TABLE OF CONTENTS

DAY ONE AFTERNOON SESSIONS

Thursday, February 8, 2018

Session 1G:
Economists' Perspective

Moderator: **Christina Schwarz**, Partner, Fitzpatrick Cella Harper & Scinto LLP, NY
Presenters & Panelists:
Prof. Henry Grabowski, Professor Emeritus of Economics, Duke University, Durham
Alex Brill, Resident Fellow, American Enterprise Institute, Washington, D.C.

Session 1H:
The Physician & Pharmacist

Moderator: **Simon Spink,** Bristows, London
Presenters & Panelists:
Dr. Amitava Banerjee, UCL Farr Institute of Health Informatics, London
Prof. Janis Shute, Professor of Respiratory Pharmacology, University of Portsmouth
Prof. Graham Russell, Emeritus Professor of Musculoskeletal Pharmacology, NDORMS, University of Oxford
Prof. Jayne Lawrence, Head of the Division of Pharmacy and Optometry at Manchester University

Session 1I:
The Payor's Perspective: Regulating to incentivize value creation and repair a failed market

Moderator: **Nancy E. Taylor,** Greenberg Traurig LLP, Washington D.C.
Presenter: **Dr. David Cavalla,** Numedicus, Cambridge, England
Panelists:
Prof. Peter Neumann, Professor of Medicine, Tufts University School of Medicine, Boston
Sergio Napolitano, Director, Legal & External Relations, Medicines for Europe, Brussels
Erik Komendant, Vice President Federal Affairs, Association for Accessible Medicines; Formerly Head of Policy, AHIIP, Washington D.C.

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 – 2:25 p.m.

Session 1G: Economists' Perspective

Moderator:
Christina Schwarz
Partner, Fitzpatrick Cella Harper and Scinto LLP, New York

Presenters & Panelists:
Prof. Henry Grabowski
Professor Emeritus of Economics, Duke University, Durham

Alex Brill
Resident Fellow, American Enterprise Institute, Washington

* * *

MR. CORDERY: Thank you all for coming back so promptly, and thanks to Georgetown for providing an excellent lunch.

We are going to start this afternoon with some views from the economists' perspective. I will hand over to Christina Schwarz of Fitzpatrick Cella, who is your moderator for this afternoon.

MS. SCHWARZ: Great. Thanks, Brian.

Good afternoon, everyone. We have a great panel today with two economists who between them have a wealth of knowledge about issues surrounding economics and healthcare and second medical uses: Prof. Henry Grabowski, who is Professor Emeritus and Director of the Program of Pharmaceuticals and Health Economics at Duke; and Alex Brill, a Resident Fellow at the American Enterprise Institute, a think tank based here in Washington, D.C.

Unfortunately, we lost the European contingent of our panel today. Prof. Margaret Kyle got trapped in Paris. Maybe at the end of the presentation today, if there are people in the audience who have some thoughts about how some of

these economic issues may differ in Europe, we would love to hear some of your views. So we are going to co-opt you to help with our panel.

Our goal today is to have an informal panel discussion. We will be talking about four categories — costs, benefits, reimbursement, and policy — and the panelists have indicated that they would be happy to field questions from the audience at the end of each of those four categories, so I will turn it over to you if anyone has questions.

With that, let's get started with the cost segment. How are the costs associated with developing a second use similar or different from the costs associated with the first use of a particular product?

PROF. GRABOWSKI: I have been a coauthor of some studies of the cost of R&D with Joe DiMasi and Ronald Hansen. The Tufts Center for the Study of Drug Development is sort of a keeper of numbers in terms of pharmaceutical R&D and other industry aspects, and Joe DiMasi is its chief economist. Our last study was published in the *Journal of Health Economics* in 2016, "Innovation in the Pharmaceutical Industry: New Estimates of R&D Costs." It is focused on new medical entities, new molecular entities, but you can get some insights into the cost for a new use from that study.

To the extent that a second use would require similar Phase III clinical studies, the median out-of-pocket cost for a Phase III study was $200 million, and the time involved was three and a half years for Phase III clinical trials. And then you would have some preclinical, some dosing, maybe proof of concept as well, that would increase those costs. And then there is some risk adjustment: the probability of success may be significantly higher than starting at the very beginning of the discovery phase, but it is not 100 percent certain that this new second use would be successful, so companies typically risk adjust for the probability of success. Also, if it is, say, a five-year period rather than a twelve-year period, there is still some cost of capital for the investment.

So, at the end of the day, the new second use is maybe 25 percent to a third of the R&D costs of a new molecular entity, which we estimated in this latest study to be well over $1 billion in out-of-pocket costs.

MR. BRILL: I would add that the work Henry and his coauthors have done in this area is probably the most extensive of any in the literature on cost of drug development. However, there are challenges with thinking about these numbers. Henry talked about the median numbers. But, of course, there is a significant variance in these costs from product to product.

A more sophisticated model would include not only what the *expected cost* might be (the mean or the median cost), but incorporate some of the risks and the variances of these costs. For example, it might be likely on many occasions to develop a second use for far less than the costs that Henry just described, or far more.

I think there are development cost risk questions that are important for the innovator to consider about that uncertainty. There are not only the risks of failures, as Henry noted, but there is the variability in the costs that are a separate risk. For example, you might think that you have a great second use and you might think you could pull it off for $200 million; however, when you are $150

million into the project, you learn that you have another $150 million to go. That risk dynamic should drive our thinking about these costs in some respects.

Second, when we think about this issue from a policy perspective, we also need to remember that the development of a second use (or a first use for that matter) might work out to have a relatively low cost. When policymakers try to develop policies around the median cost framework, when in reality half the time it is much higher and half the time it is much lower, policy is going to be missing the mark on many occasions

PROF. GRABOWSKI: If it is for an orphan indication, generally the FDA would allow many fewer subjects and the cost might be significantly lower, and then there are other cases where there are many more subjects and higher cost.

MR. BRILL: Those would be examples of known variation, right?

PROF. GRABOWSKI: Right.

MR. BRILL: Those are variations in cost that one could anticipate. But there is another class that I think was probably unanticipated.

MS. SCHWARZ: What are the economic differences between an innovator company that is developing a second or third use for a drug compared to a use where physicians are just simply prescribing the drug off-label for that second use?

MR. BRILL: The economics for the innovator are fundamentally different. If they are not making the investment in the trials, their costs are lower; and their returns are not differentiated. At the same time, without the evidence and without the confidence for the prescriber that is associated with a clinical trial, the uptake is potentially much lower. In that sense, the economic loss is to the patients who are not getting the product because we do not have the evidence that we need. Therefore, it is dissipated in a very different sense than if the investments are made.

Then the question is: when those investments are made, who is capturing those benefits? From a welfare perspective, some of those benefits are captured by the innovator, by the risk taker, and some by society, by the patients themselves.

PROF. GRABOWSKI: As most of you probably know, there are areas where there is significant off-label use, like in oncology very often there will be an initial approved use and then many other uses that come to bear based on observational data from patient treatment experiences and published information from limited clinical trials. There is not enough data for regulatory approval, but there still can be significant prescription and company revenues from off-label uses in particular circumstances.

MR. BRILL: As you mentioned earlier, the sample size could be smaller for an orphan drug. There could be strategic decisions, of course, to pursue an indication where the costs of the trials are lower, expecting or hoping that you are going to make your sales on an off-label use. So you can be strategic in that process.

MS. SCHWARZ: We will transition now to some questions about benefits, unless there are questions from the audience on the cost segment.

QUESTION [Prof. Robin Jacob, University College London]: You talked about the costs of second-use clinical trials, and I think you gave us a figure of around $200 million. We are told that some could be lower and some could be higher. How do they compare with the costs for a new molecule?

PROF. GRABOWSKI: That was just for the Phase III. For a new molecule that successfully completes all phases, we are dealing with mean out-of-pocket costs of close to $400 million, but then it builds up as you add in the discovery phase and as you add in the probability of not succeeding at each stage. So the total out-of-pocket cost estimate for a new molecular entity is $1.4 billion when you figure in the discovery stage and the cost of the drugs that fall by the wayside, which is a big factor in the overall R&D costs for a new molecule.

We also estimated, on average, that a new molecule will have post-approval R&D costs of close to $400 million. That $400 million is for new indications, new formulations, as well as Phase IV testing.

QUESTIONER [Prof. Jacob]: Just putting the two next to each other, for a first use you are putting it at $1.4 billion plus a bit extra after. Is the total cost for a new use for a known medicine $200 million, or does that get a bit of extras as well?

PROF. GRABOWSKI: The second-use indication has extras as well. People have estimated it is between 25 percent and a third of what you would be spending for a new molecule. It is more than $200 million on average, but, as Alex emphasized, it could vary dramatically.

QUESTIONER [Prof. Jacob]: Correct me if I am wrong, but I think I've got it right. If you have a new use for a known medicine, for all practical purposes, as far as the doctors are concerned, that is a new medicine, it is a new treatment, and it costs about a third to a quarter compared with another kind of new medicine which is a new molecule or kind of molecule. Would that be right?

PROF. GRABOWSKI: I think that is a fair characterization, yes.

MR. BRILL: Just to follow up — maybe a clarification question for you, Henry — could you relate what the out-of-pocket costs are in the $1.4 billion, because only a fraction of the costs are actual out-of-pocket costs, right?

PROF. GRABOWSKI: Right. The out-of-pocket costs are actually $1.4 billion, and if you include in the cost of capital or the opportunity cost associated with the lengthy twelve-year investment period, our estimate of the total cost increases to $2.5 billion to discover and develop an FDA-approved new medicine..

MR. BRILL: This is the difference between economists and accountants, right?

PROF. GRABOWSKI: Right.

MR. BRILL: Economists think about costs that do not actually exist in a transactional sense, because of the time value of money and costs like that, versus the actual out-of-pocket costs, which are obviously much lower.

PROF. GRABOWSKI: That is one element. But the probability of success increases at each phase. In this study of the drugs that start Phase I, only about 12 percent eventually become a marketed medicine. Now, the odds go up as you get to each stage, so by the time you are in Phase III the odds are 80

percent or so. However, you have to account for the fact that for every drug you get approved as a new medicine eight fall by the wayside. Hopefully, they fall by the wayside as early as possible because the costs go up dramatically as you get to Phase III.

MS. SCHWARZ: There is another question.

QUESTION [Jürgen Dressel, Novartis]: When I hear comparisons between developing second medical uses and new chemical entities and you give us these numbers, I try to relate that to our internal efforts to actually come up with such numbers, which is extremely difficult because of many reasons, due to the fact that regulatory requirements change over time and that it really heavily depends on the indication. I think Alex emphasized that you have a huge spread.

MR. BRILL: Exactly.

QUESTIONER [Mr. Dressel]: As a patent attorney, I am now asking the economist: do you think the fact that you have a higher probability of success, that you have shorter times in which you can actually recover the R&D costs that you put into such a project, should automatically lead to lower prices for second medical uses in the end?

MR. BRILL: I do not think it does. I think it is more complicated. Obviously, to the extent that we have a pricing model that involves an effort to recoup the fixed costs, you might say, "Well, the fixed costs are lower so the price should be lower." But the market may be smaller as well.

This comes back to the question of why is that the second use and why wasn't it the first use. Maybe it is the second use because it is the smaller opportunity, or maybe it is the second use just by luck. If you are trying to recoup a smaller cost over a significantly smaller base, then you are going to get a different pricing outcome.

I do not think that you can interpret the variation in the development costs into a unit price, other than to say that in the aggregate you are just trying to recoup a different amount.

PROF. GRABOWSKI: I think a key thing there, though, is the time to recoup the required R&D investment. Our analysis suggests the average market life in the United States from first FDA approval is about twelve years, with some variability. But if this new use only has half of that market life, then you have to recoup your investment in a much shorter time.

MR. BRILL: Over a shorter period of time, right.

MS. SCHWARZ: We will take one more question on costs.

QUESTION [Sir Alasdair Breckenridge, Former Chair of MHRA, UK]: Are there any examples of a repurposed drug that has undergone accelerated approval or early access, so that you would have one simple clinical trial and then real-world data, which would be considerably cheaper than the figures that you are quoting? Are there any examples of that?

PROF. GRABOWSKI: I think there would be. In the audience there are probably some pharmaceutical people. Sometimes the second use is far more important than the first use and it would get accelerated approval.

PARTICIPANT [Dr. David Cavalla, Numedicus]: Actually I looked into that recently because somebody posited that it was not possible to obtain

breakthrough therapy designation from the FDA for a repurposed molecule. There is an example of sirolimus for a very rare condition called lymphangioleiomyomatosis, so there is an example of that kind of thing having been done. But I do not know anything more than just that headline.

MR. BRILL: Prospectively we might anticipate there would be more of that, which is really another issue.

I know we are trying to move to the benefit discussion, but one more point on the cost. Our cost knowledge is retrospective. We are looking back over time, sometimes decades in the past, at our costs, and at this conference we are trying to think forward about our policies, which can lead to a mismatch. In other words, we may not know as much as we think if the economics of drug development are changing in the future and we are relying on evidence from the past.

MS. SCHWARZ: Turning now to benefits, who stands to benefit from the investment in developing a drug for a second use? Is it the patient, the payor, the innovator, or society as a whole?

PROF. GRABOWSKI: You really want all of the above to benefit. It is not always the case, but if the second use is for an unmet need or is a valid medical advance, then patients benefit. If it is early in the life cycle, then the innovator can benefit, and the payor can benefit in many cases too because it might prevent other costs. That is the ideal situation. It does not always occur that way.

MR. BRILL: Yes, I think that is right. We are trying to allocate these benefits broadly and create a framework, and I think in many senses there is a necessity to create this win/win between not only the innovator, but the payors as well, in order to get the cooperation that is necessary.

There is also a question about whether the alternative is an off-label use of the product that might exist otherwise or might exist for some patients otherwise. In theory, you could have a net welfare gain to patients. But if the prices are changing for the second use, if they are higher than they otherwise would have been, and there would have been an off-label market, then some people are paying more for what they would have otherwise gotten at a lower cost. That is not a bad thing, but within these groups of patients there could be winners and losers.

QUESTION [Prof. Robin Jacob, University College London]: Two more questions. Have you done any studies of the time it takes to do these things for second medical use from concept to bringing it to market compared with a new molecule? Is there any timing factor which might be relevant here?

MR. BRILL: Not that I find.

PROF. GRABOWSKI: I would guess there is some savings, but it would depend on the individual case. On average, we estimated from beginning of proof of concept to approval it is a twelve-year cycle. I would guess it is at least half that for a second use.

QUESTIONER [Prof. Jacob]: Prof. Mondher Toumi is coming tomorrow because he is messing around in the snow in Paris at the moment. He presented some information at the conference we had in Seattle about off-label use. It is an extraordinary piece of work that he has done.[1] I do not know whether you are

[1] *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

familiar with his work at all. You need to be. He demonstrated that quite a lot of off-label use is either useless or worse than useless, positively damaging. It is very convincing work indeed on quite a big scale.

None of your cost research includes damaging off-label use, which might be more preventable if you have a system of encouraging well-researched off-label use so it becomes on-label.

