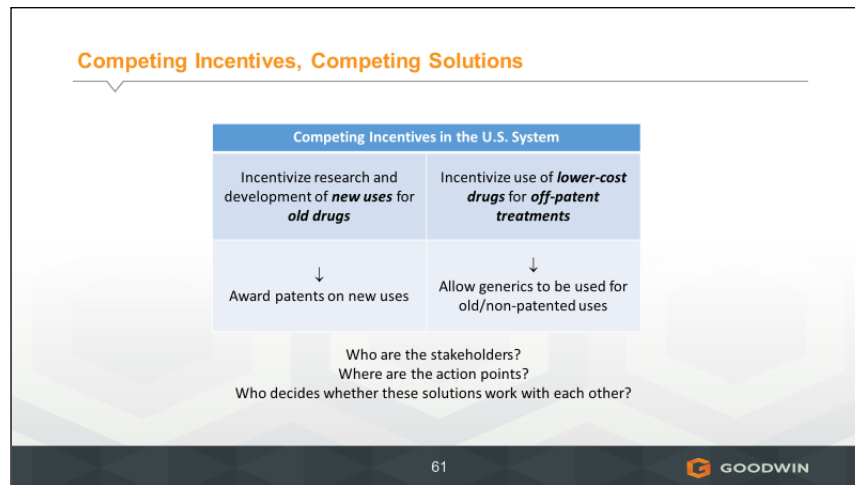
We are also seeing a lot of litigation about causation now and the question of whether, for example, doctors read generic labels. If they have not read them, did the generic cause the infringement, or was it just the system working the way that the system has been intended to work? That is an issue that is being litigated now and that we are watching very closely.

Another really interesting question here is: let's assume that the brand does prove inducement of a patented use where there is a nonpatented use; what is the remedy? Are we going to have lost profits paid, in which case you create a system where the amount of money the generic might owe is more than the money that they brought in, in which case we might just see the generic drug industry shut down and say, "Forget it; if there's a patented use at all, we are not going to participate"? Many would say that is not a good result.

If there is an injunction, that obviously then extends the scope of the patented use to knock out the entire market. That also seems unfair.

So the question may be whether a reasonable royalty is the right result if infringement is found, a royalty on the basis of damages that have actually been proven with the specificity that is required for damages.

These are open questions, all very interesting, and being actively litigated in a lot of cases across the country.



Finally, this slide summarizes the competing incentives in the U.S. system.

We obviously want to incentivize research and development of new uses for old drugs. We have had some great examples this morning of why that is important. For that reason, the patent system awards patents on new uses.

At the same time, we want to incentivize use of lower-cost drugs for off-patent treatments, and that is why we allow for carve-outs and we allow generic drugs to go on the market even when there are patented uses.

I think what we are talking about for these two days is who are the stakeholders, where are the action points, and who decides whether these solutions work with each other, and a two-day conference dedicated to this makes sense because it is pretty darned complicated.

MR. KRACOV: I am going to focus on two particular issues on the regulatory side of this: (1) what is the pathway for second medical uses (SMUs) in the United States; and (2) what are the incentives that apply to such products?

The 505(b)(2) Application

- Type of new drug application (NDA) – not an abbreviated new drug application (ANDA)
- Relies, in part, on published information or FDA's past finding of safety and efficacy for which the 505(b)(2) sponsor does not have a right of reference
 - Application containing "investigations . . . relied upon by the applicant and for which the applicant has not obtained a right of reference or use from the person by or for whom the investigations were conducted." FDCA Sec. 505(b)(2)
- Sponsor typically needs to submit new studies to support change
- Pathway can reduce development time and costs

Before the enactment of the [Hatch-Waxman Act](#), it was recognized that there was a category of products that were not generic and were not wholly branded or innovator products or destined to be reference-listed

products, but that had attributes of being both an old drug and a new drug in terms of changes to the drug, in terms of new indications, etc.

Prior to Hatch-Waxman, there was a mechanism called the “paper New Drug Application (NDA)” that essentially addressed this, in a very rough way, without dealing with a lot of the knotty issues that arose from IP and other perspectives. It was a somewhat makeshift version of what in Hatch-Waxman was embodied as the 505(b)(2) New Drug Application. That is really the primary type of application for SMUs. Obviously, for a SMU use you can file a full NDA, whatever it might be, but the 505(b)(2) NDA is really the primary pathway for getting an SMU to market in the United States.

However, it is bounded in terms of how it can be used. It is not a generic drug application. You are not simply demonstrating — I use the word “simply” broadly there — bioequivalence or therapeutic equivalence to another product in that sense.

What you are doing is taking an old product and relying, at least in part, on information that is out there on that product or information that is in FDA’s files or FDA’s findings with respect to that product for which you do not have a right of reference. So you do not have everything you need to get approval or you are relying upon information to which you do not have a right.

Typically, in the case of a 505(b)(2) NDA, the other aspect is you are submitting clinical studies, something that you cannot do through the generic drug pathway typically. There are some technical exceptions to that, but if you are submitting clinical data in an application, the Abbreviated New Drug Application (ANDA) pathway is not generally available to you.

The notion here is that we are taking existing data with respect to a product and we are going to piggyback on that data and fill the gap. Our application is going to submit just the information that is necessary for approval of that follow-on.

When is it Used?

- When the proposed drug product is different from the Reference Listed Drug
 - New dosage form (e.g., tablet capsule) →
 - New indication
 - Different strength
 - Different route of administration
 - Different active ingredient (e.g., enantiomer, racemate, salt, ester)
 - Substitution of active in combination product
 - Rx-to-OTC switch
 - Formulation changes outside 505(j)/ANDA limits
 - Naturally-derived v. recombinant active ingredient

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When is this used?
A broad variety of scenarios. A new dosage form; a new indication, strength, route of administration; a different active ingredient in the combination product; prescription to over-the-counter switch of a product; and

various other changes can be made to a product through the 505(b)(2) NDA pathway.

When is it Not Used?

- Cannot be used when
 - The proposed drug product could be submitted for approval by the 505(j) ANDA pathway
 - Only difference is the extent to which the active ingredient that is absorbed is less than the RLD
 - Only difference is that the rate that the active ingredient is absorbed is unintentionally less than the RLD

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The 505(b)(2) NDA pathway cannot be used to end-run the generic drug process. If it could be submitted through the 505(j) Abbreviated New Drug Application pathway, you cannot use the 505(b)(2) NDA pathway. If

the only difference is the extent to which the active ingredient is absorbed is less than that of the reference-listed drug, unintentionally or otherwise, then you cannot use this pathway. It is not intended to be something to get a generic drug to market by avoiding the established pathways for generic drugs.

505(b)(2) — Patent Considerations

- Hybrid patent requirements
- Must comply with patent certification and notice requirements (like ANDAs)
 - Must address all patents listed in the Orange Book for the RLD upon which the applicant relies
 - May be delayed from FDA final approval by the existence of blocking patents for the RLD
- Still subject to patent listing requirement (like NDAs)

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In addition to being a hybrid from a data perspective, the 505(b)(2) NDA is also a hybrid from a patent perspective, in that these are like generics in the sense that you have to comply with the patent certification-and-notice requirements

because you are still citing a reference-listed drug and you need to address the patents listed in the Orange Book, and, like a generic drug, you may be delayed from the market because of those patent certifications; and, like an NDA, the true hybrid situation, you are also subject to patent listing, so if there are patents that pertain to your 505(b)(2) NDA, you need to list them as if it was a full NDA. So it really is a true hybrid to both deal with the patent issues associated with SMUs as well as deal with the issue of not creating repetitive data to the detriment of patients and the time associated with getting to market.

This is a well-established pathway. There are obviously a lot of details around how it is administered by FDA, but actually in many cases a lot of very innovative drugs have gone down this pathway. Some of them have been combined, changed in some fairly fundamental ways, delivered in different ways, but yet relied upon the original database for the reference-listed drug.

Regulatory Incentive Provisions	
Drugs (NDAs)	Biologics (BLAs)
<ul style="list-style-type: none"> • 5-year exclusivity for new chemical entities (NCEs) • 3-year exclusivity <ul style="list-style-type: none"> ◦ New indications, clinical exclusivity, etc. • 7-year orphan drug exclusivity • 6-month pediatric exclusivity • 5-year QIPD exclusivity (antibacterials/antifungals) 	<ul style="list-style-type: none"> • 12-year reference biologic exclusivity • 7-year orphan drug exclusivity • 6-month pediatric exclusivity

There are also well-established incentives for products that go down these routes.

- If it is a new chemical entity (NCE), which typically would not apply here, although there are circumstances in which you have

what is essentially an SMU that could get five-year exclusivity as a NCE — and a good recent example was a deuterated form of a product that had previously been approved that was deemed a NCE, in the United States at least, that did receive NCE exclusivity, even though it was essentially the same molecule except for the deuteration.

- Three-year exclusivity, which is a type of exclusivity that applies when you submit clinical studies that are essential to the approval of that application. This is data exclusivity for new indications, etc. These are the most typical form of exclusivity for an SMU, and typically you end up for that new indication for which you have exclusivity having to deal with the issue of a carved-out label, which we have talked about.

- There is seven-year orphan drug exclusivity.

- Six-month pediatric exclusivity, which is an add-on exclusivity to the longer of whatever other exclusivities or patent term remain for a given product, and it is based upon complying with a written request for pediatric studies from the FDA.

- Finally, there is a very targeted form of exclusivity that is called qualified infectious disease product (QIPD) exclusivity. That is really focused on antibacterials and antifungals. Those products that are so designated get five years of additional add-on exclusivity beyond the other statutory exclusivities it may have.

It is really an interesting case study as to the difficulties in incentivizing the development of products. Recently, a report came out showing it has had mixed success. Even though it is a very substantial period of exclusivity that you can get for one of these qualified infectious disease products, it has not spurred the type of innovation that we would like to see, and many are talking about what else we need in terms of trying to get people to invest in the development of new antibacterials and antifungals.

For biologics it is a very different story. There is no 505(b)(2) NDA equivalent on the biologic side, or no exact equivalent. You have full Biologics License Applications (BLAs), and then you have the biosimilar process in the United States in which you can be determined to be either biosimilar or inter-

changeable with the reference-listed biologic. But you cannot add new indications via that particular pathway.

Moreover, the twelve-year exclusivity, which is quite generous for biologics and a very important development in that area, is very, very limited in terms of changes that are made to an existing product. You need to make some fundamental changes to a biologic that cause a change in the safety or effectiveness of the product in order to obtain another period of exclusivity. That is much more constrained on the biologic side than the more flexible mechanisms for drugs, and with respect to biologics the seven-year orphan exclusivity and pediatric exclusivity are also available as incentives.