MR. BRILL: We would be really limiting our assets in oncology, as Henry noted, if we were restricting ourselves in that way. I think it is very disease-specific.

QUESTION [Jürgen Dressel] May I ask another question regarding costs? It just popped into my mind.

PROF. GRABOWSKI: Sure. I think that is part of our value added for this session.

QUESTIONER [Mr. Dressel]: If I understand the numbers correctly, the costs you take into account are the R&D costs leading to approval.

PROF. GRABOWSKI: Yes.

QUESTIONER [Mr. Dressel]: Again, usually the drugs do not sell by themselves and commercial success is not guaranteed. I have seen many drugs that were hailed as future blockbusters which then fizzled out in the low-digit-millions arena and the developers never got their money back. Is that something that should be taken into account when you do your calculations?

MR. BRILL: Those are in the models.

QUESTIONER [Mr. Dressel]: So when you say something like $1.4 billion, that includes these costs and also includes something like product liability, if you have to take your drug off the market because of side effects and have to pay huge costs for that?

PROF. GRABOWSKI: That is a different model. What the model then goes on to do, or some other work I have done with other colleagues, is we look at expected rates of return. You get a very highly skewed distribution. You have blockbusters that return many times their R&D costs, even a billion-dollar cost; you have products like Revlimid® that currently sells $9 billion worldwide, as well as other blockbusters like Humira® and Herceptin; and then you have many drugs that were, as you say, thought were going to be blockbusters but their sales are mediocre at best and they do not come close to recouping their lengthy and costly R&D investment.[2] That is where a lot of the uncertainty in drug development occurs, because one cannot know a drug's full benefit and risk profile until clinical trials are complete and patient experiences cumulate over time.

MR. BRILL: In addition, the issue, in part, is these costs that you are referring to in many of the models are considered variable costs. So, we do not

---

Dec 23. doi: 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.

[2] *See* Ernst R. Berndt et al, *Decline in Economic Returns from New Drugs Raises Questions About Sustaining Innovations*, HEALTH AFFAIRS Vol. 34, No. 2, at 245−52 (2015), available at https://www.healthaffairs.org/doi/abs/10.1377/hlthaff.2014.1029.

think of the cost being a one-time cost to get to market. A portion of the revenues might be booked as profits, but we have variable costs. We need to market those products, and there are costs associated with that; and we need to worry about liability risks, and we need to book reserves, in essence, against those other risks. Those are variable costs that one would put in the model as well.

MS. SCHWARZ: Can you comment on some of the economic benefits to society associated with second medical uses and whether those are likely to be short term or long term or a little bit of both?

MR. BRILL: I think it is a little bit of both. We are talking about a very diverse environment. In a sense, we can think about this as a process by which we are bringing more information to the marketplace, and so there are benefits because innovators are making investments in what they are bringing to the market. Someone said earlier that they are bringing a new medicine. In some sense they are bringing a new medicine, of course, and in some sense they are just bringing new information about an existing molecule. They are sort of two sides of the same coin. There are those benefits associated with that information, which might include reducing the risks associated with off-label uses as we gain more information.

But in terms of what the horizons might be, I would not expect, in general, big differences in the returns or benefits that we would expect from an initial indication. My sense is there is a degree of either randomness or strategic decision-making on the part of the innovator in terms of which indication to bring first; or it is just by luck which indication or discovery comes first, which means that the one that comes second is therefore also in a sense by luck. So we might expect a similar set of outcomes in the long run.

PROF. GRABOWSKI: One area where there has been a lot of second, third, and fourth uses is biologics. Part of that may be scientific or medical. If you look at the TNF inhibitors, because they are a class of drugs that can be effective against a lot of autoimmune diseases, you have initially rheumatoid arthritis, then you have psoriasis, Crohn's disease, as well as several other indications. This reflects, in part, the fact that until recently there was no generic- type competition for biologics. We now have a regulatory pathway for biosimilars, follow-on drugs which are close competitive alternatives (but not identical) to the originator drug.

Historically, many biologics had an effective market exclusivity period of eighteen years or more and products engaged in quality competition with other drugs in the same class. Therefore, there was an incentive to really investigate biological drugs for new uses and an opportunity for companies to expand their market through this R&D competitive process.

Now it will be interesting to see how the future competition with biosimilars evolves. Because biosimilars are similar but not yet interchangeable to the reference innovator's drug, there may be still a lot of incentives for originators to pursue additional uses if brand erosion occurs more slowly than for generics in the case of small molecule drugs.

MS. SCHWARZ: Let's turn to some questions about reimbursement. Do supplementary patent rights and regulatory exclusivity provisions provide

sufficient reimbursement revenues and return on R&D investments, especially where the first use of a product is late in its life cycle?

PROF. GRABOWSKI: I think we have aired that issue a lot already. That is where the big problem is: if you are close, say within a few years, of a generic introduction, how do you recoup the substantial R&D investment, given current practices and institutions? I think Denmark has shown a way to deal with this issue, namely to have prescriptions by indication with differential payments by indication accompanied by legal enforcement measures. There are obviously other ways to think about it.

But I think that is the nub of the problem here, that if you are facing generic introduction and if you have automatic substitution laws as in the United States, there are no real incentives to make a large R&D investment, unless you can somehow differentiate the new use through a new patented formulation or if the markets are segmented — that is, sometimes the markets involve totally different specialists and a different dosage strength and they may offer a way to bridge the gap in select circumstances.

MR. BRILL: Right. There are market-based solutions to bridging that gap. Henry's examples are good examples, I think, but they are not rock-solid guarantees. It depends on the class.

MS. SCHWARZ: Any questions from the audience on reimbursement?

QUESTION: In the case of the anti-TNF therapies, which start with rheumatoid arthritis and, as you say, go to other conditions, what was the process? Were there separate patents taken out, was there some other form of protection, or was it just that there was enough patent life that you could incorporate all those other indications?

PROF. GRABOWSKI: I am not the expert on this, but biologics have patents where sometimes it is the active ingredient, but there are also process and method-of-use patents. People say Humira® has over sixty patents, so there are multiple patents. There was brand-to-brand competition among TNF inhibitors, but there was no prospect of a close generic-type substitute. That environment created the economic incentives to engage in product quality competition and to investigate many follow-on indications.

QUESTIONER: The original patents are expiring shortly, aren't they?

PROF. GRABOWSKI: Yes.

MR. BRILL: The question is, sir, how this market will evolve and whether what we know about the small-molecule market serves as a roadmap. My view is that in many respects it does not serve as a roadmap. The competition dynamic that we experience in small molecules is that we very quickly see high rates of generic utilization and relatively quickly see lower prices; generic prices even of zero, as Ben described earlier. That is the model that we are most familiar with in terms of generic competition.

The biosimilar marketplace is likely to be very different, as everyone knows, in many ways, including the behavior of the innovator. Here is just one example: the typical behavior of the innovator in a small-molecule drug is that prices hold about constant. The behavior of the innovator in a biologic/biosimilar dynamic, a duopoly price-competition model, could be very different and we

could see the brand product chasing the biosimilar. Even if we did not have some of the other barriers that we have about perception and things like that, we can see very different uptakes in that marketplace. So, the reimbursement is uncharted territory in terms of the economics.

My macro view is that we should not rely on our experiences in the thirty years since Hatch-Waxman was passed to think forward about this new space.

PROF. GRABOWSKI: We do have a lot of experience from Europe. Countries differ dramatically in biosimilar uptake. Norway had an almost similar experience in terms of generic-type erosion for biologicals, and they have done it by very strong tendering. But I do not think that would be the model for the United States.

MR. BRILL: Yes. If we were to look for a model, I would think first about brand-to-brand competition in the United States perhaps.

MS. SCHWARZ: A comment over here on the right?

PARTICIPANT [Elaine Herrmann Blais, Goodwin Proctor LLP]: I agree with what Mr. Brill was saying about the disconnect between what we know about the patents.

And then I was just going to answer the question over here, which is that we do see method-of-use patents for rheumatoid arthritis and many, many different oncology indications. There are large patent suites and they do include the different indications.

MS. SCHWARZ: Turning now to a policy question, can you give us your thoughts on what economic incentives may motivate the development of second medical uses? I know this is related to what we have just been discussing, but do you have any additional thoughts on policies that could be specifically implemented?

PROF. GRABOWSKI: Yes. If we stay within the paradigm of the existing patent system, method-of-use patents or regulatory exclusivities, then I think in the United States, and probably elsewhere, having an indication-specific prescription process would produce the basis for a viable policy solution.

It is relevant to note that this is not a hard problem from an information flow aspect. Right now there are electronic clinical records for patients. The insurers have those. One could think of lots of different ways to electronically hook up the indication on a prescription with the pharmacist. You could even get around some of the privacy issues that people talked about. As an economist, I think that is the most efficient way to do it.

At the same time, there are stakeholders that are likely to resist and possibly block this policy approach. In that case, one could consider other models, other incentives. We have in the United States and elsewhere laws that have been targeted toward market failure situations that can provide insights in this regard.[3]

One poster child is the Orphan Drug Act. The Orphan Drug Act provided tax credits, initially 50 percent (recently reduced to 25 percent) of clinical trial costs, so your costs were cut in half. Then there was also the possibility of

[3] *See* Henry G. Grabowski, Joseph A. DiMasi & Genia Long, *The Roles of Patents and Research and Development Incentives in Biopharmaceutical Innovation*, HEALTH AFFAIRS, Vol. 34, No. 2, 302−10 (2015), available at https://www.ncbi.nlm.nih.gov/pubmed/25646111.

government grants for research into rare diseases. There was a seven-year exclusivity period, which was longer than the five-year period, but it was indication-specific.

This basket of incentives has been really powerful for orphan drugs for rare diseases. Some of the analysis by the FDA indicates that for the ten years prior to the Orphan Drug Act of 1983, there were only a dozen drugs approved in the United States for rare diseases. After the Orphan Drug Act was approved, in the next twenty-five years there have been 350. It is almost a policy that has had too much success, in the sense of more than a third of the new drugs, sometimes approaching half, are now for rare diseases. The policymakers are starting to question if it is diverting resources from bigger disease populations.

Nevertheless, I think the 1983 Act is a good model for thinking about supplementary market incentives that could be used in the present situation. As in the orphan drug case, you could lower the R&D cost through tax credits or subsidies (what economists call a push incentive) or institute some kind of a pull incentive, which includes market exclusivity or it could include prizes.

Another case example arises from U.S. actions to counter bioterrorism threats. The United States passed the Project Bioshield Act of 2004. Given the lack of existing market incentives to develop medical remedies for possible future bioterrorism attacks, in this case the government contracts for R&D for new and repurposed medicines to address these potential threats. It is similar to what occurs in the national defense area. That is another possibility.

All these different policy options would require legislative change, which could be very challenging, especially if they require additional costs or reduced revenues to the federal budget.

MR. BRILL: I am a little less inspired by the orphan drug case study because of what Henry mentioned at the end about whether that balance is really struck. On one hand, you may say we are drawing resources away from non-rare diseases, and that cost does exist.

Also, I think some of our blockbuster drugs were originally approved as orphans. So not everything that is an orphan — this is sort of a second use you might say in a sense — is really a molecule that is exclusively for an orphan indication. In those cases, the good news is that it is not diverting resources away from a broad-based disease; but, on the other hand, we are rewarding with our orphan incentives products that have multiple uses or broader uses, and that is probably not good policy design.

We need to do something that is sort of impossible: we need to strike the balance here, getting these incentives right. We want to make sure that we do not have a lack of incentive for innovation, but we also want to be conscious of not wasting resources, incentivizing things that do not need to be incentivized. These are taxpayer resources, these are taxpayer dollars that are being forgotten in many of these policies, or payors that are paying more.

I am a little more drawn to policy innovation not in the sense of the government deciding to impose a new policy through federal legislation, but that there would be win/win situations between innovators and payors. That is easy to say and hard to do.

Going back to the idea of the medical record, economists love to say, "Oh, the medical record is going to be a great solution." The medical record works sometimes and doesn't work other times. Some hospitals use them really well. And we have interoperability problems, and people who live in the world of medical records know that they are not always working perfectly.

But there is, I think, an opportunity, particularly in the hospital setting perhaps first before the retail setting, for more cooperation between payors and manufacturers. We talked about that a little bit on the last panel when we talked about new contracting ideas.

In a sense, there may be a role for government, and we see this a little bit in the Center for Medicare and Medicaid Innovation (CMMI) world, at the Centers for Medicare and Medicaid Services (CMS), in some innovative payment models and things like that. But really, I think it is more the large insurers that are trying to think more creatively about how they do their contracting and value-based payments that, hopefully, over time will reward the innovators for their truly innovative work.

It is not a perfect system, obviously, as patients are moving from insurer to insurer and there is turnover, and your insurer today may not want to pay a cost today for what might be your medical bills in ten years knowing that they may not be insuring you in ten years. So these systems are not perfect, but I think there is a lot of unexplored potential opportunity in that cooperative environment.

MS. SCHWARZ: Please join me in thanking Henry and Alex.

[Session adjourned: 3:12 p.m.]

University College London | Georgetown University Law Center

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

Georgetown University Law Center
600 New Jersey Avenue NW
Gewirz Student Center
Washington, D.C.
Thursday, February 8, 2018 – 3:10 p.m.

Session 1H:
The Physician & Pharmacist

Moderator:
Simon Spink
Bristows, London

Presenters & Panelists:
Dr. Amitava Banerjee
UCL Farr Institute of Health Informatics, London

Prof. Janis Shute
Professor of Respiratory Pharmacology, University of Portsmouth, Portsmouth

Prof. Graham Russell
Emeritus Professor of Musculoskeletal Pharmacology, NDORMS, University of Oxford, Oxford

Prof. Jayne Lawrence
Head of the Division of Pharmacy and Optometry at Manchester University, Manchester

* * *

MR. SPINK: Good afternoon. Welcome to the Physicians' and Pharmacists' Perspective.

Unfortunately, there is a change to the advertised programme. I am not Laetitia Benard. [Laughter] Laetitia was also caught in the snowfalls in Paris and cannot be with us today. Accordingly, I have been released from timekeeper's corner for this session and will endeavor to fill Laetitia's shoes. My name is Simon Spink and I am from Bristows.

I have with me two familiar faces, Prof. Graham Russell and Dr. Amitava Banerjee, who were with us earlier today, so I will not repeat what was said before but I will welcome them back.

Also we have with us Prof. Jayne Lawrence, who is Head of Pharmacy and Optometry at Manchester University. A pharmacist by training, Jayne was previously on a part-time secondment as Chief Scientist at the Royal Pharmaceutical Society, where she regularly commented in the media on issues of the day, such as antimicrobial resistance, biotics, and biosimilars. Jayne's research is focused on improving drug delivery and genes.

Finally, we have Janis Shute, Professor of Respiratory Pharmacology at the University of Portsmouth. Her research involves the repurposing of heparin for inhalation for respiratory diseases, such as COPD. Janis is also the Founding Director and Chief Scientific Officer of Ockham Biotech Ltd., which is currently taking forward her research in the repurposing of heparin.

Without further ado, I would like to welcome up Dr. Amitava Banerjee to give his presentation.

DR. BANERJEE: Thanks very much, Simon.