There are also a number of expedited programs that can apply to SMUs as well, and they have become extremely important in the United States:

- Breakthrough designation and Regenerative Medicine Advance

Therapy (RMAT) designation, the latter of which is for gene and cell therapies. These are products for which there are unmet medical needs, there is no substitute for these products, no available therapies or little available therapy. The notion is we are going to give FDA's full time and attention and consulting assistance in the development and approval of that product and give it priority review.

- Fast-track and accelerated approval. Accelerated approval is the mechanism for using surrogate markers for obtaining approval and then confirming that use, the determination of effectiveness, post-approval.

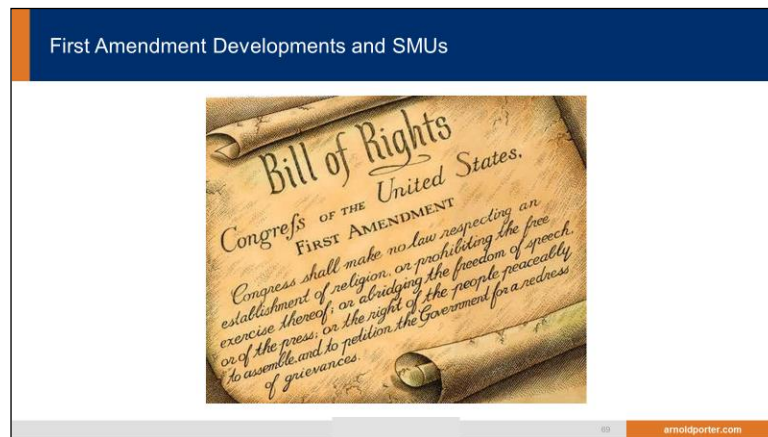
- An interesting development over the last decade has been priority review vouchers. These can be obtained for applications in certain particular areas. Essentially — and this is really the interesting part about priority review vouchers — unlike in other areas, they are transferrable. A voucher that would allow review of a product within six months may be transferred, may be sold, by a company once it is obtained for, for example, getting approval of a product for a rare pediatric disease.

That is a very interesting mechanism. A lot of people have talked about the notion of transferability as an important potential focus in the future for increasing incentives for products, because once something becomes transferable, it becomes a much more potent incentive. In fact, some of these priority review vouchers have sold for between \$100 million and \$200 million. So it is quite a potent incentive.

- I will mention another one that is interesting. In addition to the [Generating Antibiotic Incentives Now \(GAIN\) Act](#) of 2012, the qualified

infectious disease product designation, there is also, under the [21st Century Cures Act](#), which was passed in late 2016, a limited-population pathway that now exists in the United States just for antibiotics when a product can be approved and controlled for that use in a limited population of patients, as opposed to approving it for a broad array of treatment of infectious diseases. This essentially is the closest that we have come in the United States, other than accelerated approval, to a limited-population conditional approval type of framework.

That is the landscape in the United States of the opportunities and the weaknesses for SMUs.



The last issue — and this is really not an IP issue, it is not an exclusivity issue, but it is probably in many ways as important a development for SMUs as any other development that has occurred — is the First Amendment developments

in the United States, which have essentially undermined the FDA's approach to determining when something is a new drug.

[The Federal Food, Drug, and Cosmetic Act](#) (FD&C Act) is an intent-based statute that traditionally has looked to what people have said about their products, particularly with respect to off-label uses, as being evidence of a criminal violation because you are marketing a product for an off-label use.

The recent First Amendment case law has called into serious question the FDA's fifty years of interpreting the law in that way. It basically says that if you are conveying truthful and nonmisleading information about your product, even with respect to an off-label use and you make clear that it is not within the label, and in fact it is truthful and nonmisleading, FDA can attack whether what you are saying is in fact truthful and nonmisleading, but they cannot use the mere fact that you are conveying that information to patients, to physicians, or to payors as evidence that you have violated the FD&C Act if your intent was simply to provide that information and not specifically to market the product for a particular use.

That has opened up the ground in the United States for much broader communications by follow-on products about uses for which they are not approved. Will they get paid for those uses? — a totally different question. But the landscape has changed in terms of what you can say about your product as long as it is truthful and nonmisleading, and that is probably the most momentous change in FDA law, at least in drug law and device law, that has occurred in many decades.

Thank you very much.

MR. MORGAN: I will wrap up now.

Overview of UK P&R
<ul style="list-style-type: none"> • Drug Tariff works to maintain drug price competition • Category C includes pre-generic innovative products • Price set in accordance with the PPRS • Upon generic entry drugs usually undergo reclassification • Category A includes readily available generics • Pricing then becomes set by DoH (based on average wholesaler/generic company prices)
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I will summarize the UK position on pricing reimbursements in ninety seconds. In some ways it is easier to understand than in Germany, and in other ways perhaps a little more idiosyncratic. In the United Kingdom, the way that pricing reimbursements works is that

the government has a drug tariff set up — and again, I am talking generalities — for mainly small-molecule products that are sold by companies that contract with the government through the Pharmaceutical Price Regulation Scheme (PPRS). There are other systems that operate in the United Kingdom, but for the purposes of my ninety-second summary this will have to do.

The drug tariff works to set prices. Category C in that drug tariff contains all the pregeneric innovative products for which, through this PPRS scheme, companies work with the government and they set a price which is generally regarded as not fair by the industry.

Upon generic entry, those drugs will undergo reclassification in the drug tariff. Category A is the drug tariff category that relates to generics. The significance of that reclassification is that the pricing then becomes set by the Department of Health, and the Department does this based on an average of generic pricing. What happens at that point is that, obviously, the price will come down.

Overview of UK generic approvals
<ul style="list-style-type: none"> • Where SMU patents exist generic companies will "carve out" • Removal of protected indications from product literature • Gives rise to "skinny labels" • Risk this runs is these products are nevertheless used "off-label" • UK prescriptions do not carry intended use so the pharmacist dispenses blind

In terms of generic approvals, this mirrors the U.S. situation. No surprises here. Where second medical use patents exist, generic companies can carve those indications out of their label. Again, the policy reason for that is obvious:

it is to make a generic product available where a nonprotected use is now available for generic competition.

That gives rise to what we call "skinny labels." The risk that runs then, though, is that those products are used by a health service that is very keen to reduce its drug bill. When you add to that the fact that, whilst a formal automatic generic substitution does not apply, physicians in the United Kingdom are trained very well to prescribe by International Nonproprietary Names (INN) and to ensure generic dispensing wherever possible in their practice because that reduces the costs of the treatments that they are prescribing.

The UK prescriptions also do not carry intended uses. I am not sure if it is for formal data protection reasons, as it is in Germany, but it is probably just

laziness on the part of the doctors, and/or that if they wrote them anyway, doctors' prescriptions in the United Kingdom are famous for being completely illegible, so you would not know what it was even if they did write it down. The point being there that the pharmacist has to dispense blind and — again exactly the same situation as in Germany — that there is no way that the pharmacist knows whether that product is going to a patented or a nonpatented use.

Resulting situation
<ul style="list-style-type: none"> – So on generic entry: <ul style="list-style-type: none"> • Reclassification occurs in the Drug Tariff • Takes a number of months • Price is set by DoH • Reflects generic pricing • Therefore leads to a rapid decline – Regulators practice of approving "skinny labels" creates a dual product market in terms of labelling – Drug Tariff does not recognise the products as being different – Therefore protected indications are exposed to generic competition from first generic product entry into an unprotected indication
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Recapping on that, on generic entry we get reclassification of the product in the drug tariff. That does take a couple of months, but then you have a much lower price set by the Department of Health. That leads to a rapid decline in price.

The regulators' practice of approving skinny-label generics simply means that then creates a single market across what should be two different products. The drug tariff does not recognize these products as being different, and that certainly is one first point of entry where the possible solutions to this issue could start to be considered in terms of maintaining patented indications as separate from the generic classification of products in the drug tariff.

How have the markets/courts reacted?
<ul style="list-style-type: none"> • Some companies have succeeded in creating a dual market • Glivec has generic competition in its CML indication but GIST is protected by a SMU patent • Product is supplied direct into the hospital market • NHS in the UK splits its hospital tenders for Imatinib between CML (with generic competition) and GIST (no generic competition)

How have the courts reacted in the United Kingdom? There are two situations that I will focus on.

Some companies have succeeded in creating a dual market. Glivec has had generic competition on its chronic myeloid leukemia (CML) indication for

a couple of years, but another cancer indication, gastrointestinal stromal tumors (GIST), is protected by a second medical use patent.

Novartis had the good fortune that this product is directly supplied into a hospital market, and thus largely is sold by way of tenders. The way that the NHS has now set up the market in the United Kingdom is that it splits its tenders between CML that does permit generic competition and the GIST market where no generic competition obviously can exist without the generic marketing a skinny label and infringing the patent.

How have the markets/courts reacted?

- Lyrica is more complex - no ability to create a split tender market
- Courts have indicated certain steps have to be followed in order to satisfy patentee generics are attempting to avoid the protected SMU
- NHS has implemented prescribing guidance but this is not binding and not "hardwired" into P&R
- Comes down to individual prescribing physicians
- That is the point the generic prescription for the protected SMU occurs

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The Lyrica® case is far more complex. That stems from the fact that Pfizer could not create this sort of split-tender market simply because of the routes into the marketplace that the product takes. The courts have gotten to a place now

where, subject to the UK Supreme Court hearing on this patent next week, the Court of Appeal have indicated that, whilst a generic does infringe a second medical use patent, if it is foreseeable that the product is going to be used for a patented use, there are a number of steps they can take to negate that presumption of infringement, and it will obviously depend on the products as to what those steps actually are.¹

In this particular case, Actavis was demonstrating that it had, for example, written to every superintendent pharmacist in the NHS to explain that their product could not be used in patented indications. That obviously is quite an exercise, but if you get Pfizer off your back, then it is actually quite a sound move, frankly.

The NHS has implemented prescribing guidance in the Lyrica® case, but there is a fair bit of evidence — and again, depending on whether you are a generic company facing interim injunctions or you are Pfizer looking for them, you will argue that the guidance is either very effective or not. The evidence at the moment that I have seen is pretty equivocal as to whether the NHS prescribing guidance is working in this particular case.

In reality, where the problem lies is that we have this inability to split the products in the drug tariff. Therefore, physicians are seeing a generic substitute for the branded product coming up whenever they access their prescribing software. Given their good training in INN prescribing habits, the doctor will then just simply prescribe the INN and the pharmacist will not see that the patented indication is being dispensed.

The solution to this problem, certainly in the United Kingdom, seems to lie well and truly within that process of drug tariff to prescribing physician to pharmacist, and somewhere in the chain, maybe in a couple of places, there just

¹ 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 Feb. 12–15, 2018. See LifeSciencesIPRReview, Summary from the UK Supreme Court Hearing, available at <https://www.lifesciencesipreview.com/news/warner-lambert-v-actavis-a-summary-from-the-uk-supreme-court-hearing-2723> (Feb. 21, 2018).]

needs to be a way to differentiate the patented and nonpatented products.

MS. BLAIS: We are out of time, so maybe approach us if you have questions. Does that sound right?

MR. CORDERY: I was going to suggest is that this is kind of a part one, and we are now going to go on and look at the Lyrica® case in Denmark; and part two will be a discussion of all that you have laid out. So I suggest we should park questions for now and carry on. Obviously, if there are questions for any of these panelists, I would ask them during the session at the end, which is quite a long session just before lunch, if that works for you.

Let's have a final thank-you and move on.

[Session Adjourned: 11:32 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.
Thursday, February 8, 2018 – 12:15 p.m.*

**Session 1F:
A Critical Review of the Current Landscape — Discussion**

Moderator:
Dr. Ute Kilger
Boehmert & Boehmer, Berlin

Presenters:
Prof. Arti Rai
Professor of Law, Duke University, Durham

Prof. Rebecca Eisenberg
Professor of Law, University of Michigan, Ann Arbor

Prof. Ben Roin
MIT Sloan School of Management, Boston

Todd Volyn
Patent Attorney, Johnson & Johnson, New Brunswick

Panelist:
James Horgan
Head of European Patents, Merck Sharp & Dohme, Hertfordshire

* * *

DR. KILGER: Let's continue with our critical review of the current landscape, actually Part 2.

Please let me introduce my panelists: Arti Rai, Professor of Law from Duke University; Rebecca Eisenberg, Professor of Law at the University of Michigan; Ben Roin, Professor of Entrepreneurship at the MIT Sloan School of Management; Todd Volyn, a patent attorney at Johnson & Johnson, who is

involved in big mergers for Johnson & Johnson; and James Horgan, Head of European Patents from Merck Sharp & Dohme.

Now I will give the first word to Arti, who will start by looking at public incentives for finding new uses or how to encourage to find new uses, and she will talk about private and public approaches to new uses and private-public partnerships.

PROF. RAI: Thank you very much.

The purpose of this conference is to focus on generic repurposing — that is, new medical uses for drugs that are already generic. But I want to begin with the lens of so-called “rescue drugs,” drugs that have failed for their original indication, and talk about some of the ways that the National Center for Advancing Translational Sciences (NCATS) in particular has worked to try to rescue those drugs.

Now, the economic challenges are easier perhaps in that context, but I think there is still relevance for thinking about challenges in the generic repurposing context. One area of potential overlap is the use of crowdsourcing, to translate a little bit of what Dr. Banerjee was talking about, trying to get as many eyes on the data as possible. A related overlapping issue is the challenge of getting a patent. Even if patents can be carved out, one initial step is just making sure that you can get the patent, and that is an issue that comes up with rescue drugs as well.

Rescuing failures	Repurposing generics
<ul style="list-style-type: none"> • Life on composition of matter patent • Use patent that cannot carved out • No concern about discovering negative information on marketed drug • Some de-risking • Use patent may be vulnerable <p><i>Private rescue does happen (though public role can be useful)</i></p>	<ul style="list-style-type: none"> • No life on composition of matter patent • Skinny labeling • Hard to win indirect infringement theories • Significant de-risking <p><i>Generic repurposing rare, usually involves public funds – can private incentives work?</i></p>

Fortunately for us, a lot of the relevant territory has been cleared out by previous speakers. We know that for repurposing generics — and this is pretty much true across jurisdictions, although we have seen some very interesting differ-

ences between jurisdictions as well — there will be no life on the composition of matter patent, there will be skinny labeling, and it is going to be hard to win indirect infringement theories. On the other hand, there is significant, we have significant de-risking. As I will show with a little bit of data, generic repurposing is rare and usually involves some public funds, and the question is to what extent can we bring private incentives to bear.

In the rescuing failures context, the economic challenge is less grave. There is usually some life on the composition of matter patent left. The use patent cannot be carved out because there is no drug on the market. There is no concern about discovering negative information on the already-marketed drug; that is always a concern with repurposing a drug that still has a little bit of composition of matter patent life left on it.

There is some de-risking, but the use patent can still be vulnerable, as it can be in the repurposed generic space.

Again, the challenges, in my view, that are common between these two spaces are: (1) Where does the money come from — that is always a challenge; and (2) is the use patent going to be a problem to obtain and maintain, especially if we think that there are good reasons to have trial or real-world data available as broadly as possible so many eyes can see the data, the so-called open-source model.

Those are my aims. I do not think I will have answers, but I hope I will raise some interesting questions.

<p>Historical Data on Rescue</p> <ul style="list-style-type: none"> 12/170 new molecules approved between 1996-2004 relied solely on use patents (Rai and Rice (2014)) 	<p>“Contracting for Rescue”</p>  <p>National Center for Advancing Translational Sciences</p> <p>Discovering New Therapeutic Uses for Existing Diseases</p>
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Historical data on rescue is somewhat promising. This is some data I gathered for a paper I wrote in 2014.¹ Twelve of the 170 new molecules approved by the FDA between 1996

and 2004 did rely solely on use patents. These were rescue drugs, so there was no generic that could compete through skinny labeling. But that is pretty interesting, and I think that is part of what has motivated the National Center for Advancing Translational Sciences (NCATS) to try to do something about all of those failures that could be rescued. I have worked with them a fair amount on what I call the the “contracting for rescue” model that they have developed.


Goal:
To identify new therapeutic uses of proprietary compounds and biologics across a broad range of human diseases in areas of medical need.

- Match candidate Agents from pharmaceutical partners with innovative ideas for new indications from the biomedical research community.
 - NIH provides:** template Collaborative Research Agreements (CRAs) and Confidential Disclosure Agreements (CDAs), FOAs, review, funding, and oversight
 - Pharmaceutical partners provide:** compounds, biologics, in kind support, and pertinent data
 - Academic researchers provide:** deep understanding of disease biology, new concepts to test, and access to appropriate patient populations

[Adapted from Presentation by Christine Colvis PhD]



National Center
for Advancing
Translational Sciences



This slide is taken from Christine Colvis, who is heading up that project. Basically, NCATS takes failed assets from industry, matches those assets with academics who have interesting ideas regarding what to do with the assets,

and has tightly drawn contractual agreements so one does not lose the possibility of use patents. The NCATS approach has worked reasonably well. The asset of which I am aware that is furthest along is an Alzheimer’s drug which is being worked on at Yale, and there is a use patent on that.

¹ Arti K. Rai & Grant Rice, *Use Patents Can Be Useful: The Case of Rescued Drugs*, SCI. TRANSL. MED. 6, 248fs30 (2014), available at https://papers.ssrn.com/sol3/papers.cfm?abstract_id=2477420.

Repurposing generics

- Historically, public/non-profit funds
- Stevens et al. (2011): in period from 1990-2007, only 10/1541 new drug approvals for new uses
 - 9 of 10 involved public funding

Now let's go to our main event, which is repurposing generics. The data that exists — this is not my data; it's drawn from an article by Ashley Stevens² — indicates that in the United States, at

least in the period between 1990 and 2007, only ten of the 1541 New Drug Approvals (NDAs) were solely for new uses. That's a pretty low number. The number is probably not a surprise to you, given that we have had this whole morning regarding all the challenges to repurposing generics.

Nine out of ten involved public funding. An economist might say, "This is really a situation where we just need more public funding because it is a public good problem." That is the term they would use. In this context I think we should think about that a little bit. But then the immediate rebuttal is, of course, public funding is a very scarce good, and so we need private incentives as well.

Potential private incentives

- Mechanisms for preventing generic substitution
 - Regulatory
 - Formulation patents
- *Ex ante* commitments by buyers' side?
- How much off-label is okay?

We have discussed some of the potential private incentives at some length already. But one thing to think about — and I hope Dr. Bloom from Cures Within Reach will talk about this a little bit — is to

what extent simple off-label use is okay. I know Cures Within Reach has done some funding of clinical trials, not for purposes of getting approval, but for purposes of getting sufficient data out there for doctors to feel comfortable prescribing off-label.

We could, of course, also put in various regulatory barriers to automatic substitution — a lot of that has been discussed this morning.

Another incentive we could think about that I do not think has been mentioned as much is formulation patents. At least in the United States, if you get a formulation patent on your repurposed drug, a generic cannot get AB substitution on that particular formulation. In fact, that is the strategy behind what some have pejoratively called "product hopping."

² Ashley J. Stevens et al., *The Role of Public-Sector Research in the Discovery of Drugs and Vaccines*, 364 NEW ENGL. J. MED. 535 at 364 (2011), available at <http://www.nejm.org/doi/pdf/10.1056/NEJMsa1008268>.



Last but not least, I did promise to talk about some of the challenges of allowing data to be crowdsourced while at the same time maintaining the potential for use patents. I think there are some real challenges here. Professor Roin and I have had some discussions about this

in the context of some work I did for the National Academies on clinical trial data release.

First of all, when clinical trial data is released, we need to redact all confidential commercial information, which might include exploratory endpoints and the like, because we cannot have those out there or else we will never get a use patent. People fear that the [European Medicine Agency's \(EMA\) approach](#)³ to this will not sufficiently careful and, therefore, there will be trial data put out there that does reveal new uses, thus creating a novelty problem for a use patent. I think that is a possibility.

But there is even a more subtle possibility — and I credit Professor Roin for this possibility — that I think is actually at the end of the day not necessarily going to be a real problem, but it could be. If the data is out there and patients have been benefiting inherently from these new uses because they have had the condition and you can do a subgroup analysis and see that they inherently benefited, is there an inherency problem for a new use patent in that context? Some food for thought.

References

- Arti K. Rai and Grant Rice, Use patents can be useful: The case of rescued drugs. *Sci. Transl. Med.* 6, 248fs30 (2014).
- Ashley Stevens et al., The Role of Public Sector Research in the Discovery of Drugs and Vaccines. *N Engl J Med* 2011; 364:535-541.

I will give you these references that you can take a look at and turn it over to my colleague, who will talk about more data.