My conflict of interest is that I spend half my time as a clinician in the National Health Service (NHS), which I am very fond of, and the other half doing research, some of which is in relation to access to medicines.

What I thought I would talk about here is the opportunities to right some of the wrongs — not just with repurposing but with new drugs as well — that might be possible with new data opportunities.

Here are some of the current problems or missed opportunities:

• First, one of the reasons for the relatively low success rate of new drugs, or even repurposed drugs, is poor prediction from preclinical studies.

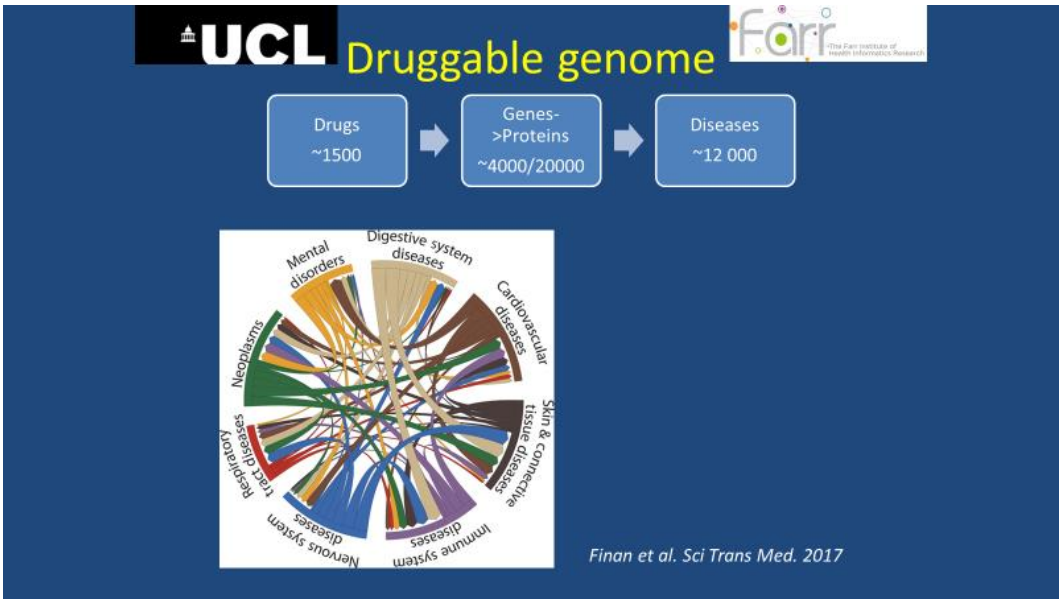
• Second, we do not get definitive evidence about whether a drug works until late in the process, classically Phase III or Phase IV of the randomized trial process.

• Third, not enough is made of the use of drugs — full stop — whether primary or secondary. We have evidence they work, but they are not actually used.

• Fourth, we tend to look at drugs alone, as in one-by-one, or we look at drugs in isolation and not in the context of the health system.

• Finally, we've got problems in the way we gather and use data.

Let's take these first two.



This concept has been around since about 2015. Once the human genome was mapped, people started talking about the "druggable genome." If you accept that we have on the order of 1500 drugs that are used in healthcare, we know from the International Classification of Diseases of the World Health Organization that there are about 12,000 diseases. We also know that there are 20,000 protein-encoding gene regions in the human genome of which we think about 20 percent (about 4000) encode proteins which are relevant to drugs.

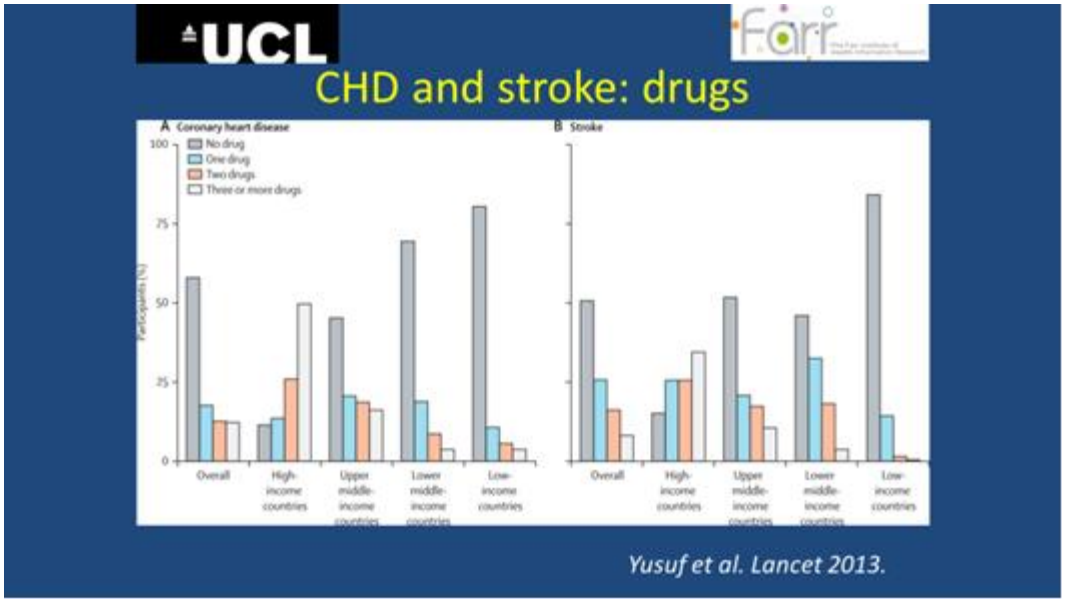
This massive undertaking has taken place over the last three to four years whereby drugs known to affect certain proteins whose genomes we know have been matched with the genes for proteins which are associated with diseases. We are looking at the disease and drug overlap. This is the most scientific way that we have so far of trying to map secondary uses.

This rather messy diagram is where, for example, we've got gene regions that mapped originally for digestive system diseases that also may be relevant to immune system diseases. This kind of analysis will guide drug repurposing and try to take a little bit of the serendipity out of the process. This is work done by colleagues of mine at UCL, Chris Finan and colleagues. This kind of study would inform better preclinical studies and would, hopefully, inform studies that would be better at the Phase III stage.

Now, do we use the drugs that we already have? The answer is a resounding no

Salim Yusuf, who is at McMaster University, did a study called the Prospective Urban Rural Epidemiology Study (PURE), where he looked at coronary heart disease (CHD) and stroke across all the continents of the world in select countries.[1]

[1] Salim Yusuf et al., *Prospective Urban Rural Epidemiology Study I. Use of Secondary Prevention Drugs for Cardiovascular Disease in the Community in High-income, Middle-income, and Low-income Countries (the PURE Study): A Prospective Epidemiological Survey*, 378 LANCET 1231 (2011), *available at* http://www.thelancet.com/journals/lancet/article/PIIS0140-6736(11)61215-4/abstract.

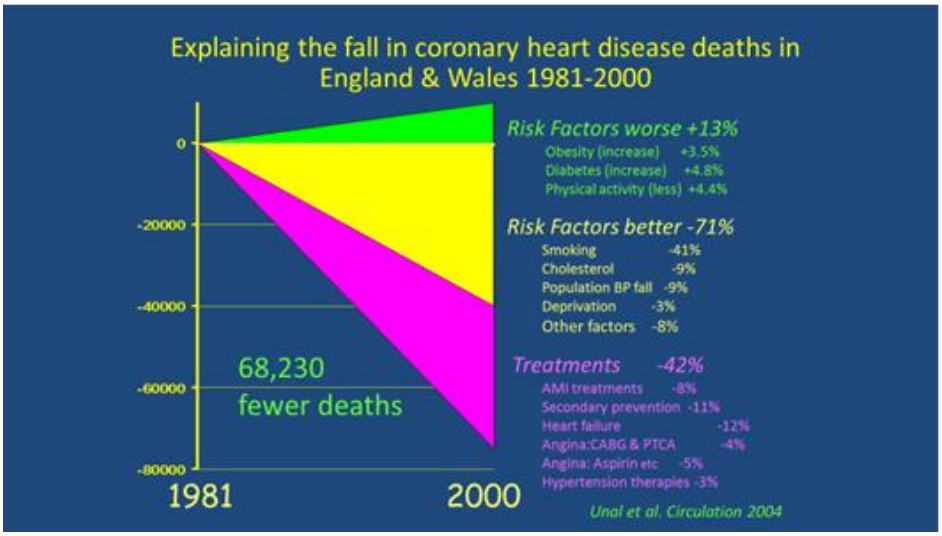


For heart disease and stroke, we have four drugs which are off-patent, they are generic: angiotensin-converting-enzyme (ACE) inhibitors, such as Ramipril; antiplatelet drugs, such as aspirin; beta-blockers, such as bisoprolol; and statins. One of the questions they asked is whether people are taking no drug, one drug, two drugs, or three drugs. These are all drugs that according to guidelines should be taken.

We see that even in high-income countries, such as the United States or the United Kingdom, for coronary heart disease there are still 10 percent of people taking no drugs at all and only 50 percent of people are taking all the drugs that they should be under the guidelines. These are generic off-patent drugs, so forget where you have to pay for your drugs.

In low-income countries, you can see it is more like 80 percent of people take no drugs at all. And for stroke it is even worse. So at the moment we've got drugs with primary and secondary uses which are not being used.

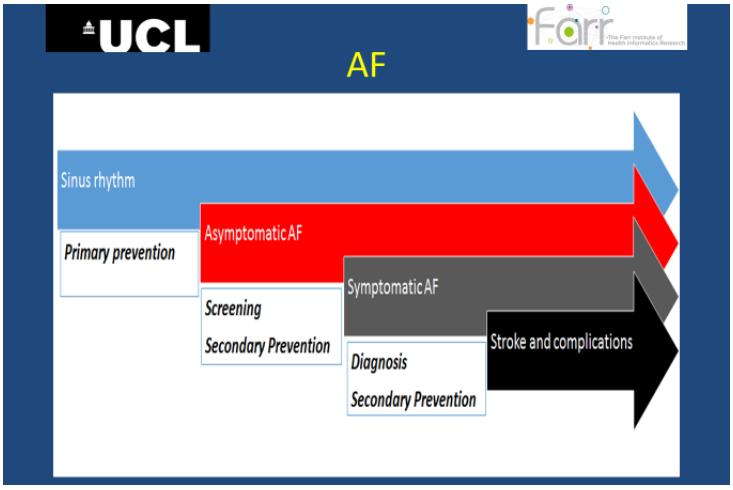
Too much focus on drugs alone or in isolation.



This is work done by my colleague Simon Capewell in Liverpool looking at why coronary heart disease mortality has plummeted in the period 1980-2000.[2] There are several blockbuster drugs which no doubt contributed, including the statins, including much wider-spread use of aspirin and anti-platelet drugs.

But actually, when you look at the epidemiology, he estimates that about 40 percent is due to better treatments. You can see he has broken down which drugs they are, whether we are doing more angiography, more bypass surgery. But a hell of a lot of it is due to less smoking, lower cholesterol, population blood pressure drop, more physical activity. There are some risk factors that have gotten worse — obesity, physical activity, and diabetes — but that is offset by drops in smoking at the population level.

So when we were talking about effectiveness earlier or drugs in isolation, we have to think of it in the context of the health system. The trial that we do has to look at the drug's efficacy. How relevant is that to this world setting that we work in?

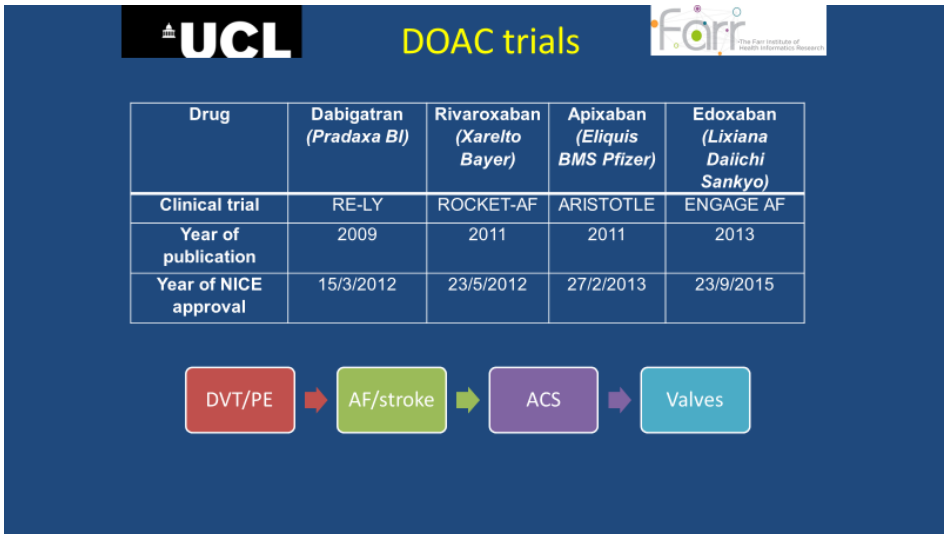


I specialize in atrial fibrillation (AF). That is a heart rhythm problem, the so-called "fluttering of the heart." Sinus rhythm is normal heart rhythm. The problem with atrial fibrillation is that a lot of it goes undiagnosed so you do not know that you have an irregular heart rhythm. That is the stage at which we want to pick people up by checking their pulse judiciously if they are at risk. But you may go on and get symptoms, such as breathlessness, palpitations, and chest pain.

The complication we all want to avoid is stroke or death. Just to give you an idea, in over-65's the prevalence of atrial fibrillation is about 5 percent; in over-80's it is more like 10−15 percent; and per year in the over-80's the stroke rate is upwards of 10−15 percent.

Now, we have had a treatment for the last sixty years in the form of warfarin, which prevents stroke, reduces the risk by 80 percent or so.

[2] Unal B, Critchley JA, Capewell S., *Explaining the Decline in Coronary Heart Disease Mortality in England and Wales Between 1981 and 2000*, CIRCULATION (MAR. 9, 2004);109(9):1101−07. Epub 2004 Mar 1, *available at* https://www.ncbi.nlm.nih.gov/pubmed/14993137.



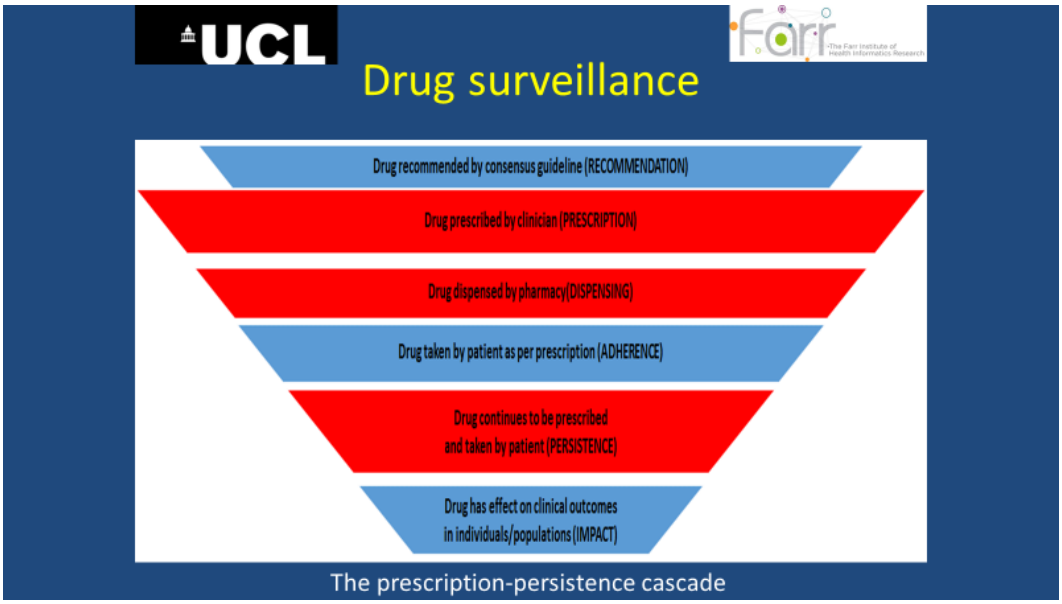
Probably the greatest period of innovation happened in cardiovascular medicine in the last decade, or less than a decade, where we now have four alternatives to warfarin where previously we had no alternative. All of these drugs sound like transformers — Dabigatran, Rivaroxaban, Apixaban, and Edoxaban. They all came, if you look at the year of the published trial, in a four-year period. They are all different chemical entities working in similar ways, all from different companies. They all show either superiority or non-inferiority to warfarin. The National Institute for Health and Care Excellence (NICE) approved all of these drugs on the basis of this trial data.

The problem I have as a clinician is: which one do I use for the patient sitting in front of me? I could use any of them. Do I use the one whose company logo I like best? I might as well. There is certain real-world evidence data to push me towards one or the other in certain subgroups, but there is no head-to-head trial.

I mentioned earlier that in Denmark there actually is a trial happening, called Direct Oral Anticoagulant (DOAC). These are novel anticoagulants. In that trial in Denmark, each hospital is being randomized to one of these drugs. Using electronic health records, publicly funded trials are happening where this trial would not have happened otherwise. So we are going to get this answer of which drug I should be using in the next three-to-four years for a fraction of what that study would cost in the private sector.

By way of secondary use, the route that these drugs have all taken is very interesting. First of all, they prove efficacy in deep-vein thrombosis or pulmonary embolism; then, once that is proven, they move on to do trials in atrial fibrillation to see if they can prevent stroke.

Some of these compounds, for example Rivaroxaban, have proven efficacy in acute coronary syndromes, such as heart attacks and myocardial infarction. Three have been tried in patients with prosthetic heart valves, metal heart valves, and they have not been successful in that setting. So there is a done-and-dusted cascade of looking for secondary uses which has emerged with this class of drugs.

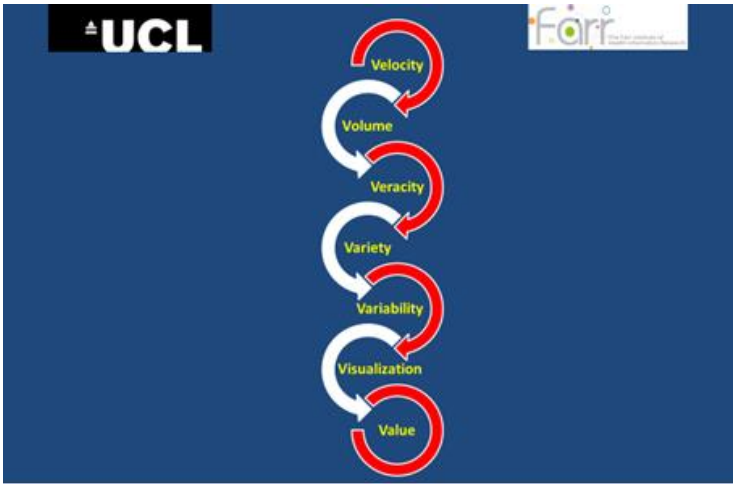


To continue with the theme of drug efficacies in everything, of course when we look at big data and electronic health records, we have to remember this cascade, what I call the prescription-persistence cascade.

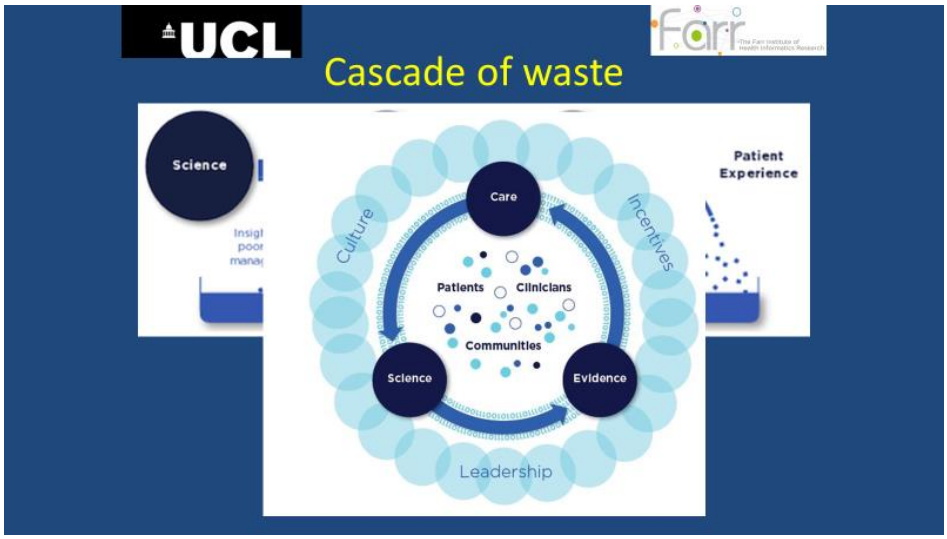
A guideline on the basis of drug efficacy will recommend use of a drug; then I will prescribe it; and the patient will go on and get that drug dispensed in the pharmacy.

They may or may not take it as prescribed. Any of you who have taken a course of antibiotics know how easy it is to miss a dose. Most of the dugs that I dish out are for life, so you can imagine adherence is a big issue. After a heart attack, adherence for all drugs is about 50−60 percent, regardless of health system. That is how many people are taking their drugs at one year.

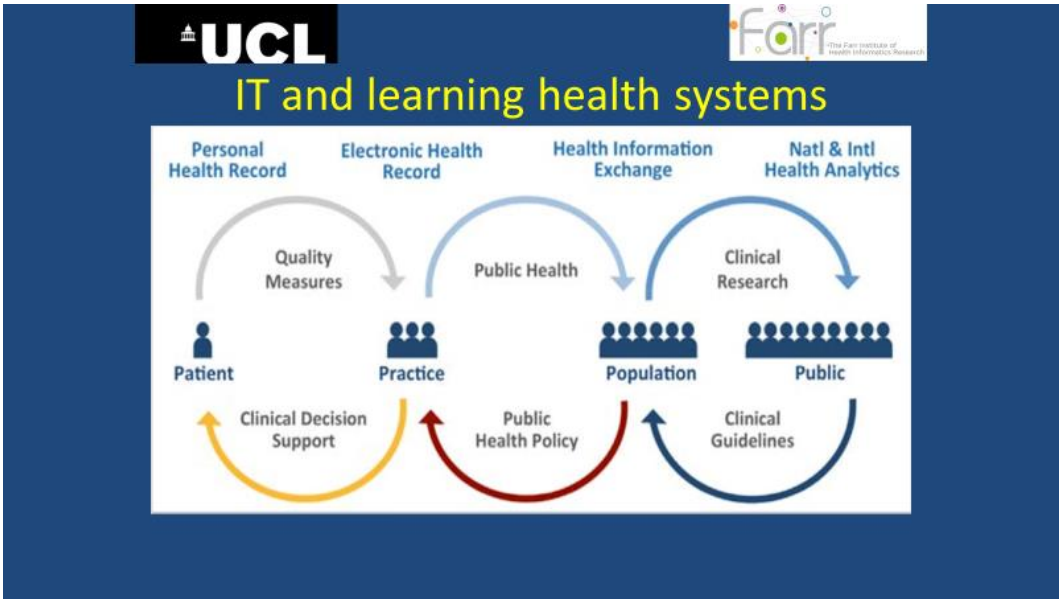
Persistence is whether you continue, and impact is what we call "effectiveness."



This is big data, the circles, the "Seven V's." People have talked about big data for quite some time. It has become a very sexy topic again, but it is because there is speedier data; there is more of it; it is of variable formats; and, if it is gathered well, then it can be of substantial value.



This is the problem at the moment. This is from the National Institute of Medicine's 2007 report[3] showing that at every stop of this cascade there is wastage: 80 percent of science does not reach guidelines; 80 percent of guidelines are not followed in healthcare, which leads to poor experience for patients and, worse, poor patient outcomes.



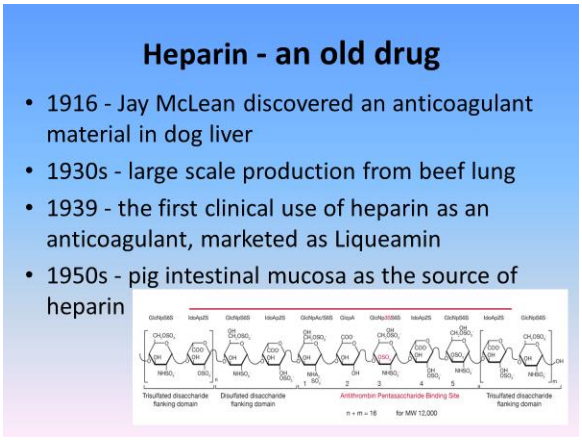
They suggested that this is what we should be doing. The learning health system has to be driven by better data collected at every stage, including data about drugs. Only then can we really get to where we are talking about, having prescription data with indication. That has to be in the context of personal health records, electronic health records, and national analytics, which then feeds back.

Thank you very much.

[3] *See* National Institute of Medicine, http://www.learninghealthcareproject.org/index.php.

PROF. SHUTE: Good afternoon, everybody. My name is Janis Shute. I am a Professor of Respiratory Pharmacology at the University of Portsmouth and, as Simon mentioned, I am Scientific Director of Ockham Biotech Ltd.

Like 95 percent of life science companies in the United Kingdom, Ockham Biotech is a small-to-medium-sized enterprise. It was formed to commercialize and develop repurposing heparin for inhalation and obstructive airways diseases: first, in patients with cystic fibrosis, which is an orphan disease, and in Europe that means that it affects 1 in 2000 of the population; and, second, in chronic obstructive pulmonary disease (COPD), which is on a scale at the other end of the spectrum, where the World Health Organization estimates that about 10 percent of the world population has COPD. I would like to use this short presentation to give a snapshot of this project and where we have got to so far.



Heparin is an old drug. It is a centenarian, so older than Graham's bisphosphonates but younger than the aspirin we heard about earlier on. It is widely used intravenously as an anticoagulant.

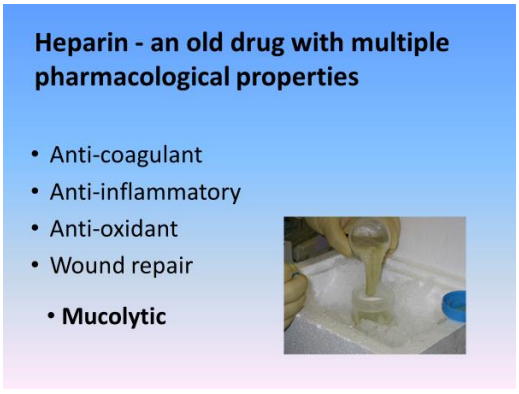
It was discovered in 1916 by Jay McLean, a medical student working in Toronto.

To cut a long story short, by the 1930s large-scale production of heparin was produced from beef lung.

1939 saw the first clinical use of heparin as an anticoagulant in the form of Liquemin, a beef lung product.

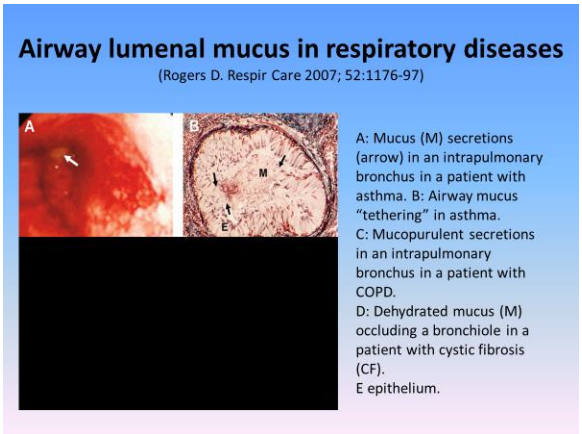
Beef lung became widely used for pet food and there was a shortage, and in due course the source of heparin changed to pig intestines. Since the 1950s, pig intestinal mucosa is the source of heparin and hundreds of millions of tons of heparin are produced globally every year from pig intestines.

Heparin is a rather unique molecule. It is made up of linear carbohydrate polymers. It has a highly diverse molecular structure, randomly sulfated, and highly negatively charged. These biochemical properties alone mean it is a unique molecule. It cannot be chemically synthesized, so heparin is a natural product of natural origin and a true biologic.



Sir John Vane pointed out that the specificity of a drug decreases over time. Heparin is an old drug with multiple pharmacological properties that go beyond the anticoagulant properties it was first described with. We know that heparin has, in addition to anticoagulant properties, anti-inflammatory, antioxidant, and wound repair properties. It was while I was

doing some research on the anti-inflammatory properties of heparin in patients with cystic fibrosis that I noticed by chance an effect on mucus thinning.

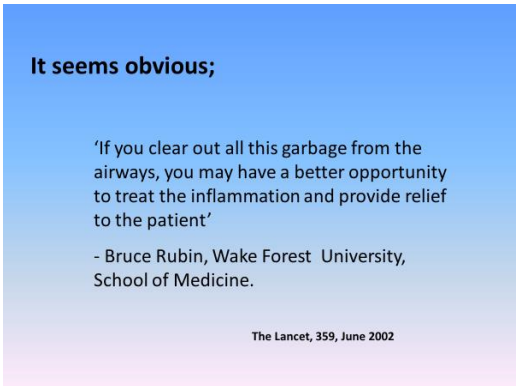


This picture illustrates the fact that in patients with cystic fibrosis their airways are obstructed by large volumes of dehydrated mucus. They produce about 25 milliliters of this material every day, and the lungs may be filled with about 150 milliliters of mucus. And it is a very difficult-to-shift material.

The chance discovery — back to serendipity again — was when I was investigating anti-inflammatory properties of heparin, I noticed that this material was actually thinning. This was a really important observation and led us to consider repurposing heparin for inhalation as a mucolytic.