³ As of October 2016, the European Medicines Agency (EMA) publishes clinical data submitted by pharmaceutical companies to support their regulatory applications for human medicines under the centralised procedure. This is based on EMA's flagship policy on the publication of clinical data, available at http://www.ema.europa.eu/ema/?curl=pages/special_topics/general/general_content_000555.jsp.

DR. KILGER: Rebecca will now talk about the 21st Century Cures Act, which is a program to evaluate the use of real-world evidence.

PROF. EISENBERG: Thank you.

If you are trying to make something more profitable, you could either try to expand the revenues that it generates, which is where patents and regulatory exclusivity come in, or you could try to decrease its costs. A big source of costs for drug development is clinical trials.

21st Century Cures Act § 3022

(codified at 21 U.S.C. § 355g)

- (a) The Secretary shall establish a program to evaluate the potential use of real world evidence —
- (1) *to help to support the approval of a new indication for a drug approved under section 355(c); and*
 - (2) *to help to support or satisfy postapproval study requirements.*
- (b) In this section, the term “real world evidence” means data regarding the usage, or the potential benefits or risks, of a drug derived *from sources other than traditional clinical trials.*
- ...
- (f) **Rule of construction**
- (1) Subject to paragraph (2), nothing in this section prohibits the Secretary from using real world evidence for purposes not specified in this section, provided the Secretary determines that sufficient basis exists for any such nonspecified use.
 - (2) *This section shall not be construed to alter—*
 - (A) *the standards of evidence under—*
 - (i) *subsection (c) or (d) of section 355, including the substantial evidence standard in such subsection (d);*
 - ... or
 - (B) *the Secretary’s authority to require postapproval studies or clinical trials, or the standards of evidence under which studies or trials are evaluated.*

Shortly after the 2016 election in the United States, the lame duck Congress overwhelmingly passed the [21st Century Cures Act](#) and President Barack Obama signed it into law.⁴ Part of what that legislation is trying to do — although its likely success remains uncertain — is to reduce the costs of collecting data on the effects of drugs.

In one of its more controversial provisions, the 21st Century Cures Act directs the FDA to evaluate and issue guidance on the use of real-world evidence to support regulatory decisions in two specific areas: (1) approval of new indications for previously approved drugs; and (2) fulfilment of post-approval study requirements.⁵ The statute defines “real-world evidence” broadly as “data regarding the usage or the potential benefits or risks of a drug derived from sources other than traditional clinical trials.” What makes this provision so controversial is that FDA has long maintained that randomized controlled trials are the gold standard for establishing the effects of drugs in patients.

Back in the 1950s and 1960s, long before everyone was talking about evidence-based medicine, FDA worked with toxicologists and pharmacologists and statisticians to try to bring serious empirical rigor to standards for drug approval. Congress endorsed this approach in 1962 amendments that added

⁴ 21st Century Cures Act of 2016, Pub. L. No. 114-235, __ Stat. __, codified at 21 U.S. Code § 355g [*hereinafter* Cures Act], available at <https://www.gpo.gov/fdsys/pkg/PLAW-114publ255/pdf/PLAW-114publ255.pdf>

⁵ *Id.* § 3022, codified at 21 U.S.C. § 355(g).

21 U.S.C. § 355(d)

If the Secretary finds ... that

(1) the investigations, reports of which are required to be submitted to the Secretary pursuant to subsection (b), do not include *adequate tests by all methods reasonably applicable* to show whether or not such drug is safe for use under the conditions prescribed, recommended, or suggested in the proposed labeling thereof;

... or

(5) evaluated on the basis of the information submitted to him as part of the application and any other information before him with respect to such drug, there is a *lack of substantial evidence that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the proposed labeling* thereof; ...

he shall issue an order refusing to approve the application. ...

As used in this subsection and subsection (e), the term “*substantial evidence*” means *evidence consisting of adequate and well-controlled investigations, including clinical investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved*, on the basis of which it could fairly and responsibly be concluded by such experts that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling or proposed labeling thereof.

statutory language, which is still on the books and which the Cures Act does nothing to change. That language requires that a New Drug Application must be supported by “adequate tests by all methods reasonably applicable to show whether or not such drug is safe for use under the conditions prescribed, recommended, or suggested in the proposed labeling” and “substantial evidence that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the proposed labeling.”⁶

“Substantial evidence” is defined from the perspective of experts in drug development rather than from the perspective of clinical care providers such as treating physicians. The statute says: “Substantial evidence means evidence consisting of adequate and well-controlled investigations, including clinical investigations by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved.”⁷

Back in the day, FDA relied on this statutory language to remove from the market quite a few products that doctors testified they considered safe and effective that had come to market in an earlier era without having cleared the substantial evidence threshold.⁸ FDA wanted to see randomized controlled trials, not clinical experience.

The Cures Act does not change this “substantial evidence” language in the statute. Quite the contrary, the Cures Act explicitly says under its rules of construction that the new provisions “shall not be construed to alter” that statutory standard.⁹

But the Cures Act challenges FDA to consider whether, in light of all of these new data sources, it has now become possible to meet that standard in some circumstances without requiring clinical trials. More specifically, the statute asks

⁶ 21 U.S. Code § 355(d).

⁷ *Id.*

⁸ See, e.g., *United States v. 50 Boxes More or Less*, 909 F.2d 24 (1st Cir. 1990), available at <https://law.justia.com/cases/federal/appellate-courts/F2/909/24/431426/>.

⁹ 21 U.S. Code § 355g(f)(2).

FDA to consider whether data regarding the usage or the potential benefits or risks of a drug derived from sources other than traditional clinical trials might, in the case of an already-approved drug, help support approval of a new indication or help satisfy post-approval requirements.¹⁰

In other words, Congress is keeping the old standard in place, and ultimately leaving it up to FDA to decide whether or when or how far or under what circumstances these new data sources might be helpful.

The statute gives FDA a list of marching orders with deadlines, but these directives are all about establishing a program, drafting a framework for implementation of the program, consulting with stakeholders and experts, perhaps entering into contracts or grants or conducting workshops, and then using that information to prepare guidance as to when FDA might rely on real-world evidence, and what methodologies it would require for collection and analysis of such evidence.¹¹

Congress is not telling FDA to change its standard, and is leaving it up to FDA to figure out what it takes to satisfy this standard. They are still to apply the same statutory language that in the past has led FDA to embrace randomized controlled trials, but with a mandate to consider whether these new data sources might now be up to the job.

This is a nudge, in effect, to make FDA think about it, go through some process, but not a substantive directive that displaces FDA's judgment in the final analysis. FDA has until 2021 to issue draft guidance in this area.¹² Meanwhile, FDA is being quite transparent about their current thinking on the use of real-world evidence for regulatory purposes.

There are two recent documents that are particularly illuminating in this respect. First is a December 2016 Sounding Board in the *New England Journal of Medicine (NEJM)* from a very large group of FDA authors, entitled "Real-World Evidence: What Is It and What Can It Tell Us?"¹³ This came out just as the Cures Act was signed into law.

Second is a more recent August 2017 FDA Guidance Document on "Use of Real-World Evidence to Support Regulatory Decision Making for Medical Devices."¹⁴ This guidance was already in the works in draft form before passage of the Cures Act.

¹⁰ 21 U.S. Code § 355g(a).

¹¹ 21 U.S. Code § 355g(b), (c), (d), (e).

¹² 21 U.S. Code § 355g(e)(3).

¹³ Rachel E. Sherman, Steven A. Anderson, Gerald J. Dal Pan, Gerry W. Gray, Ph.D., Thomas Gross, Nina L. Hunter, Lisa LaVange, Danica Marinac-Dabic, Peter W. Marks, Melissa A. Robb, Jeffrey Shuren, Robert Temple, Janet Woodcock, Lilly Q. Yue, & Robert M. Califf, *Real-World Evidence — What Is It and What Can It Tell Us?* NEJM Sounding Board, N. ENGL. J. MED. 375(23):2293-297 (Dec. 8, 2016) [hereinafter NEJM Sounding Board].

¹⁴ FDA, *Use of Real-World Evidence to Support Regulatory Decision-Making for Medical Devices, Guidance for Industry and Food and Drug Administration Staff Document* issued on Aug. 31, 2017, available at <https://www.fda.gov/downloads/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm513027.pdf> [hereinafter 2017 Device Guidance].

Nudges towards postmarket evidence for medical device regulation

Preference for postapproval standards where adequate to meet statutory standards for medical device approval, e.g., 21 U.S.C. § 360c(a)(3)(C):

“In making a determination of a reasonable assurance of the effectiveness of a device for which an application ... has been submitted, the Secretary shall consider whether the extent of data that otherwise would be required for approval of the application with respect to effectiveness can be reduced through reliance on postmarket controls.”

“Least burdensome” requirement, 21 U.S.C. § 360c(a)(3)(D)(ii), (iv):

“Any clinical data, including one or more well-controlled investigations, specified in writing by the Secretary, for demonstrating a reasonable assurance of device effectiveness shall be specified as result of a determination by the Secretary that such data are necessary to establish device effectiveness. The Secretary shall consider, in consultation with the applicant, the least burdensome appropriate means of evaluating device effectiveness that would have a reasonable likelihood of resulting in approval.”

“Nothing in this subparagraph shall alter the criteria for evaluating an application for premarket approval of a device.

For devices, Congress has been nudging FDA to rely more on post-market monitoring and less on premarket testing for a long time, so FDA has had to confront some of the epistemological questions that this shift poses in the device context before it has had to consider similar questions for drugs.¹⁵

But if you compare these two documents, you will see a lot of similarities in how FDA is thinking about the use of real-world evidence. Considered together, these two documents suggest that while FDA is eager to get the benefits of the additional information that come from observational data about real-world use, they are much more cautious about using them other than as an adjunct to the kind of information that they are used to relying on.

FDA plainly recognizes that data gathered in the course of clinical healthcare can be a useful supplement for their consideration. That is because they recognize the limitations of randomized controlled trials, which are necessarily limited in size and duration, and tend to have strict enrollment criteria that make it harder to generalize their findings to a broader population. Post-approval clinical use can reveal what happens when the product is used for a longer period of time in a more diverse patient population that may, for example, have comorbidities or be taking other drugs

¹⁵ FDA, *Use of Real-World Evidence to Support Regulatory Decision-Making for Medical Devices Guidance for Industry and Food and Drug Administration Staff Document*, issued Aug. 31, 2017, draft issued July 27, 2016, available at <https://www.fda.gov/downloads/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm513027.pdf>.