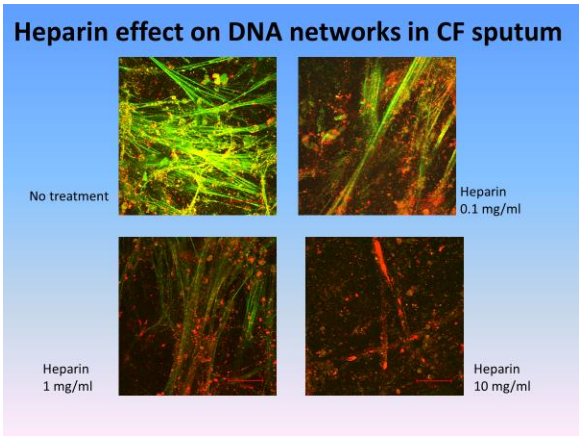
The potential benefits of an inhaled mucolytic, such as inhaled heparin, is not limited to patients with cystic fibrosis. This slide illustrates mucus obstruction of the airways. A is a large airway in a patient with asthma obstructed by mucus; B is a small airway from a patient with asthma with mucus tethered to the epithelial cells lining the airway; C is a large airway from a patient with COPD filled with mucopurulent sputum; and in D you can see dehydrated mucus filling a small airway in a patient with cystic fibrosis.

Of course, this mucus does not just obstruct air flow, but it invites infection and inflammation, and, apart from that, it restricts the delivery of other inhaled drugs. So whether your drug is an inhaled corticosteroid or a bronchodilator, the target cells for those other drugs lie underneath a barrier of mucus and have to penetrate through to the target cells underneath.



It seems obvious then that if you clear out all this garbage from the airways you may have a better opportunity to treat the inflammation and provide relief to the patient. This is where we saw the therapeutic opportunity for inhaled heparin.

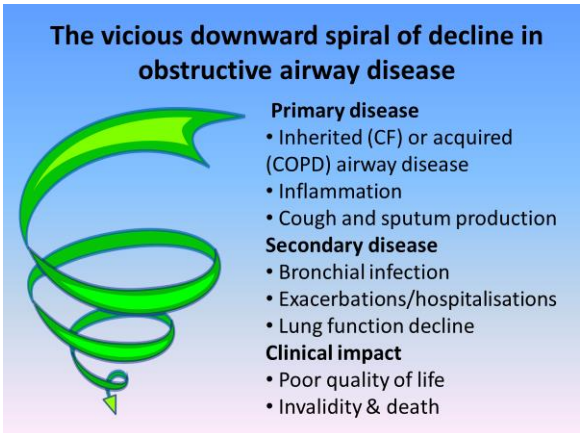
Ockham has been granted patents around the use of inhaled heparin in these diseases both alone and in combination with other drugs. So we went on to investigate the nature of the garbage that heparin was shifting as a mucolytic.



This slide illustrates the makeup of sputum in a patient with cystic fibrosis. What you can see here is the sputum is filled with the debris of the inflammatory response. These green fibers represent extracellular DNA released by inflammatory cells dying in the airway. The DNA is forming a three-dimensional molecular sieve, and this is the barrier to the diffusion of other inhaled drugs. And, apart from that, DNA supports the growth of bacterial biofilms and it also increases elasticity of sputum, so it makes it very difficult to cough and clear these secretions. So there are a number of reasons why you would want to get rid of DNA.

When we added heparin *ex vivo* to sputum samples in the laboratory with increasing concentrations, the results were really astonishing. We could see that the DNA bundles were disaggregating and the DNA was disappearing. We were able to show that this reduced the elasticity of the material and it had properties of a material that could be easily cleared by a cough.

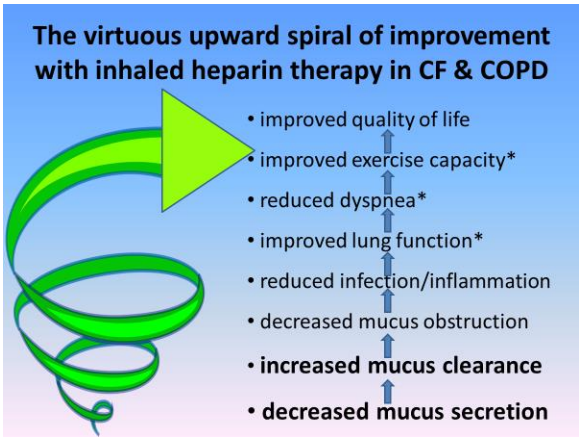
So now we had a mechanism for the mucolytic effect of inhaled heparin. We are now redefining the units of heparin activity in terms of mucolysis instead of anticoagulation.



A vicious downward spiral of decline has been used to describe the disease progression in both cystic fibrosis and COPD. Inflammation in the airways in patients with cystic fibrosis is inherited as a defect in the cystic fibrosis transmembrane conductance regulator (CFTR) protein. In COPD inflammation is triggered by smoking or other irritating factors.

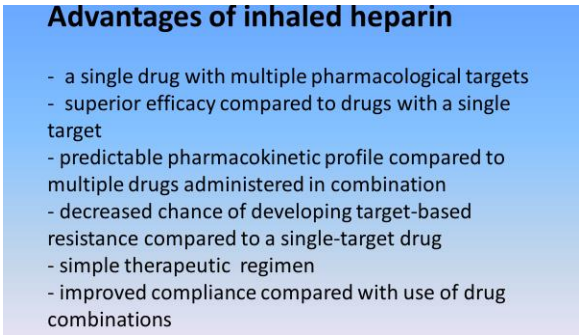
Inflammation stimulates excessive coughing and sputum production, and this hypersecretion of sputum is a feature of both cystic fibrosis and COPD.

Sputum, in turn, leads to repeated episodes of bronchial infection, severe exacerbations leading to hospitalization, and lung function decline. This spiral impacts on quality of life and leads to invalidity and death.

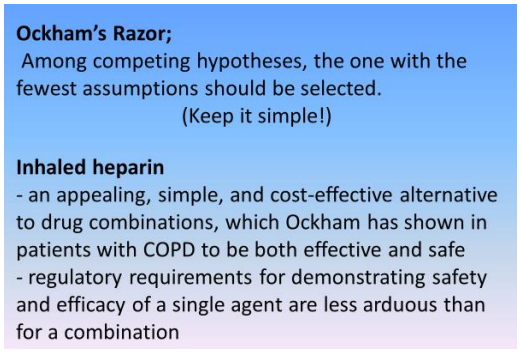


Conversely, we propose that the multiple pharmacological effects of heparin lead to a virtuous upward spiral of improvement in lung function. The direct effects of heparin, starting down at the bottom, are: decreased mucus secretion and increased mucus clearance; reducing mucus obstruction of the airway and reducing the opportunity for infection and inflammation lead to self-amplifying cycles of improved lung function, reduced breathlessness, improved exercise capacity, and improved quality of life.

Importantly, we have conducted a Phase II clinical trial of inhaled heparin in patients with moderate to very severe COPD. Over a twenty-one-day treatment period, we measured clinically significant improvements in these features: improved lung function, reduced breathlessness, and improved exercise capacity.[4]



This suggests that there are a number of advantages of using inhaled heparin, a single drug with multiple pharmacological targets — listed here — with superior efficacy compared to drugs with a single target. Heparin is targeting a network of mediators of inflammation in the airway. It is likely to have a predictable pharmacokinetic profile compared to multiple drugs if these were administered in combination. There would be a decreased chance of developing target-based resistance compared to a single target drug. Clearly, a simple therapeutic regimen is possible, and patients are likely to have improved compliance compared with the use of drug combinations if a single drug with multiple effects was on offer.

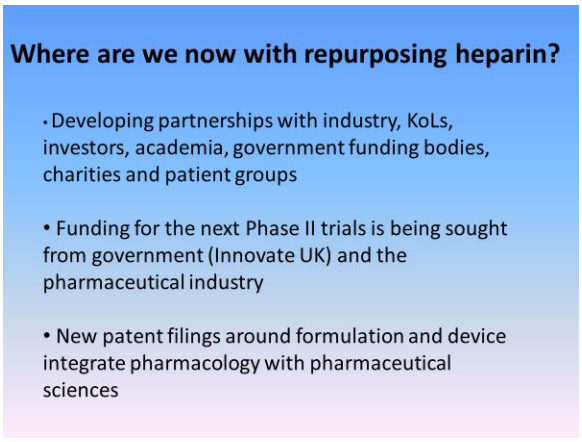


The company I mentioned at the beginning, Ockham Biotech, is named after Ockham's Razor, and this statement I have just shown here: "Among competing hypotheses, the one with the fewest assumptions should be selected." In other words, keep it simple.

[4] Janis K. Shute et al., *Inhaled Nebulised Unfractionated Heparin Improves Lung Function in Moderate to Very Severe COPD: A Pilot Study*, PULM PHARMACOL THER. (Feb. 2018) 48:88−96, *available at* https://www.ncbi.nlm.nih.gov/pubmed/28986203.

We believe inhaled heparin is an appealing, simple, cost-effective alternative to drug combinations, and which Ockham has shown in patients with COPD to be both effective and safe. No study in which inhaled heparin has been tested — studies in patients with asthma, cystic fibrosis, COPD, idiopathic pulmonary fibrosis, burns injury — has ever indicated adverse effects or effects on systemic coagulation.

Further to that, the regulatory requirements for demonstrating safety and efficacy of a single agent are less arduous than for a combination.



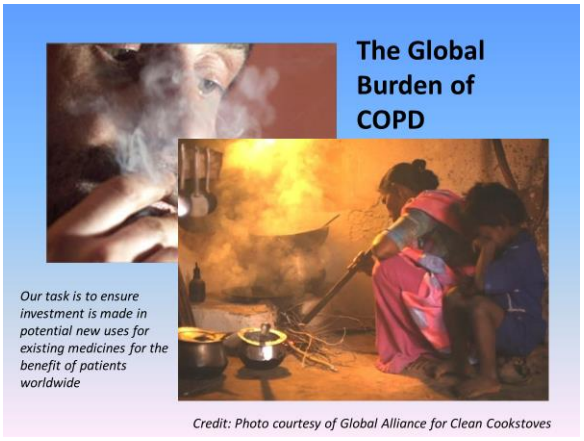
Where are we now with repurposing heparin? Well, to get across the Valley of Death we are developing partnerships with industry, key opinion leaders, investors, academia, government funding bodies, charities, and patient groups.

Funding for our next Phase II trial, which will be on cystic fibrosis, is being sought from the government. Before I left the United Kingdom this week, I submitted a bid to Innovate UK for our next trial in patients with cystic fibrosis.

We are also approaching the pharmaceutical industry. And I should have included charities, because the Wellcome Trust have invited an application for funding the next clinical trial.

Because delivery of heparin to the airways requires a novel formulation in a specific device to achieve the dose we want in the airway, our recent published patent is based around a combination of formulation and device. So we are integrating pharmacology with pharmaceutical science.

At the end of the day, the task for all of us is to ensure that investment is made in potential new uses for existing medicines for the benefit of patients worldwide.



I mentioned the global burden of COPD. It is enormous. While cigarette smoking is strongly associated with COPD, we now recognize that in developing countries COPD is strongly associated with indoor pollution and, in particular, cooking over open wood fires indoors, affecting the lungs and the health of mothers and their children, as you can see in this image.

More needs to be done to bring medicines to these underserved populations.

Thank you very much.

PROF. LAWRENCE: Hi. I am Jayne Lawrence. I have been asked to give the pharmacists' perspective. As was said before, I am actually a pharmacist. However, I dread to think how many years ago I actually stood in a pharmacy dispensing a medicine, so if you do come in one and see me standing there dispensing, you should run a mile.

Just a little bit about pharmacists. I am obviously going to give a UK perspective because I am from the United Kingdom.

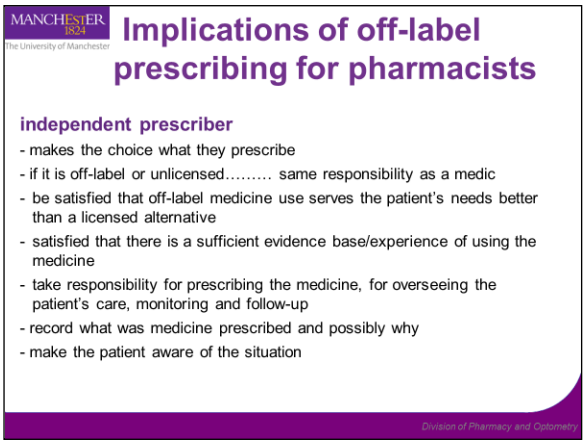
There are about 45,000 UK pharmacists. The vast majority of pharmacists work in community pharmacies and in hospitals and will do what we have been talking about so far today, that is dispense medicines. However, pharmacists are increasingly found in other areas of the healthcare system. For example, they may be found working in GP surgeries where they may take on a prescribing role and will be involved in ensuring that patients are given the most appropriate medication. They may be also found in accident and emergency departments in hospitals.

The roles of pharmacists, certainly in the United Kingdom, are fast changing and they are taking on much more of a prescribing role. This has been the case in the United Kingdom since 2006, with about 10 percent of registered pharmacists in the United Kingdom being able now to prescribe medicines.

Let's go back to the more traditional role of the pharmacist, the one we are all very familiar with, that is dispensing medicine in a community or in a hospital pharmacy.

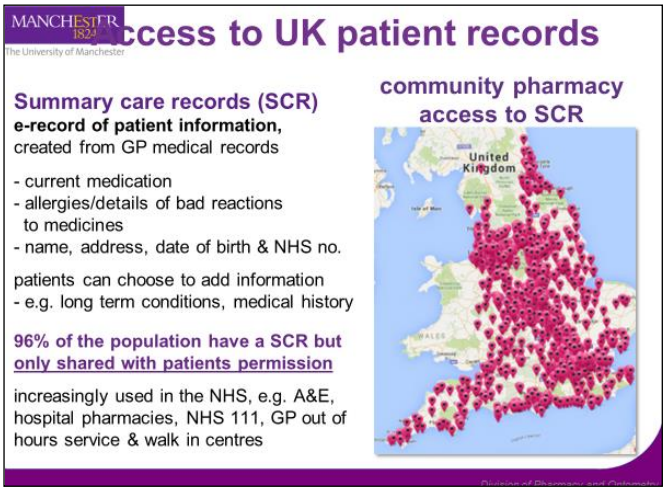
As has been said today, pharmacists, particularly community pharmacists, often unknowingly dispense medicines off-label. You should also realize that in hospital pharmacies it is increasingly no longer pharmacists who are dispensing medicines but actually highly trained pharmacy technicians.

Regardless, there is an obligation on the pharmacist to ensure that if a patient is using a medicine off-label, that patient has given their informed consent to take that medicine off-label. That is something I am going to come back to in a minute.



Let's now look at the role of prescribers. Pharmacists are not the only "independent prescribers." Optometrists, dentists, and podiatrists now, after appropriate training, have the ability to prescribe medicines in certain cases — obviously in the case of optometrists they can prescribe medicines for eye conditions. It is the responsibility of the independent prescriber, just as there is of any medic, to ensure that an off-label medicine prescribed better serves the patient's needs better than any licensed alternative.

The prescribers also have to satisfy themselves that there is a sufficient evidence base to use the medicine off-label. Additionally, the prescriber should take responsibility for checking that the patient using the off-label medicine is okay: following them up, monitoring them, etc.; recording why that medicine was prescribed; and also obtaining patient consent to ensure that the patient is aware that they are taking a medicine off-label. The vast majority of patients know that medicines have been through a rigorous regulatory process, but they might not realize the reason they are being given that drug is not one that the medicine has been authorized for.