Usefulness of real-world evidence

- Key to understanding the usefulness of real-world evidence is an appreciation of its potential for complementing the knowledge gained from traditional clinical trials, whose well-known limitations make it difficult to generalize findings to larger, more inclusive populations of patients, providers, and health care delivery systems or settings that reflect actual use in practice.
- Real-world evidence can inform therapeutic development, outcomes research, patient care, research on health care systems, quality improvement, safety surveillance, and well-controlled effectiveness studies. Real-world evidence can also provide information on how factors such as clinical setting and provider and health-system characteristics influence treatment effects and outcomes. Importantly, the use of such evidence has the potential to allow researchers to answer these questions efficiently, saving time and money while yielding answers relevant to broader populations of patients than would be possible in a specialized research environment.

FDA has concerns about the quality of the data gathered in ordinary clinical settings rather than in research settings, but FDA sees value in the use of these data nonetheless.

Nudges towards postmarket evidence for drugs

Food & Drug Administration Amendments Act of 2007

Directed FDA to assemble a network of sources of health-related electronic data for postapproval monitoring now up and running (Sentinel System)

Expanded FDA's postapproval regulatory authorities

Without changing approval standards, directed FDA to avoid requiring postapproval RCTs when other data sources might suffice, 21 U.S.C. § 355(o)(3)(D):

(i) Postapproval studies

The Secretary may not require the responsible person to conduct a study under this paragraph, unless the Secretary makes a determination that the reports under subsection (k)(1) and the active postmarket risk identification and analysis system as available under subsection (k)(3) will not be sufficient to meet the purposes set forth in subparagraph (B).

(ii) Postapproval clinical trials

The Secretary may not require the responsible person to conduct a clinical trial under this paragraph, unless the Secretary makes a determination that a postapproval study or studies will not be sufficient to meet the purposes set forth in subparagraph (B).

Other legislation and FDA initiatives have encouraged earlier approval of many new drugs, making post-approval studies and monitoring more important to ensure safety and efficacy.

"Accelerated approval," "Breakthrough therapy" designation, "Fast track designation," "Priority review designation," often allow drugs to get to market earlier, but with further postapproval requirements.

Congress previously gave FDA another nudge to rely more heavily on data from clinical care for post-approval safety monitoring in the Food and Drug Administration Amendments Act of 2007.¹⁶ FDA responded by creating the [Sentinel Initiative](#), a network of databases maintained by health insurers that consists primarily of administrative claims data.]

¹⁶ Pub. L. No. 110-85, 121 Stat. 823 (codified as amended in scattered sections of 21 U.S. Code) (FDAAA).

But FDA continues to worry about the quality of these data, which were generated for billing purposes without the quality controls that are required in a research setting.

Data quality

- “EHR and claims data are not collected or organized with the goal of supporting research, nor have they typically been optimized for such purposes, and the accuracy and reliability of data gathered by many personal devices and health-related apps are unknown. Furthermore, the use of any of these sources, including social media, raises important questions about the quality of the data they provide and about privacy.” [NEJM Sounding Board]

FDA has also been approving more new products on an accelerated basis, with requirements for further post-approval studies.¹⁷ In other words, Congress is asking FDA to consider whether real-world evidence might be adequate to satisfy

post-approval study requirements as these requirements are becoming an increasingly important part of FDA oversight of safety and effectiveness. It is easy to see why FDA would be concerned about the quality of these data.

Bias

- “An existing RWD source, however, may have some inherent bias that could limit its value for drawing causal inferences between medical device exposures and outcomes. Therefore, to mitigate potential bias, careful study design is needed, and a study protocol and analysis plan should be created prior to accessing, retrieving, and analyzing RWD, regardless of whether the RWD are already collected (retrospective) or if they are to be collected in the future (prospective design). Protocols and analysis plans for RWD should address the same elements that a traditional clinical trial protocol and statistical analysis plan would cover. FDA recommends use of the pre-submission process when considering the development of a study using RWD in a regulatory submission.” [FDA Guidance]

FDA also worries about sources of bias in the data, which is a long-standing concern they have had about observational data that do not include randomization and controls and may therefore be of limited value to support causal

inferences. In order to address these concerns, FDA seems, at this point at least, to want to incorporate into the collection of real-world evidence many of the safeguards that they have long required to meet the substantial evidence requirement in the context of premarket randomized controlled trials. These components include prospectively planned interventions, randomization, and use of controls.¹⁸

In other words, real-world evidence as FDA is thinking about it will not be cheap. FDA is likely to be skeptical about accepting retrospective observational studies based on claims data that are of poor quality and affected by bias, so it

¹⁷ 21 U.S. Code § 356 (a)-(c), FDA Center for Drug Evaluation & Research, Center for Biologics Evaluation and Research (2014) Guidance for Industry: Expedited Programs for Serious Conditions — Drugs and Biologics, available at <https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm358301.pdf>.

¹⁸ NEJM Sounding Board, *supra* note 13, at 2294–95

may be necessary to invest more in order to generate the kind of data that will satisfy FDA.

On the other hand, to the extent that data collection occurs in the course of clinical care, it may be possible for product developers to shift more costs onto healthcare payors rather than to absorb the full cost themselves, as they more typically have done in the premarket stage.

Many of the examples that FDA provides in its guidance on the use of real-world evidence to support regulatory decision making for medical devices have involved the use of data from registries that were designed for the purpose of collecting data for evaluating safety and effectiveness.¹⁹ Who will pay the costs of these registries? It is not clear.

“Plus ça change, plus ça reste la même chose?”

- “We believe that when the term ‘real-world evidence’ is used, the primary attribute that distinguishes it from other kinds of evidence is related to the context in which the evidence is gathered – in other words, in clinical care and home or community settings as opposed to research-intensive or academic environments. Most important, the distinction should not be based on the presence or absence of a planned intervention or the use of randomization. Real-world research and the concepts of a planned intervention and randomization are entirely compatible.” [NEJM Sounding Board]

The NEJM Sounding Board also says that there is no reason why you could not incorporate randomization into data collection in the context of clinical care. They like the idea of large, pragmatic clinical trials conducted not in a university setting necessarily, but out in a

real-world clinical care setting. Their favorite example is the early clinical trials of the Salk vaccine that incorporated randomization and controls but were administered out there in the real world.²⁰

FDA is plainly interested in considering real-world evidence alongside data from traditional clinical trials, but as they elaborate their framework for the use of real-world evidence in regulatory decision making under the same standards that have been in place since the early 1960s, these two sources of evidence might start to look more alike than different.

The result may well be more data, and that is a good thing, it may lead to better regulatory decision making, but it is less clear how far use of real-world evidence will bring down the costs of testing new uses.

DR. KILGER: Thank you so much.

Before going to the next presentation, I would like to ask some questions to the panelists, because I think we have here a new angle, looking at the problems or challenges related to second medical indications.

You were talking about public partnerships; you were talking about lowering the costs by real evidence data. How could you envision the business model then that would bring the second medical indication to the patients? Do you think the pharma industry shall find only the new drugs, the new entities, and then it is the task of the public to develop the second indications through public partnerships or whatever? What would be the model to bring this really into reality?

¹⁹ 2017 Device Guidance, *supra* note 14, at 17–21.

²⁰ NEJM Sounding Board, *supra* note 13, at 2295.

PROF. RAI: I think that the conceptual problem is one where if you do not have a thing to which you can attach the patent, all you have is the patent on the information and the thing is already out there. That is the conceptual problem: what do you do and how do you propertize that?

I think there are ways to propertize that, and that presumably is through some sort of fairly heavy-duty regulatory mandate, which is a totally plausible way. Denmark has led the way in thinking about how to propertize pure information essentially.

But there are costs associated with propertizing pure information as well. Whether the public is willing to bear those costs is always a question. It is not conceptually a difficult question to propertize pure information, but it can lead to public rejection of that approach.

PROF. EISENBERG: I think new uses tend to arise in the course of clinical care. That is, off-label use is quite common. The question is: how do we get good information about the effects of off-label use, and who do we expect to pay for it?

In my dreams insurance companies are interested in this question. Insurance companies might figure: "We already often pick up the tab for these off-label uses. Wouldn't it be good to know whether they are working or not or whether the risk-benefit analysis makes sense?"

Insurers are sitting on a lot of this observational data. It does not necessarily have to be the product-developing firm that decides to scrutinize available data to figure out whether these innovations are useful or not.

DR. KILGER: Before we proceed, I would be interested to have the view of industry, if possible. Do you see a role for the pharmaceutical industry maybe using real-world evidence, or are there some partnerships possible to accommodate these needs that you have, to lower costs for bringing the drug on the market? Is there some room for public partnerships? What do you think?

MR. VOLYN: I would say that real-world evidence, not knowing very much at all about it, is a freight train and it is coming. You see the Googles of the world and the IBMs trying to get into healthcare. They profess to have a strong point of being able to analyze data better than anyone else can do it.

It reminds me of a scenario some years back when I was more involved in the diagnostics area. We were looking at genetic-based diagnostics at that time, and the thought was "Now that we know everything there is to know about the human genome, we should be able to associate disease states and other things with genetic information."

We had very large computers with very smart people making those associations. The one thing that was missing from all of that was that we really did not understand the disease state any better. We were just making mathematical associations. While helpful, those associations still require developing a deeper understanding of the diseases involved to be truly beneficial. So I am bit afraid, to be quite honest, that we are going to fumble around for a while before we figure out exactly how to use real-world evidence, and it is going to take quite a bit of fumbling.

As to the involvement of public enterprise together with industry, I think most pharma companies are already doing that in a multitude of ways — just, for example, funding various types of drug developments. So you see organizations like the Biomedical Advanced Research and Development Authority (BARDA) willing to step forward and provide funding for the development of certain types of drugs, or approval of drugs, or some aspect of getting drugs that are in the public interest out into the public.

The concern from a business point of view, as you could imagine, is if you have government funding, the government is never going to do something like that without having some strings attached to it. The extent of those strings and whether or not that impacts your ability to make a viable business model out of that is in some cases difficult to determine, and in other cases you just know upfront that it is going to be difficult to deal with. They are not all like that, but there are a number of them like that.

I would say it works best in areas where there is a very strong public interest in getting some drug to the market — I think HIV was probably a good example of that — and maybe not so well in other areas where pharmaceutical companies are looking at unmet medical needs but they do not necessarily match up with the objectives of a government entity.

DR. KILGER: Thank you.

Ben, it is your turn.

PROF. ROIN: Thank you for having me.

PROF. JACOB: Well, thank you for coming. Let me just break in. He's a hero. He came from Boston this morning, he is going back to Boston this afternoon, and he is coming back here tomorrow.

PROF. ROIN: It is not nearly as bad of a commute as you might think. It is about two hours each way. Other people do it.

Why are we here? I am going to start this off with a summary of the problem we are facing, but then I am going to lead back to something that was discussed in the last two panels quite extensively, so we will connect back to that.

We are here because we have this problem: when companies develop a new drug, they usually develop it for a fairly specific use that gets stuck on its label. The vast majority of drugs have at least other potential uses, and, depending on how you think about a new use, that becomes a lot of them, almost all of them. Some new uses are maybe for an entirely different disease that you would never expect; others are for related conditions or different age groups or something like that.

But also, a personalized application of a drug is a new indication, a new use. It is like, "Well, don't give them to these people because they are likely to have this problem" or "Do give it to these people." Those are all new uses, and so it is actually everywhere in the medical system.

After a company develops the drug for its first use, they almost always have patent protection that is running for somewhere between eight and fourteen-fifteen years once their drug is on the market. They are going to have an incentive maybe to develop some of those new uses, or at least some of the ones they

are aware of, while their patent is running, because if they can expand the sales base and they can make the drug more valuable, they can make more money.

But, as I will talk about in a moment, that certainly does not give them an incentive to develop all new uses, including ones they do not know about. But as the patent term runs to a close — so as they start getting toward five, three years to the end of the patent term — there is very little money to be made by expanding their market, and so you start to see those investments drop off.

The reason why we think that is a problem is that we do not think that the universe of potential new uses, or potentially quite valuable new uses, ends at that point. We think they are often discovered much later than that or that companies are not developing all of the possible really valuable ones for a variety of reasons. Just to quickly make this point, there are two inevitable forces that are driving this discovery of new uses.

One force, which was just mentioned, is clinical innovation. When smart people are on the job and they are confronted with problems that they do not have an answer to, they often try to think of a solution. They cannot help it; they just do that. When doctors are presented with a patient who is complaining about or has some serious symptoms that they do not have a treatment for, they are going to think, *Well, is there something I can do?* They innovate, and they are going to come up with stuff sometimes, ideas for how to use something, and that includes observing weird side effects that are going on, thinking, *Well, how might this be useful?* — and patients actually do it, too — that is inevitable, and it is just going to happen as physicians gain experience with the medicine and as new patients are exposed to it.

The other force is just an inevitable byproduct of advances in medical knowledge. As we understand more about the underlying biology of diseases, as we understand more about the mechanisms of action of drugs, we are going to see connections that we did not previously see. In particular, because none of that stuff is intuitive, there is no way that we are going to understand all those things at the time a drug is discovered. Medical knowledge is going to keep progressing, our understanding of those things will keep improving, there is no end in sight, at least for when we will have perfect knowledge about that, so we are going to see new stuff. It is just a phenomenon of having something being in use and knowledge progressing, science progressing.

There is a third point to make, which is as scientific tools increase — so we have *in-silico* screening and stuff like that, all that, and just more knowledge to build into those *in-silico* models — all that is going to make the discovery of new uses a pretty common phenomenon perhaps five, ten, fifteen, twenty, fifty, a hundred years after the discovery of those drugs. The problem is that when they get discovered later, there is no real incentive built into the system for anyone to invest in their development. This panel is not about solving that. We will talk more about that tomorrow morning.

But I want to make a conceptual point that I find really helpful, and I think we discussed this particularly in relation to Denmark in the second and the previous panel — that is, it might be helpful to think about this not as a patent problem but as a pricing problem.

Here is what I mean. When a new drug gets on the market, how do we set the price? A drug company negotiates with in some places the government, but someone acting as the insurer. In the United States it is usually pharmacy benefit managers (PBMs) negotiating on the behalf of insurers; in other countries it is the government regulator. But there is some sort of negotiation.

Different insurers and different countries will end up paying different prices, but they do not negotiate different prices — although there is some experimentation with this — for the different uses of that drug. Some drugs have a number of different uses, sometimes a lot, other times there are just a couple. But when you think about it, the optimal price for those different uses is very likely to be different. They are serving usually a different group of patients or potentially a different severity of diseases. There will be different alternatives with different prices available for those different conditions. And you know what? Having a different use requires a different investment in clinical trials where those are distinct goods, so we will have a different optimal price.

But we do not get different prices negotiated, we get a single price negotiated, and that is going to do something. Let me throw this out just to expand our conception of what the problem of new use is about. Companies are not going to have the best incentives to develop new uses if they cannot charge the optimal price for them. If you have a new use for a drug, but the price that insurance companies will be willing to pay for it is much lower or much higher than the price that you are charging for whatever the current use it, that is a problem. Companies think about that ahead of time, and they just do not make those investments frequently.

The other place this comes up, and this happens a lot, is if it requires a very different dose. If it requires a very different dose, you need to worry about a compounding pharmacy splitting the drug when it is purchased for one thing to create multiple doses of the other. That makes it a very difficult economic proposition. You actually see instances where companies will pull one use off the market and just stop making a particular formulation because they do not want to deal with the arbitrage.

Those problems will happen during the patent term. It is not just limited to drugs going off-patent.

But this pricing problem becomes much, much worse once generics enter the market. Once generics enter the market, you are still limited to a single price, but the whole generic system is designed to drive that price down to something you could just sort of describe as zero. It is not actually zero, but from an economic profits to drive innovation standpoint it is effectively zero. That is the purpose of it; the whole goal is to push prices down to a competitive level, which will not sustain significant investments in R&D.

So we do that, the single price is zero, and that means that it does not matter what the dose is or what the price is; it is just not going to be enough to support investments in R&D, and so companies bow out. We know they do that.

Once you see that it is, in a sense, a pricing problem, it allows us to think, *Well, what is driving that?* There is actually some very simple, very basic economic theory that describes this. We are talking about a lack of price

discrimination; we are not charging different prices for the different uses of a drug. So when the drug is on-patent we are not charging between use for Disease A and Disease B; and when it is off-patent we are not used to charging for old use A versus new patented use B or new FDA exclusivity-protected B.

So why wouldn't they do that? It has to be one of two things or a combination of both. One of the problems is that the sellers cannot identify the different types of users, and if they cannot identify the different types of users, then they cannot charge them different prices. The other is that they cannot prevent arbitrage. Arbitrage is when you sell it to one type of user and then they turn around and sell it to another user who would otherwise be charged a higher price. Both of those will undermine a system of price discrimination.

Which of those is going on here? This is what the second-to-last panel and also sometimes the last panel were getting at.

Arbitrage is probably an issue here, but not a massive one. The reason why is that you cannot just go out and buy prescription drugs whenever you want them; you need a doctor's prescription. So you actually have all sorts of very curtailed access to prescription drugs that is based on you needing it. It is not perfect, but it is a pretty big barrier to someone just running around and buying huge numbers of drugs at a low price and then selling them to someone else for a higher price.

The problem is that drug companies do not know when a doctor has prescribed a drug for Condition A or Condition B, and if they do not know, they cannot charge different prices. That is true when the drug is on-patent and it is true when the drug is off-patent.

Once you see that, you are like, *Well, okay*. Actually implementing this within the patent system or within the FDA exclusivity system does not happen rotely. It is not automatic, but more or less it does not require massive changes.

If the relevant parties knew the prescribed indication — and here the relevant parties would be the drug company, the insurer, PBM, whoever it is that is watching; and the pharmacist, but those would be the three that are most important — it is not hard to imagine a system working in which you have different prices set for that, and that would be true both for drugs that are on-patent and drugs that are off-patent.

The other thing worth noting — and Robin was getting at this in one of his comments — is that once you start seeing the problem like this, you ask: “Well, gosh, there are probably a whole bunch of reasons why we would want to be paying attention to what the drug is prescribed for at the time of dispensing, at the time of billing. Are we providing the right one to the right people? Will it allow us to monitor more effectively what is going on with the drug? Will it allow insurance companies to better understand what the various effects are or other research?”

The other thing that is nice about this is you immediately realize that we kind of already have a solution, at least at a basic level, to the problem that is confronting us, and that is that insurers have already developed systems to try to observe what the prescribed use is because they have all these sort of restrictions

on whether they cover a particular drug that is based on what it is used for. In the United States it is called prior authorization.

So we already have a system in place that gets at the fundamental problem that is preventing new use patents, FDA exclusivity periods, or incentives like any other system, from working in this space. Reframing it as a pricing problem really helps in both seeing the magnitude of the problem, which is bigger than you might otherwise think, and also the set of solutions.

Thank you.

DR. KILGER: Thank you so much. I think this raises a lot of questions about how to achieve these split markets, how to achieve the different prices, what about acceptance, how to avoid substitution. But, as time is progressing, I think I will leave the discussion for the end of the panel.

Todd, the stage is yours.

MR. VOLYN: Maybe some of you have gotten this advice before. It came to me about six years ago. My son graduated from basic training in the United States Army and I went down to his graduation. A colonel stood up and said, “You know, in any public presentation you want to stand up to be seen, speak up to be heard, and sit down to be appreciated.” I am going to try to pay attention to that.

Maybe I should first note that it has become very clear to me that Brian Cordery is an evil genius, because he has very cleverly had Elaine deliver my exact presentation, knowing that I work best under pressure. So what I have in front of me here is the new use of an old presentation.

When Elaine was speaking, I got the slight hint that there was just a touch of a bias toward the follow-on drug community — you can call them “generics” if you like; I will just call them “follow-ons” — and I, of course, come to this from a little bit different perspective. So what I thought I might do is just go through some of those same points and just bounce off of you some of the ways that gets reflected in what it is that goes on inside the thinking of innovator companies or in the industry as a whole with respect to developing these new uses.

A lot of what happens to incentivize the new use happens totally internally in the companies that are trying to do these things and those internal discussions never really see the light of day. I cannot really give you deep insight into that, but I just want to point out a couple of things along these lines.

Standard Regime

- Use Claims: Use of Composition X to treat Disease A
- Method of Treating: Administering an effective amount of X to treat A
- Determining the concentration of Y [some diagnostic marker] and administering an effective amount of X to treat patients with more than A concentration of Y [the diagnostic marker]
- Combination products: Treating a patient with an effective amount of composition X and effective amount of composition Y to treat B

The standard regime for patenting and new use is, as Elaine pointed out, you will have a claim that reads something like “a method of treating Disease A by administering Compound X.” We have all come to understand those claims.

Two other types of claims that are becoming popular are diagnostic claims and combination claims. They have been around a while, but they are becoming more popular, and I think they have added legs to them, let's say, in this regard.