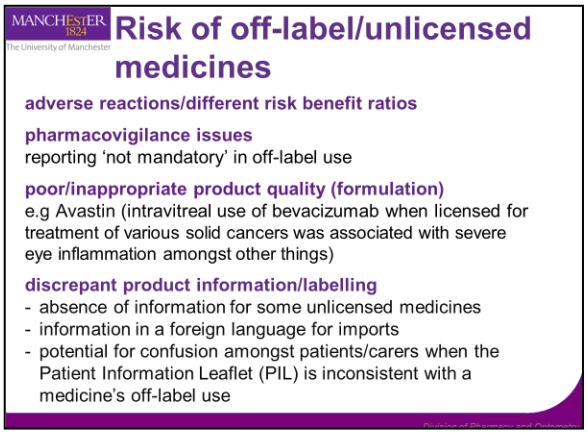
We spoke before about having indications on prescriptions, and that certainly would be an advantage. But until we do get decent healthcare records the situation is never going to be ideal. Unfortunately, in the United Kingdom, although government has tried, we have not managed to get a unified patient record system.

Currently, pharmacists can access what is known as the NHS Summary Care Record (SCR), an electronic record that is created from GP medical records. This is the most complete record available for a patient, and it will detail current medication, any allergies, any bad reactions to medicines, and some basic information about the patient.

It does not give any indication of disease, so the pharmacist does not know why any particular medication is being prescribed, although patients can add that information themselves if they wish. It should be noted that even if a diagnosis is present it does not necessarily mean that the pharmacist will know the reason

why a particular drug has been prescribed.

But, more importantly, the pharmacist can only access that information if the patient has allowed them to do so, i.e. given their informed consent; the patient can deny them access. That is the current situation, and it goes back to what we were talking about before, i.e. whether or not patients allow the sharing of their records.



It is worth just thinking for a minute — I do not think we have addressed this so far — about the risk of giving patients unlabeled/ off-labeled medicines.

Professor Breckenridge mentioned earlier that the risk-benefit ratio may change in the case of a medicine being used for an indication for which it has not been licensed.

In addition, there are issues around pharmacovigilance. Increasingly in the United Kingdom patients are being encouraged to record and report to the Medicines and Healthcare Products Regulatory Agency (MHRA) any counter-indications through the yellow card system. It might be that a patient will ask the pharmacists to help them fill in the record, or perhaps fill in that record on their own, regardless if the patient does not know they are being given an off-label medicine. This may cause a variety of problems with pharmacovigilance monitoring of the medicine. Now, that is not the only problem encountered with the pharmaco-vigilance of off-label medicines, but it gives you some idea of the complications that can be encountered with off-label use.

Another example of a complication is a formulation might be inappropriate for the indication for which it is being used off-label. Avastin is the classic example of this; namely, Avastin is a formulation developed for intravenous use that is being injected into the eye. Such off-label use has caused problems with some patients. In this example we need to ensure that the type of formulation being used is appropriate for its intended off-label use.

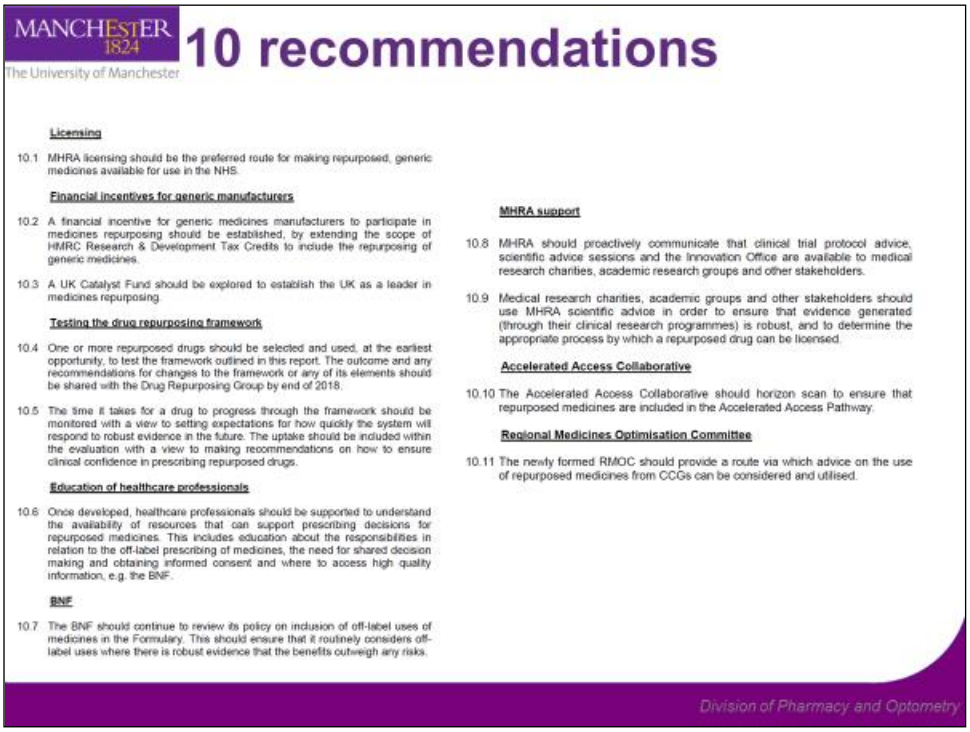
Another very practical problem is not having an appropriate patient information leaflet that the patient can read. I have had to stand in a pharmacy in the past and explain to patients why the patient information leaflet is totally inappropriate for the indication they are taking the medicine for. I have had cases where patients have been given medicines in the United Kingdom and been told to Google and find the equivalent patient information leaflet in the United States because in the United States the drug has been authorized for the use for which they have been given it. This situation is really confusing to patients and does not really give them confidence in using the medicine the way they should.

I am just going to mention a report that was fairly recently produced in the United Kingdom.[5] Some of you may have come across this. This report followed

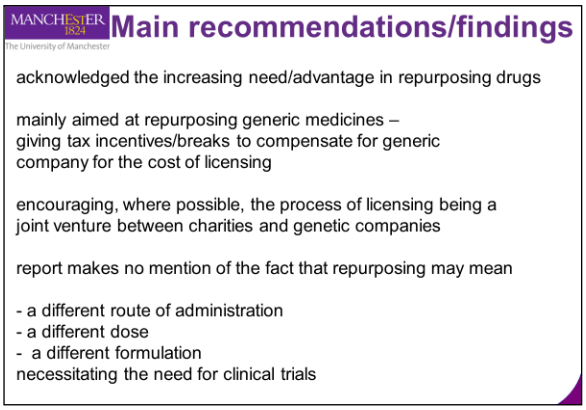
[5] ASSOCIATION OF MEDICAL RESEARCH CHARITIES, FACILITATING ADOPTION OF OFF-

some very controversial bills that Lord Saatchi was trying to push through Parliament. The report was produced under the auspices of the Association of Medical Research Charities (AMRC) and was trying to develop a pathway to facilitate the adoption of off-label medicines.

Many of the major stakeholders in medicines in the United Kingdom were involved in the production of this document: NHS Health, the Medicines and Healthcare Products Regulatory Agency (MHRA), the National Institute for Health and Care Excellence (NICE), the Association of the British Pharmaceutical Industry (ABPI), and the Generic Manufacturers Association, among others.



The report came up with ten recommendations for developing a pathway to help facilitate the off-label use of medicines.



I will not go through the report's recommendations in detail but in summary:

• The report acknowledged there was an increasing need and an advantage in repurposing drugs.

• It talked about trying to get charities to put up the money to help with the clinical trials, and working with the manufacturers of generic medicines to achieve this goal.

PATENT, REPURPOSED MEDICINES INTO NHS CLINICAL PRACTICE (December 2017), *available at* https://www.amrc.org.uk/sites/default/files/doc_lib/Drug_Repurposing_Report.pdf.

• It proposed that the manufacturers of medicines be given tax break incentives to compensate for being involved in the cost of licensing for the generic and for the off-label medicines.

So far we have been talking very much about repurposing, taking a medicine that is on the market and using it for something else, but what we are talking about is far bigger than that. We might be talking about a different route of administration or a different dose of that drug. The classic example that has been mentioned here is aspirin. The dose of aspirin for pain relief is 300 milligrams, but for prevention of stroke it is 75 milligrams. Aspirin is just one example of different doses of the same drug being used to treat different conditions. In some cases repurposing of a drug may mean administration via a different route, thereby necessitating a different type of formulation.

We have been talking about costs, but in some cases the costs in making a medicine of a different dose or a new formulation for administration via a different route so the cost of repurposing may be a lot higher than we first think, and may also necessitate quite extensive clinical trials.

Hopefully, I have given you a slightly different perspective on things. That is the perspective of the pharmacist.

Thank you.

MR. SPINK: Thank you very much, Jayne.

Thank you very much for all three presentations.

We have about twenty minutes left for questions. I have a couple that I want to kick off with and then I am going to throw it out to the audience.

Starting off with the first question to the prescribers on the panel: What would be the primary objection of a prescribing doctor to recording the indication on a prescription?

DR. BANERJEE: My poor handwriting, first. [Laughter]

I do not think there is any objection. I think we are all limited in time. If it was mandated, then we would do it. I cannot organize a scan for a patient without saying why I am doing it. I absolutely agree it should be there.

PROF. RUSSELL: Well, I trained in the last century. We had to write down that information on any prescription. Also, when requesting any lab test, if you did not provide the clinical information, they would refuse to do it.

Maybe people have become lazy, busier. I do not know what it is.

Obviously, there is a privacy issue, which, like many modern things, is probably not to be encouraged.

MR. SPINK: In terms of the privacy issue, is the danger there that a name and an indication appear together on a prescription which could be lost; or is it more the fact that the prescription is going to go to another data controller in the pharmacist?

PROF. LAWRENCE: When somebody comes into a pharmacy, they automatically assume that the pharmacist knows what the prescription is for. I think most of the public do not have a problem with this because the assumption is that the pharmacist already knows.

QUESTION [Prof. Robin Jacob, University College London]: Since most medicines do not have second uses still — I suppose I may be wrong about that

— but if they only have one use, when you tell the pharmacist "I take trundleamine" — which is the name we always used to use in chambers for a patented chemical; it was named after the patented device, which was called a "trundle-humper" — the pharmacist will know what the patient has because this medicine only has one use.

DR. BANERJEE: From a data angle, I think the privacy argument is, frankly, a total red herring. If you accept that dispensing is part of the healthcare process, then you are no more likely to have data insecurity when you have your medication dispensed than when you come to see a cardiologist, for example.

QUESTION [Rian Kalden, Senior Judge, Court of Appeal, The Hague]: In the Netherlands we also have a huge dispute about the electronic patient files, as we call them. I think the main concern of most patients is that this information gets to the insurers, because as soon as it gets to the insurers they obtain information about raising your premiums, or even refusing to insure you. I think the concern is not so much that it actually is known by the pharmacist —

DR. BANERJEE: It is how it will be used otherwise.

QUESTIONER [Judge Kalden]: — but that it gets into a computer and then finally it comes on the insurers' desks. I think that is a serious concern.

DR. BANERJEE: In the United Kingdom, the Wellcome Trust commissioned a large study that was published early last year on the back of a failed program called Care.Data, which was trying to get patients to use an opt-out system for their GP practice records in the United Kingdom.[6] So it was assumed that your electronic data could be usable.

That survey — I believe it was of 20,000-plus people — showed that people's biggest concern was what you say. They did not mind their data being used for their healthcare or for research, even if it was not anonymized, but they were worried about it being sold on to somebody else. I think that is a real concern. I guess we need to have regulations about that.

Also, there are bigger issues now with non-healthcare data, whether it is social media or my credit card or the loyalty points that I collect at the supermarket. All of that data, particularly if I am using over-the-counter pharmaceuticals, can lead back to my personal health information as well, which is being sold on. So it is not just health information.

PROF. RUSSELL: I have an example which I heard about recently where linking the indication to the drug actually alerted people to a potential problem.

We mentioned earlier a drug that is an alternative to bisphosphonates, called denosumab, which is an Amgen drug. It is an antibody to receptor activator of nuclear factor kappa-B ligand (RANKL), which in some respects is analogous to and resembles the antibodies to tumor necrosis factor (TNF) used to treat rheumatoid arthritis. Denosumab is a very effective way of inhibiting bone destruction, and is used in osteoporosis and cancers.

The antibody is given to patients every six months. If you do not give the second dose, the bone resorption increases and it even overshoots the value that you started with. This appears to have been associated with a measurable increase

[6] *See* Welcome Foundation, https://wellcome.ac.uk/what-we-do/our-work/our-policy-work-using-patient-data-research.

in fractures in people who stop treatment inadvertently. Here we have an example of a drug that you have to be 100 percent compliant with, because if you are not, you may end up worse off than not having taken it at all. This survey of prescriptions for osteoporosis and denosumab showed that 15 percent of the treated population never took the second dose.

It is these sorts of things which alert you to real iceberg problems that are going to come and haunt us if we do not deal with them. So the message is you have to go out and encourage compliance in a much more vigorous way than has been done until now.

MR. SPINK: We have another question.

QUESTION [Dr. Solanki, Accord Healthcare]: I have one question each for Dr. Banerjee, Prof. Shute, and Prof. Lawrence. I will start with Dr. Banerjee. I will pose all three questions so you can answer, since I have only one chance.

Dr. Banerjee, this is something paradoxical I am asking. You were discussing the scenarios leading to the failure of the drug development programs because of the missed opportunities. Now, at the same point in time, we were discussing how a physician more often than not ends up with a confusing scenario for a drug like Rivaroxaban, which is mainly used for having BNP from effects in patients who have a history of sustaining myocardial infarction. So it is a life-saving scenario for the use of that kind of a drug.

Now you have four options available and to pick up a particular drug at times becomes difficult. The point also is raised with regard to the regulators' perspective because most of the companies, the originators, do their Phase III confirmatory trials against placebo and they are successful in introducing the drug in the market. Had they picked up the two competitors' products, they would have truly been able to present a comparative picture of how their newly discovered molecule compares in terms of efficacy and safety against already approved agents and whether it is really scoring over those competitors, so as to enable the regulators, and finally the prescribers and the consumers, to understand that yes, this particular new drug discovered by the company is a very good and effective alternative to the existing competitors.

DR. BANERJEE: So the question is whether we should have placebo trials or not?

QUESTIONER [Dr. Solanki]: Yes.

DR. BANERJEE: In these four novel anticoagulant trials, it was against usual care, which was warfarin. It was not against a placebo. It would have been unethical to do a placebo trial in that setting.

QUESTIONER [Dr. Solanki]: Not for this scenario, but for other scenarios. I am told this is lifesaving and we are looking for long-term prospects.

DR. BANERJEE: I think for a trial where there is an accepted usual care no ethical committee would allow you to have a placebo.

QUESTIONER [Dr. Solanki]: I would cite an example of an allopathic drug, like recombinant human parathyroid hormone, where a trial was done against placebo and the endpoint was to see the incidence of fracture. That was not considered unethical and the drug was approved against placebo.

DR. BANERJEE: I do not know that particular example, but I would say that is quite unusual. In general, these trials have to be against usual care. The difficulty is that all four of these agents gave positive results.

QUESTIONER [Dr. Solanki]: Do you feel that actual competitors should be considered Phase III conformity trials?

DR. BANERJEE: Yes, I do.

QUESTIONER [Dr. Solanki]: You have not had a placebo, but an additional actual competitor must be there.

DR. BANERJEE: To get Phase III as near to the real world as possible, you need as representative a patient population as possible and you need to compare it against as realistic a choice of treatment as possible. If usual care involves another drug, then that should be there.

QUESTIONER [Dr. Solanki]: Fine. Thanks.

Prof. Shute, first of all, congratulations for having done brilliant work.

PROF. SHUTE: Thank you very much.

QUESTIONER [Dr. Solanki]: How did you think of utilizing inhalation as the route of administration for heparin? How did you deal with that?

PROF. SHUTE: For the Phase II clinical trials we conducted in both cystic fibrosis and COPD, we used nebulized heparin, so heparin was reformulated to be delivered from a concentration to give the correct lung dose. We have used different nebulizers in different studies. Moving on, we are working now with the new state-of-the-art type of nebulizer.

No study has shown that heparin will cross the bronchial mucosa or have any effect on systemic coagulation. Again, there is a hundred years of data on how heparin is used as an anticoagulant. Different routes of administration were tested, including inhaled and rectal. Those old studies told us what we would expect to see in terms of the distribution of the drug and that the inhaled drug stays in the airway compartment.

QUESTIONER [Dr. Solanki]: Thank you.

Prof. Lawrence, you were referring to the problem that took place with the off-label uses of denosumab (Avastin). If we look at the recent decisions taken by some of the regulatory authorities in Europe, like l'Agence Française de Sécurité Sanitaire du Médicament et des Produits de Santé (AFFSSAPS) in France, Agencia Española de Medicamentos y Productos Sanitarios (AEMPS) in Spain, and in some other countries, they finally found it benefited the patients because of the issue of ophthalmic infections. This was raised very strongly by the originator of ranibizumab, the Lucentis product from Roche, the cost of which was kept very high because of that discovery. But later on the doctors, especially oncophysicians using bevacizumab very often for soft tumors, realized that this particular drug is also effective against macular degeneration, the ophthalmic problem for which ranibizumab was developed.

In terms of pharmaco-economics, the cost becomes much lower. And, if you look at the historical data of the usage of ranibizumab, even by an expert and experienced retinal surgeon, the incidence is equally high. It is not that this particular use of Avastin had led to the particular problem.

So how do you now see the scenario, once the regulatory authorities in Europe have allowed this particular usage of Avastin?

PROF. LAWRENCE: I cannot talk about other authorities. I just know that in the United Kingdom it was not recommended by NICE. As a consequence, there may be a lawsuit against the NHS for allowing this situation to occur because the drug had been approved through various UK regulatory processes and it was going against the license. That is the latest situation I know in the United Kingdom.

That probably did not answer your question.

DR. BANERJEE: I think Alasdair can comment on this.

MR. SPINK: And we have a question from James Horgan as well. We will go to James and then Sir Alasdair.

QUESTION [James Horgan, Head of European Patents, Merck Sharp & Dohme]: I am actually heartened by the things I have heard from the panel in relation to second medical use patents, in that from a medical and clinical perspective you actually think it is entirely rational to have indications as part of good practice on prescriptions. Clearly, from some of the issues that there have been legally trying to enforce those patents, that would resolve a large chunk of the problems. So there is actually a real meeting of minds going on here.

I think what is missing from the panel — I know there is a panel for payors later — is the European payors — someone from the NHS, for example, who I know has intervened in the *Warner-Lambert* case in a fashion not in support of Warner-Lambert's claims for infringement — who would be able to comment on issues like pricing and what they think of these procedures.

It seems to me that the actual clash that is going on is not so much between physicians, pharmacists, and patentees, because it seem their interests for various reasons can line up. The issue is actually with the people paying. So maybe another time when we have another session or a follow-on conference on this, Sir Robin, you may invite some significant NHS representation to discuss what they think about differentiated payments for different indications.

PARTICIPANT [Prof. Jacob]: We invited the NHS.

QUESTIONER [Mr. Horgan]: Maybe you need to pay their airfare as well.

PARTICIPANT [Prof. Jacob]: I think we offered that. [Laughter]

MR. SPINK: A comment from Sir Alasdair Breckenridge?

QUESTION [Sir Alasdair Breckenridge, Former Chair of MHRA, UK]: Jayne, I have a question for you. As you are aware, in the United Kingdom we all register with our general practitioner. My question to you is: Should we also register with a pharmacist?

I look at the example of the Netherlands where, as you know, you register not only with your family doctor but you register with a pharmacist as well. This has given rise to the PHARMO system. This is a research organization whereby data from the pharmacist, from the GP, and the hospital come together. It has been used for research purposes like some of the ones we are talking about today.

My take on this — and, please, do not take this too critically because I am a big supporter of pharmacy in research — is in the United Kingdom pharmacists

cannot make up their mind whether they are healthcare professionals or businessmen. If we were able to clarify that and make community pharmacists more organized towards being healthcare professionals, we might develop a situation like they have in the Netherlands, which I think is much, much better than we have in the United Kingdom.

PROF. LAWRENCE: That is a really good question. I will try to answer several of those points.

First of all, I think it would be great if patients registered with pharmacists because in that way the pharmacists could actually take much better care of the patients taking the medicines. If there were contraindications, it would be much easier to pick up on that. So I think that would be a great way forward.

With respect to pharmacists doing research in the United Kingdom, there is something called Research Ready Pharmacists. There is a big move among pharmacists in the community to provide services to try to facilitate pharmacies being used for research. I think this is a big advantage as well.

The last point, which is always a big argument, whether a pharmacist is a businessman or a healthcare professional, I think the situation is changing. Some of the blame for the ambiguity undoubtedly lies with the pharmacists, but some of it is due to the way the pharmacists are paid through the UK government.

I do not know if that addresses your questions.

QUESTIONER [Dr. Breckenridge]: I will talk to you privately about this.

PROF. LAWRENCE: That's a no. [Laughter]

MR. SPINK: With that, I see that the gamekeeper has become the poacher and I am running a minute over.

I will say thank you very much to the panel and to the audience for their questions.

[Session adjourned: 4:15 p.m.]

University College London | Georgetown University Law Center

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

Georgetown University Law Center
600 New Jersey Avenue NW
Gewirz Student Center
Washington, D.C.
Thursday, February 8, 2018 – 4:30 p.m.

Session 1I:
The Payor's Perspective: Regulating to incentivize value creation and repair a failed market

Moderator:
Nancy E. Taylor
Greenberg Traurig LLP, Washington D.C.

Presenter:
Dr. David Cavalla
Numedicus, Cambridge, England

Panelists:
Prof. Peter Neumann
Professor of Medicine, Tufts University School of Medicine, Boston

Sergio Napolitano
Director, Legal & External Relations, Medicines for Europe, Brussels

Erik Komendant
Vice President Federal Affairs, Association for Accessible Medicines; Formerly Head of Policy, AHIIP, Washington D.C.

* * *

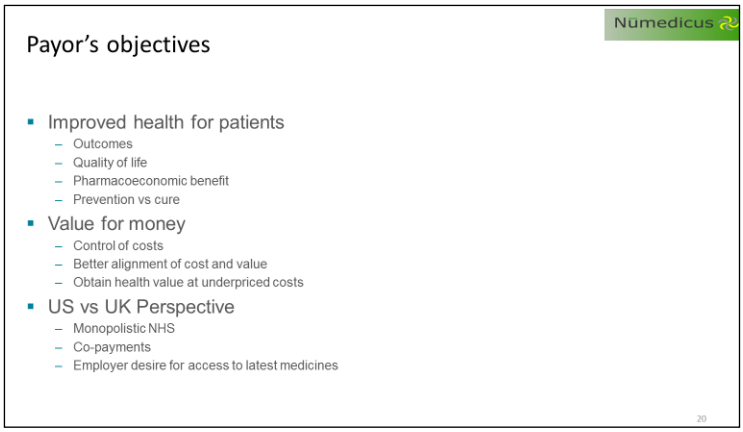
MS. TAYLOR: Hello, everyone. Thank you very much. I promise you this will be an enthusiastic discussion about issues that are affecting many of us here in the United States and in the European Union. We are going to be talking about the payor perspective. Some of this was touched on in the last conversation, and I hope we build on it. The topic of our panel is "Regulating to Incentivize Value Creation and Repair a Failed Market." We will be talking about various aspects that are occurring. I hope you find it very educational.

We have an incredibly good panel. I had a wonderful conversation with them beforehand. We are going to start first with a presentation by Dr. David Cavalla from Numedicus, after which I will introduce our panelists as we do a five-minute follow-up, and then turn to questions.

DR. CAVALLA: Thank you, Nancy, and thank you, Brian and the other organizers, for giving me a chance to say a few words about this.

My background is as a scientist and as an entrepreneur. I am in a room full of regulators, lawyers, and so on, but we do not have many people who can truly say that they represent the payor, except to the extent that, in a sense, we are all payors because systems for healthcare are either paid out of taxes or they are paid out of insurance premiums and, ultimately, they come from people like us. In another dimension, of course, we are all patients, but hopefully not for a while.

I have worked on drug repurposing for about twenty years, and I have come up with new ideas of my own. I have patented them, and some of them are in clinical trials. I have also looked at a whole range of academic ideas that have come from other people. I work with University of Cambridge Enterprise. I can say that in many areas of academic research the new use of an existing drug is one of the first ports of call for somebody looking at biological mechanisms. I feel very strongly that we have a surfeit of repurposing ideas and a deficit of repurposing development. I am very pleased to be able to address that.



Trying to put myself in the perspective of the payor, what do I see as the objectives of the payor? There are really two main objectives.

• To improve the healthcare for patients in terms of outcomes, quality of life; also, to a certain extent, pharmacoeconomic benefit, the ability to make the products work better, and to prevent rather than cure.

• Second, to achieve that in a way that gives reasonable value for money, one would want to be able to control costs and to better align costs and value.

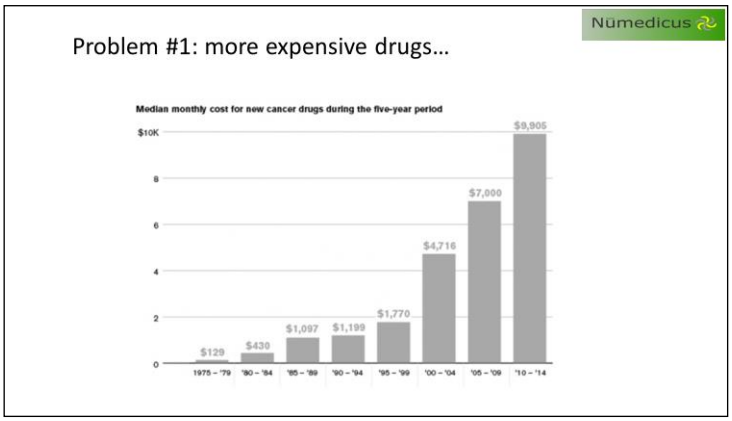
• The third bullet point, "obtain health value at underpriced costs," is not quite what I mean to say. But it is true to a certain extent that some of the things that we are talking about today represent healthcare value that is obtained at underpriced costs. That is my own belief. Perhaps where I was going a little bit too far is saying that is a payor objective, but it is certainly the case that payors seem to be benefiting from the situation. I think that has negative consequences for the payor, as will become evident from this presentation, as well as the more immediate positive consequences.

• I said in the introduction that there were different kinds of payors. I am looking at this from the perspective of the insurance companies in the United States, or in the United Kingdom it would be the National Health Service (NHS) as the payor. Obviously, the United States and the United Kingdom have different perspectives because we have one payor effectively in the United Kingdom and a diversity of payors in the United States.

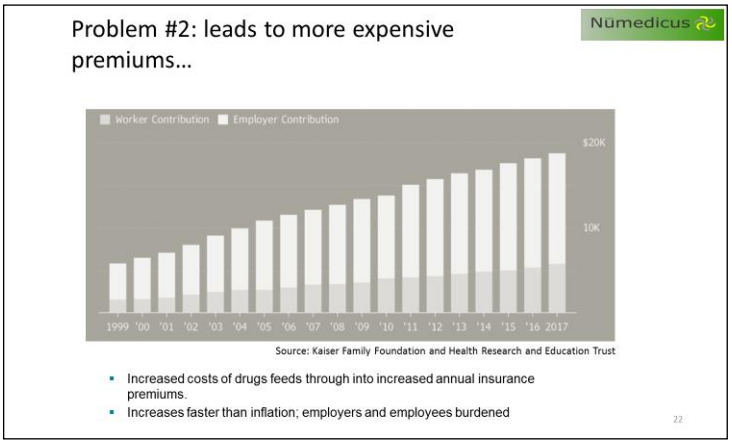
The other difference is that in the United Kingdom patients do not pay for their medicines, apart from prescription charges which are fixed — and many people do not pay prescription charges in any case because they are poor, old, pregnant, and so on — whereas in the United States a significant number of people are required to co-pay, and that makes a difference to the people's alignment.

The other difference, which is more subtle, is that, because of the way things work in the United States, it is in the insurers' interest to try to attract people paying insurance premiums. So if I am an insurer and somebody comes to me and says, "What kind of benefits do you offer in the case of colorectal cancer?" it is in my interest to be able to say to them, "We do cover the latest new drug." This drives more rapid uptake of the latest developments, usually at premium prices. Those kinds of questions lead to a much more active discussion between the insurer and the person paying the insurance premium.

So what are the problems? I lay out four of them.



The first problem is drugs are getting hugely more expensive. In the area of oncology, this is the median monthly cost for new cancer drugs during eight previous five-year periods. And they are increasing by leaps and bounds, much faster than inflation.



These increases feed through in terms of the premiums that patients or their employers are paying. It is not only the increased cost of drugs; other ancillary things related to healthcare are also increasing. But the costs of drugs are a major component.

These increases are much faster than inflation and are much faster than wage increases, and they are becoming increasingly unsustainable.

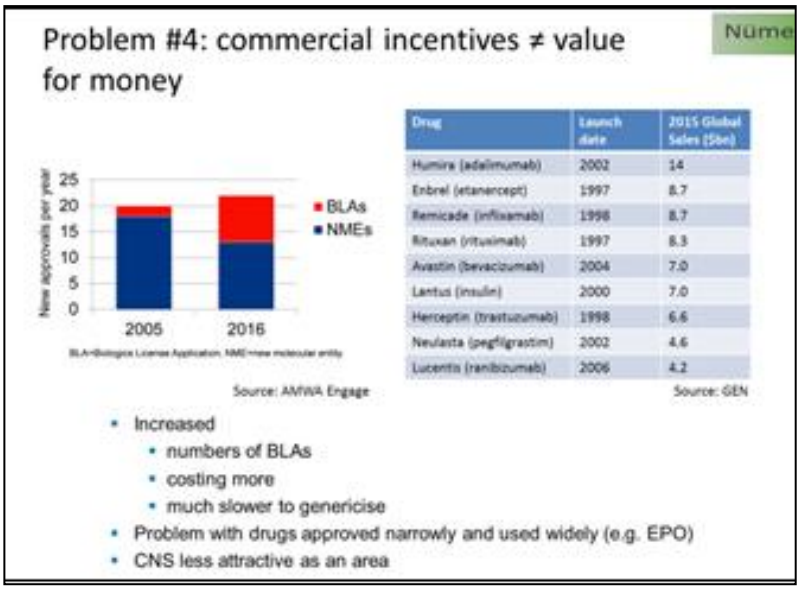
I have seen another version of this graph which is not in terms of actual amounts but is in terms of percentage of wage packets. This percentage effectively has pretty much tripled in thirty years. So if we take another thirty years, when many of us are going to be old and sere, it could be that if the same rate of increase is going on, then the proportion of the wage package which goes into insurance premiums is extremely high.