Think about diagnostic claims. I might have a claim which reads, "A method of treating Disease X comprising (a) measuring some analyte, and (b) when that analyte is within some certain range providing Compound X." If you think about the multitude of drugs that have potential liver implications, kidney implications, and so on, this is rather routine. You go get a liver function test and if you are not problematic you keep taking the drug. These might even be required on the label for the product.

But when you look at the range of diagnostics that are available today, it really changes things, because you could have diagnostic markers for specific indications, specific patient populations, or other parameters that can make skinny labeling difficult. That makes infringement of those claims a whole lot easier to make out. I just throw that out as one possibility.

The second possibility, something that we are seeing a lot more of these days, is combination treatment or combination therapy. You can have this in a variety of ways, and I am going to get to a case which describes this a little bit.

Maybe the best way to think of it is in the case of a fixed-dose combination: you take two drugs which work well together and you put them together. Now you have a new composition.

It makes it a little more difficult if somebody wants to now treat that ailment with that combination. Maybe both of them are separately not patentable now, so a follow-on drug manufacturer might be able to say, "Well, I am just going to provide A, and if somebody else provides B, well, that is up to them." But if the market for some reason demands a combination product in a fixed-dose form, you have a distinct advantage there.

You could also think about packaging things together. There are a whole variety of ways that if you think about new uses or new indications or whatever, you can address some of these things. We are starting to see some of that, especially as there is an actual need to combine compounds together.

That is some background.

Enforcement

- Generally, induced infringement requires "Active encouragement of infringement"
- *Takeda v. West-Ward*, 785 F.3d 625 (Fed. Cir. 2015):
 - "The label must encourage, recommend, or promote infringement." 631.
 - "But we need not decide whether evidence as to the invariable response could ever transform a vague label into active encouragement." 632.
- *Eli Lilly v. Teva*, 845 F.3d 845 (Fed. Cir. 2017):
 - "The product labeling here is not so tenuously related to the use covered...and Eli Lilly does not need to rely on speculation about physician behavior." 1369
 - "...evidence that the product labeling...would inevitably lead some physicians to infringe establishes the requisite intent..." 1369.
- Can a skinny label avoid induced infringement? Sometimes, always, or never?

I just want to touch on two cases very briefly. One of them involves Eli Lilly.

The first case is *Takeda Pharmaceuticals U.S.A. Inc. v. West-Ward Pharmaceutical Corp.*²¹ Takeda was selling a product that was useful for

²¹ 785 F.3d 625 (Fed. Cir. 2015).

treating gout, they had an indication for acute gout, and they had a patent for this use. The follow-on developer put the same medicine, which was off-patent for hundreds of years, I believe, out into the market, but their indication was as prophylaxis for gout. It had a vague warning in the indication which said, “If you have an acute flare-up of gout, you really should go see your doctor,” the implication being “and they will give you some of this stuff.” Takeda sued them under the theory that, as people understand this medicine and as the warning on the label suggests that you might use it in this way, that would be an act of inducement and, therefore, an act of infringement.

The Federal Circuit ultimately came down very heavily to say: “No, not so fast. We are in a Hatch-Waxman case” — and I believe this may have been limited to Hatch-Waxman cases — “and in a Hatch-Waxman case we care about what is on the label. The label has to clearly say what would be an act of actively inducing the infringement.”

That is the backdrop for one way to look at this.

Along comes *Eli Lilly v. Teva*.²² In that case there was a drug Eli Lilly produced for oncology called Altimax®. The best use of that drug was in accordance with pretreatment with folic acid and vitamin B12. You could treat yourself with folic acid and vitamin B12, and that is what most patients did. The doctor told them, “In order to make this medicine work properly you need to take folic acid and vitamin B12,” and that is what people did. You now have a very long, attenuated chain of who the actual infringers are. It takes the doctor plus the patient, and that is the act of a direct infringement.

What do you have to do in order to induce that infringement? Well, in this case again you turn to the label. The label on the follow-on product very clearly says “you have to take folic acid and you have to take vitamin B12.” So now you have what Takeda asked for — active encouragement vis-à-vis the label — and you also have induced infringement in the manner in which we had come to understand it over time, that it did not necessarily have to be done by a single person, it was the direction of the infringement. So the court found for Eli Lilly in that case.

The point that is of interest to me is that through all of this the court was being very careful to follow the guidance given in *Takeda*, but they slipped another factor in there that led to the conclusion that there was infringement, and that was there was an expert who said you would have to use the combination that way. That is evidence which is outside of the label, and there is some language in that case that would indicate maybe there is a way to do that.

I think Elaine even pointed to the case where, “Hey, you know, post-approval maybe you can gather some evidence.” In her case it was a single point of evidence, but maybe you can use that now, where it might have been more difficult in the past.

MS. BLAIS: I will just respond that both of the cases were my cases.

MR. VOLYN: Oh, again the evil genius. [Laughter]

I raise these because I want to come to the final point that I started with, which is now bringing it back to how is it that we incentivize things from inside

²² *Eli Lilly & Co. v. Teva Parenteral Meds., Inc.*, 845 F.3d 1357 (Fed. Cir. 2017).

the company's point of view.

Now think about this. You have a patented product; it has a particular life to it; we have all kinds of charts and diagrams to try to illustrate how those things are affected. I talk to management about those things all the time. Now we have clinical decisions to make. Do we provide that compound with another compound and make a combination product? Maybe that is good for the patent life. Do we do clinical studies to support that separately, or can we rely on something like a 505(b)(2) to do that? Would a clinical study be more helpful in the environment of trying to decide a patent matter? Do we invest money in those clinical trials? What kind of labeling do we pursue in the FDA in light of the patent situation?

So now, if you are following me, what you are thinking is, *These decisions are all made in the context of keeping a solid patent life so that I can expand the uses and so forth.*

But there is an element there that we never forget — and I think probably everyone in this room would agree on — and that is none of this stuff should happen without the patient in mind. If you are going to make a combination product, the first question really ought to be: does it benefit the patient? Then, once you get past that, you can start putting into the mix these questions of: can we fund it; what would it take to fund it; could we get longer patent life if we do fund it?

I just wanted to try to use that as a little bit of a background maybe to get you inside the mind of how this is analyzed in another context. I hope that has been helpful, and I will return the balance of my time to Ute.

DR. KILGER: It means we have to be even more creative in not only thinking about the shortage of second medical use patents but thinking about what other types of patents we could create or what other business tools we have to incentivize such new improvements.

As I had the impression that the European view is underrepresented in this panel a little bit, I asked James to give us a bit of a European perspective to what has been said in this panel.

MR. HORGAN: I want to talk very briefly about the situation in Europe and a couple of very recent cases that I think are very relevant. You have had some cases from some countries already.

My interest in this area has been longstanding. I have had a number of cases through the years.

I have inherited from the merger with Schering-Plough particular patents related to a product called Rebetol, also known as ribavirin. It is an unusual patent which was a leading patent at the European Patent Office (EPO) and went to the Boards of Appeal twice. I got involved at the time it went to the Boards of Appeal twice and survived.

Where do we stand on the law in Europe?

- a) German Federal Court of Justice *Carvedilol II* requires wording on label that would infringe claim.
- b) Two Supreme Court decisions in NL.
 - MSD v Teva ribavirin case. Went to a hearing (about 6 a year). Complex claim but Teva made a very imperfect carve-out of their label.
 - Having lost at first and second instance MSD won at Supreme Court.
 - SMU claims are no different to any other patent claim. They can be infringed directly and indirectly.
 - Direct infringement when manufacturer foresees or ought to foresee an infringement. Has to take all effective measures that can reasonably be required of him to avoid this.
 - Earlier Novartis v Sun zoledronate case (which did not have a hearing) reached similar conclusions.



The claim is quite unusual in that it is a claim for the treatment of hepatitis C virus (HCV) in patients who have type 1 HCV, who are treatment-naïve, who have a viral load above a certain level, in combination with interferon for a

certain period of time, I think forty-eight to fifty-two weeks. So this is really one end of the spectrum of second medical use claims. But it survived the Boards of Appeal twice. It is a valid patent. We sought to enforce this patent in the Netherlands and in Germany.

In Germany we were completely unsuccessful, partly, as has been mentioned earlier by Ute, because of some earlier case law called *Carvedilol II*²³ and this lovely phrase *sinnfälliges Herrichten* (manifest arrangement) — in other words, essentially for all intents and purposes you need language on the label and other activities or behaviors of the alleged infringer are not taken into account. So we lost in Germany.

But there were parallel cases in the Netherlands, which went very slowly because they were in limbo for a few years. Rian Kalden heard the first instance case in the District Court of the Hague.²⁴ We lost at first and second²⁵ instances in the Netherlands.

But I had a bit of confidence in this case, and we wanted very much to try to prove a point. It was taken up by the Dutch Supreme Court. That does not necessarily sound too exciting, because they take something like 350 cases a year but they only give half a dozen hearings. We got a hearing, which showed that it was being taken very seriously by the Dutch Supreme Court. The day of our hearing was actually the date that another District Court of the Hague decision came out in the *Novartis v. Sun zoledronate* case,²⁶ which augured well for us. We had a fantastic legal team doing the case.

Essentially, what the *Dutch Supreme Court decision*²⁷ did was find for us essentially on absolutely everything. I am familiar with working with lawyers,

²³ BGH, GRUG 2007, 404.

²⁴ Case 358401/HA ZA 10-437, issued by the District Court of The Hague Nov. 10, 2010.

²⁵ Case 200.082.008/02, issued by the Appellate Court of The Hague July 14, 2015.

²⁶ Case C/09/460540 / KG ZA 14-185, *Novartis AG v. Sun Pharmaceutical Industries (Europe) BV*, preliminary injunction case before the District Court of The Hague, the Netherlands, 12 May 2014.

²⁷ Decision of the Supreme Court of the Netherlands (Hoge Raad), 3 November 2017, IEF 17300; LS&R 1539 (*Merck Sharp & Dohme v. Teva Pharma and Pharmachemie*; English translation of IEF 17241), available at <http://www.ie-forum.nl/artikelen/supreme-court-of-the-netherlands-msd-teva-pharma-english-translation>.

and it is the only time I have had a lawyer send the judgment on a case to me with the single word “Wow!” in the title. So it was really good.

The Dutch Supreme Court found that a generic can infringe a claim of this type of second medical use case both directly and indirectly, and the test is one where the manufacturer foresees or ought to foresee an infringement. To avoid infringement the generic has to take all effective measures that can reasonably be required of him to avoid this.


Of course, in the Netherlands we have already heard that the Dutch Medicines Agency has on its website the unredacted label. The evidence in our case was that physicians look at that, not at the package insert. I know there is a case in the Netherlands against the Dutch Medicines Agency brought by Warner-Lambert,²⁸ but actually the Supreme Court case suggests it is not their problem; it is actually the generic’s problem to make sure that the marketing regulatory agency does not put out information that essentially they can know is inducing infringement.

On indirect infringement we were successful as well. If the generic can foresee that there will be a downstream step which essentially labels the medicine — that is something the pharmacist does — that is also going to be an infringement.

Where do we stand on the law in Europe?

c) Warner-Lambert before the UK Supreme Court.

- Court of Appeal decision upholds its earlier objective view of infringement from its decision on summary proceedings. Intention negative when manufacturer taken all reasonable steps in his power to prevent the consequences occurring.
- Indirect infringement requires supply of means for putting the invention into effect. Does not need downstream manufacture. Can include packaging/labelling by pharmacist.

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The UK *Warner-Lambert* case has been mentioned. The [Court of Appeal decision](#)²⁹ on what constitutes infringement was pretty similar, I think, to where things ended up in the Netherlands, and that is up there. There is an objective perspective

taken: to avoid the inference of infringement, a generic has to do everything reasonably within its power to prevent the consequences of infringement occurring; and, likewise, indirect infringement can occur as well downstream.

²⁸ Warner-Lambert Company LLC v. the State of The Netherlands (Dutch Medicines Evaluation Board), District Court of The Hague, The Netherlands, 15 January 2016, Case file number: C/09/498943 / KG ZA 15-1656.

²⁹ Warner-Lambert Company, LLC v. Actavis Group Pte EHF & Others, [2015] EWCA Civ 556, decision available at <http://www.bailii.org/ew/cases/EWCA/Civ/2015/556.html>.

What do I think will happen?

- Assuming Warner-Lambert's patent survives on insufficiency then hope Supreme Court will follow CA on infringement. Position similar to NL.
- The question that arises is what reasonable steps must a generic take? May be different answers in different countries due to differences in prescribing, dispensing and reimbursement laws.

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MSD

We do not know whether the **UK Supreme Court**³⁰ is going to address this question because the Warner-Lambert patent has got to survive on insufficiency. But if it does survive, I am very hopeful the Supreme Court will be taking a good

and careful look at the Dutch case that I had and come to a similar place.

I think where that leaves us for generics is the interesting question of what relief then follows. What does a generic have to do to avoid the inference of infringement, and how might that look in relation to an originator? Would they have to pay a royalty? Would they have to make sure that the software is up-to-date at the doctor's? How does the money transfer work to ensure that some infringement, if it occurs, is appropriately paid back to the originator? I think that is where we have reached on this question.

I have one or two other comments on some other issues that have come up.

One day perhaps we will have a single patent court in Europe. I have always liked to think about what would happen if a case of this type came to the **Unified Patent Court** (UPC) because although we have a single patent law in Europe, the laws on physicians prescribing, on pharmacists dispensing, and on health insurers and state reimbursing are all national. Can you think about the evidence that would have to be taken to the court and the witnesses? The evidence would arrive in a lorry and the witnesses in a coach. This would be a fascinating case. The UPC would certainly unify the case law around Europe, but it would put a lot of pressure on national countries to try to work out systems that would avoid infringement.

I am also very involved with supplementary protection certificates (SPCs) in Europe, the European equivalent of patent term extension (PTE). The law is in ferment at the moment with things like combination therapies and what SPCs cover. It is in a very unfortunate state of ferment, and combination therapies are not now well rewarded by the SPC system.

It might be that data exclusivity has to be beefed up to deal with some of these issues. I think you were right at the end to talk about who gets paid in

³⁰ 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, available at <https://www.lifesciencesipreview.com/news/warner-lambert-v-actavis-a-summary-from-the-uk-supreme-court-hearing-2723> (Feb. 21, 2018).].

indication stuff and how that works with insurers if you can do that.

In terms of IP protection, maybe data exclusivity needs to be more generously awarded for new indications. The current system that we have in Europe is fairly stingy, just one extra year, and the hurdles are pretty high. I think that perhaps should be looked at again if you want to incentivize in this area.

Someone else asked whether there is an inherency problem from clinical trials. There is on inherency law in Europe for second medical use cases. That is not a problem.

The very last thing I want to mention is that I also had a case recently in France, which we lost, but we were very pleased because the French Supreme Court in its decision³¹ presupposes that you can get patents on new uses, and limited by dosage features as well, which is a turnaround for France where these patents have been in significant doubt for many, many years.

DR. KILGER: Thank you so much.

You said all effective measures have to be taken by generics to avoid patent infringement.

MR. HORGAN: Yes.

DR. KILGER: What can you think of that they should do if you had to rule about it, and what do you think would be enough? What do you think would solve the problem?

MR. HORGAN: I think that is the big question, isn't it? What are "all effective measures?" The onus is on the generic not to infringe, which is quite normal in the world of patents, of course, isn't it? The onus is normally on somebody not to infringe a patent.

Various suggestions have been made on a country-specific basis about what needs to be done. Those sorts of issues have arisen mainly in the pregabalin cases in various countries. That has begun to show ways in which generics have to behave to avoid the inference of infringement. But you can still see that problems arise in certain circumstances, for example, where maybe medicines are not tendered, where you have prescribing laws that have compulsory substitution.

I think problems also arise, although nobody has gone quite this far, with the state in the way that reimbursement works and the way that states sometimes drop reimbursement levels on products when they go generic regardless of indication. That may also be something which is a very unfair situation, but that is a European issue perhaps more than an American issue. So there is certainly a problem there, that reimbursement systems are creaking because they do not recognize this type of innovation.

DR. KILGER: We have a minute left, so I will ask the audience whether there are questions for the panelists.

QUESTION [Dr. Amitava Banerjee, UCL Farr Institute of Health Informatics]: I am a fish out of water here. I am a clinician among lawyers. It is not surprising that Todd's words resonate with me, that we should keep the

³¹ 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.

patient at the center here. We have been through a lot of change in healthcare across various countries where both research and clinical care have been either research-centered or doctor-centered and now they are much more toward patient-driven or patient-centered.

There was an editorial in *Science* magazine where instead of saying, “Dr. Banerjee is recruiting volunteers for his trial,” it said, “This study is now recruiting investigators.” It was actually a patient-run study. So that is the world we are living in.

I want to go further actually and say that this kind of meeting should have a patient perspective because that is the only perspective that is missing in your panels.

PROF. JACOB: We did try.

QUESTIONER [Dr. Banerjee]: Actually I have organized around data security, which is my research area, and often the whole paradigm that we have in our mind is tossed on its head. That is just a comment on patients.

I want to talk about efficacy and effectiveness. We have a system where the trial tests for efficacy, and before that the patent is applied for, and basically all the reimbursement is based on efficacy. But actually we are moving to a real-world situation where you are looking for effectiveness, which is not rewarded. Nobody is looking at whether drugs actually work in the real world.

How would that reimbursement model look and be tied to the patent, because otherwise we are going to be tied into this efficacy-versus-effectiveness conundrum?

PROF. EISENBERG: I have started to notice newspaper reports of agreements between insurers and drug companies over payments for a new expensive drug that involve commitments to refund money if certain effectiveness benchmarks are not met. But, of course, the financial terms of these agreements do not see the light of day, so perhaps some of you have a better idea than I do of what is in these agreements. I only see what a reporter was able to suss out. But that might be one way of doing it.

This gets into some of the pricing problems that Ben Roin was talking about. You could imagine a world in which more nuanced pricing is established in the terms of agreements between insurance companies and drug companies.

MR. VOLYN: Actually the new models for some of these agreements — and I do licensing and acquisition, so I am not really involved in those kinds of agreements — are called “outcome-based contracting.” That is really becoming a hot topic. The audience for those is pretty broad. It is insurance companies; it is governments; it is all kinds of things. Anybody who has a say in how they are going to pay for drugs has got a hand in this.

PROF. RAI: I have worked with Margolis Center at Duke on some of these. We published a [White Paper](#) in December that everyone should read on legal impediments to value-based payment.³²

³² Duke Margolis Center for Health Policy, *Overcoming the Legal and Regulatory Hurdles to Value-Based Payment Arrangements for Medical Products* (Dec. 2017), available at https://healthpolicy.duke.edu/sites/default/files/atoms/files/overcoming_legal_and_regulatory_hurdles_to_value-based_payment_arrangements_for_medical_products.pdf.

There, one difference is the insurers pay less if the drug does not work. In this case, presumably they have to make a commitment ex ante — that is econo-speak for “before the fact” — to pay more if the drug is useful for a new use.

The money flow is always important to insurers, whether they pay less or more, and presumably when they pay more they are a little more concerned. But maybe, per Becky, they would be willing to pay more, or make a commitment to pay more, if they knew that the pharmaceutical company was going to do all the work to prove that it really did work and maybe reduced follow-on costs for hip fractures or what have you. That would be the gambit, but I think it would have to be an ex ante commitment by the buyer. I do not think it could be ex post.

PROF. EISENBERG: I was thinking about it quite differently actually. You might be able to set up an agreement that would give the payor an incentive to monitor these outcomes, and maybe to collect new data on patient experience, whatever it is that is necessary. If they stand to get some money back if it turns out that the drug is not working as promised, then they might be interested in collecting the data. Of course, there is another source of bias there, but there is a source of bias when you are relying on the drug company to supply all the data, too.

PROF. RAI: Right. I do not mean to go off on this, but the current agreements are you get money back if the drug does not work as it is supposed to. But that is usually on a drug that has been approved for a particular use and you get money back if it doesn't work. It is approved, but it is not necessarily effective.

Whereas here you would have to say, “Okay, we agree before the fact that if you do the work to try to find this new use, or we work with you to find this new use, maybe through your real-world evidence, we will agree to pay more for this new use down the line,” which is a challenge.

DR. KILGER: I think we will have more time this afternoon and also tomorrow to think about what could be new models or what could be a solution, but for now I wish to conclude this panel.

Thank you so much. Thank you for your attention.

MR. CORDERY: Lunch, everyone, is downstairs to the ground floor. Come out the lift, turn left, then left again, and you will come to the lunch door.

If we could be back here to start again at 2:30, that would be great. The room will be locked, so you can leave valuables here if you need to because it is only us who will have access to this area.

Thank you very much.

[Session Adjourned: 1:40 p.m.]