One of the things that we have been talking about today is that repurposing is a more efficient means of R&D. It reduces time, it reduces cost, and it reduces risks of development failure for new products. And, more than that, it is protectable by secondary method of use patents. That would seem to be a wonderful environment for greater efficiency in R&D.

It is true all of those things are necessary for a more efficient process, but they are not sufficient. The insufficiency revolves around generic off-label substitution. When I see proposals, for instance when I am doing work with the University of Cambridge, I would say at least 90 percent of them fall afoul of that problem; in other words, they do not represent a commercial case for investment. Under those circumstances, there is no — and I mean zero — commercial incentive to spend R&D dollars when your competitor company will not and they will be competing on the basis of price. It is the classic free-rider problem.

What do the pharmaceutical companies do as a result of that? Well, they do not sit idly by and twiddle their thumbs. They invent alternative ways of making money. That leads to a situation where, to paraphrase Henry Ford, "You can have any car you want as long as it's a Rolls-Royce."

We have talked about potentially reducing the costs of new product innovation by a factor of three or four. Effectively we are saying, "New product innovation is three or four times as expensive as it needs to be because that is the only way innovation is commercially viable in pharmaceutical R&D." It is a failed market, and I feel very strongly about that.



As a result of this problem, we see a greater proportion of biologicals and new products being introduced onto the market.

• The first problem is that there are greater numbers of biologicals. In just over a decade, since 2005, the number of Biologics License Applications (BLAs) as a proportion of new medicines has increased by a factor of about four.

• The second problem is that these are very expensive drugs.

• The third problem is that these drugs are much slower to genericize. I have listed here some of the top dozen or so best-selling drugs. There are perhaps a couple of non-biologicals in that top twelve, but essentially biological drugs represent the vast majority of the most highly selling drugs in the world today.

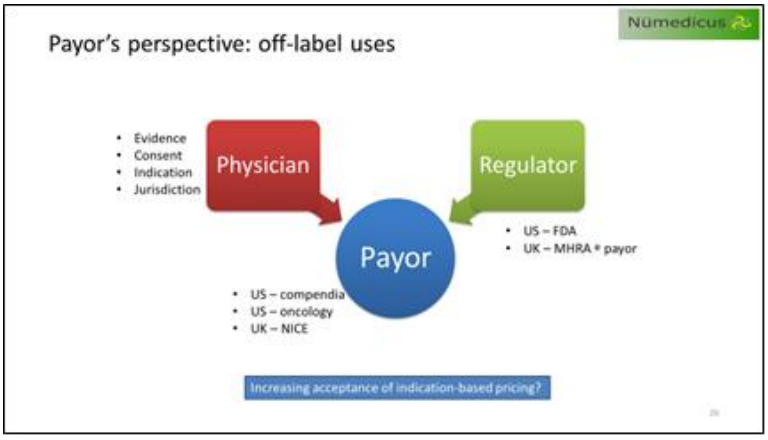
Now look at the launch dates. Some of them go back twenty years, and they are selling $8, $10, $12, $14 billion dollars a year. It is an unsustainable problem which is only going to get worse because the commercial incentive for developing a biological as an alternative to an SME is in favor of the biological. The net present value at the point of instantiation of pharmaceutical discovery for a new chemical as opposed to a new biological is positive for a new biological; it is negative for a new chemical.

Prof. Grabowski talked about the problem of the orphan drugs being enlarged in their market into non-orphan areas. When you have an expensive drug that was designed and priced for a small market that then gets used much more widely, that is another problem.

A particularly unfortunate thing is that biologicals do not penetrate into the brain very well. CNS neurological drugs are a less attractive field of endeavor than peripheral diseases, and that is a problem given how CNS is a bit of a Cinderella area in any case for new products.

When we talk about the penultimate bullet on that list, about things being introduced narrowly and used widely, that brings me to the area of off-label uses. Some of these things were talked about in the previous panel.

The decision to use a drug off-label starts with the physician. That is based on evidence, hopefully in a consenting fashion with the patient, although, unfortunately, off-label prescriptions occur in more cases than they should without consent of the patient. The ethical validity of that decision is based on a composite of the evidence, the indication, and the jurisdiction.

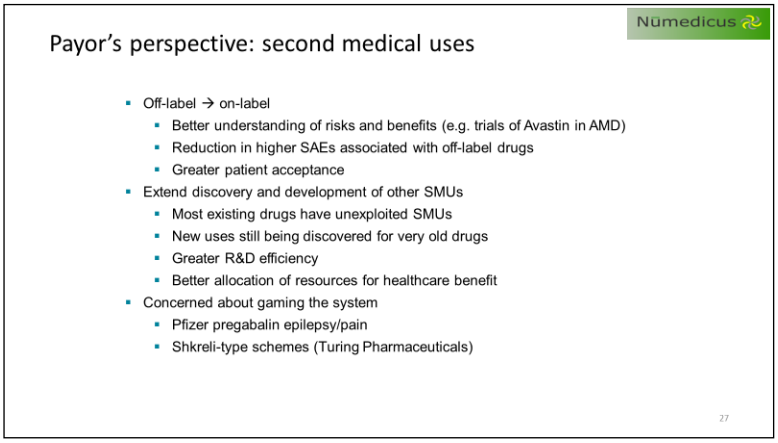


The opportunity to prescribe off-label is more difficult in certain areas of the world. For example, in Germany it is unethical to prescribe in an area where there are existing approved agents, whereas in the United States there is a greater latitude allowing physicians to prescribe off-label even without the consent of the patient.

Then the perspective of the regulator comes into play. In the United States the Food and Drug Administration (FDA) is not allowed to regulate off-label medicine but it is allowed to regulate off-label marketing, and it has been quite vigorous in so doing in the past twenty or thirty years. Whereas, in the United Kingdom and in most other European jurisdictions, where the state in effect partly acts as a regulator and also acts as a payor, there is a difficulty that the pharmaceutical company comes up against in trying to game that system.

Those two factors then feed into the payor. The payor will reimburse the drug off-label according to certain conditions. Regardless of whether or not it has been prescribed, then the decision is whether to reimburse. In the United States that is based on whether or not something is included in a compendium; and, to be included in a compendium requires a certain level of evidence being available. The one area of exception for that is oncology. You can prescribe off-label and get reimbursed off-label in oncology regardless of whether or not that particular cancer is evidenced as long as there is another oncological indication it has been used for.

In the United Kingdom the General Medical Council (GMC) has restrictions about what can be prescribed off-label. Once it has been prescribed, all medicines, up until the National Institute for Health and Care Excellence (NICE) came along, were reimbursed. When NICE came along, the whole landscape changed and a cost-benefit analysis was undertaken with respect to the particular indication. I think this is a game changer for what we are talking about, because if the payor is suddenly saying, "Reimbursement is defined by indication," then I would like to ask whether there is an increasing acceptance of indication-based pricing.



What are the interests of the payor in respect to off-label use?

• First, it is in the payor's interest to migrate an off-label use to an on-label use because you better understand the risks and you better understand the benefits. In many cases, off-label use has very limited amounts of efficacy available to it. And it has also very limited evidence for the risk. Studies that have been done looking specifically at the relative risk of off-label versus on-label show the adverse event rate and the serious adverse event rate, including deaths, for off-label medical use is two-to-three times greater than for on-label use. That is not taking into account the relatively poor level of efficacy that one would assume from off-label medical use.

Another benefit from the payor's perspective is greater patient acceptance.

• Beyond the off-label use that already exists, the second point is how to extend the discovery and the development of other secondary medical uses. I believe that there is an enormous opportunity space for second medical uses which has barely been touched upon. Many of the things we know about have yet to be developed.

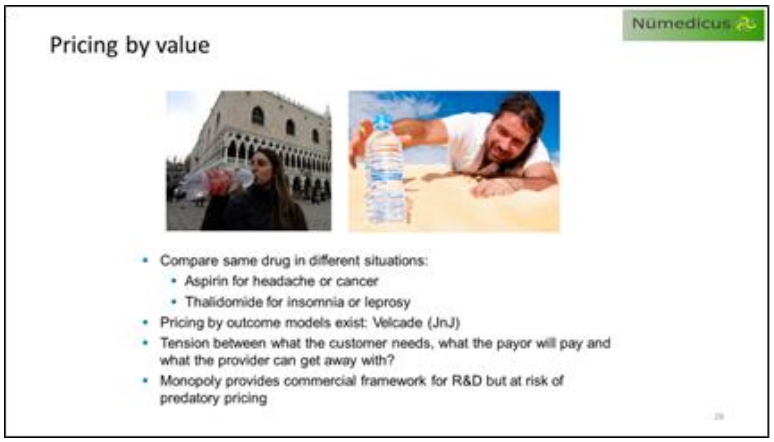
New uses will continue to be discovered because, as I said, in an academic setting academicians love to use existing molecules to exemplify and better understand new biological pathways that they have been working on. Also, this is a better opportunity to allocate resources more efficiently. Given the fact that R&D costs are lower, it is a better way of generating more medicines — as Sir Robin pointed out, to put into the physician's quiver.

• However, the payor is also concerned about any changes to the system which might be gamed. I have a couple of examples here.

We have been talking about the success of the various stories that have revolved around prescribing pregabalin for epilepsy and pain. From the payor's perspective, I think many people would struggle with the idea of a product being available in generic form for epilepsy but not being available in generic form for pain. In that particular circumstance, many physicians that I have talked to regard this as incorrect.

Also, from the payor's perspective, one would be concerned about schemes like those promoted by Martin Shkreli, who was recently imprisoned for fraud.[1] He operated Turing Pharmaceuticals here in the USA and used a monopolistic position to increase the price of pharmaceuticals enormously.

[1] See "Martin Shkreli's Legacy: Putting a 'fine point' on the drug pricing debate, https://www.cnbc.com/2018/03/09/martin-shkrelis-legacy-shaping-the-drug-pricing-debate.html



The next issue is pricing by value. These two photographs show the same product in different circumstances. There is a difference to the consumer between a bottle of water that you buy outside the Uffizi Gallery and one you might need in the middle of a hike across the desert.

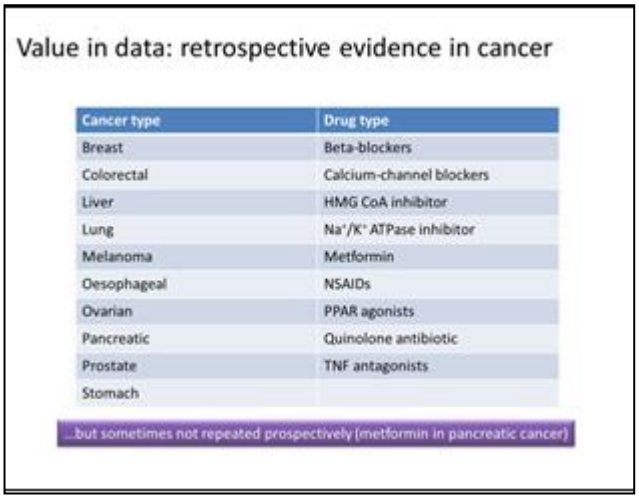
That is true in drugs as well. The use of aspirin for a headache, which is a pretty mild temporary problem, is quite different from prevention of a life-threatening condition like cancer. Similarly, it is accepted now that thalidomide is a valuable drug when used for treating leprosy and myeloma. Yet, it clearly is not just of no value, it is of negative value, for treating the original condition for which it was introduced, which was for insomnia and morning sickness.

It is true also that pricing-by-outcome models do exist. In the United Kingdom there was an agreement between the NHS and Velcade concerning bortezomib for the treatment of multiple myeloma based on very carefully defined outcome measures after a certain length of treatment; if the patient does not achieve those outcome measures, then the NHS can be reimbursed by Johnson & Johnson. However, those only really work when you have very good biomarkers for the condition. In this case, it was the measurement of serum M protein, which was indicative of the progression of the condition.

There is also a problem when you have a tension between what the customer needs, what the payor will pay, and what the provider can get away with. So if I am standing in the desert and I see this man at death's door coming up to me and I offer him a bottle of water for £100,000, he may pay it, but he will feel a bit disgruntled when he discovers that he could have bought it for £1 a few miles away.

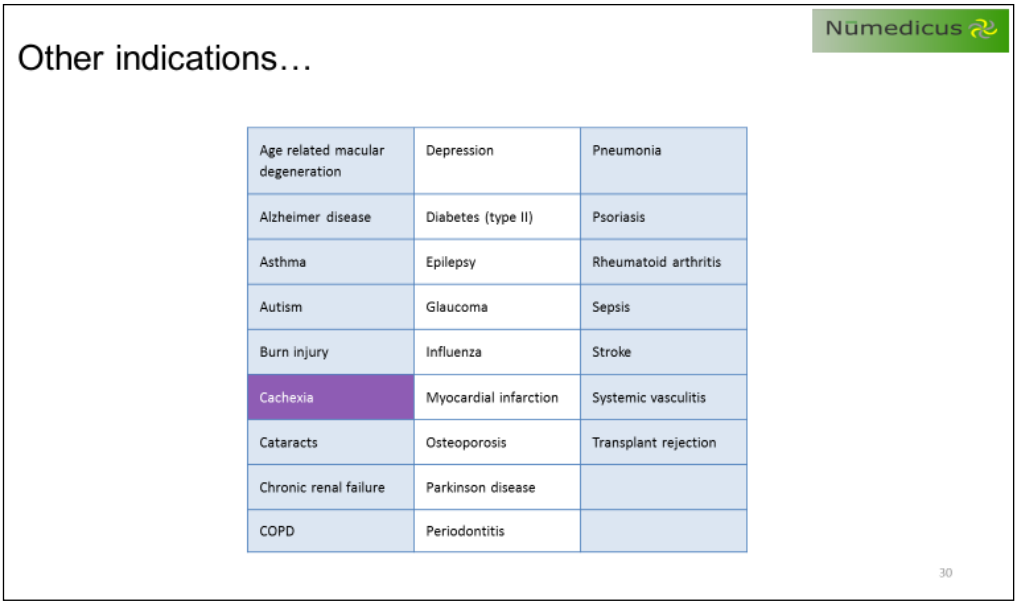
In terms of public perception, it is quite difficult to get over the idea of large discrepancies in price for the same product. The problem in that perception is that we think that "an aspirin pill is an aspirin pill is an aspirin pill," but the value in pharmaceuticals is the data.

I've got a couple of slides here on specific examples where there is value in retrospective data which is not being made use of because of the problem we are facing.



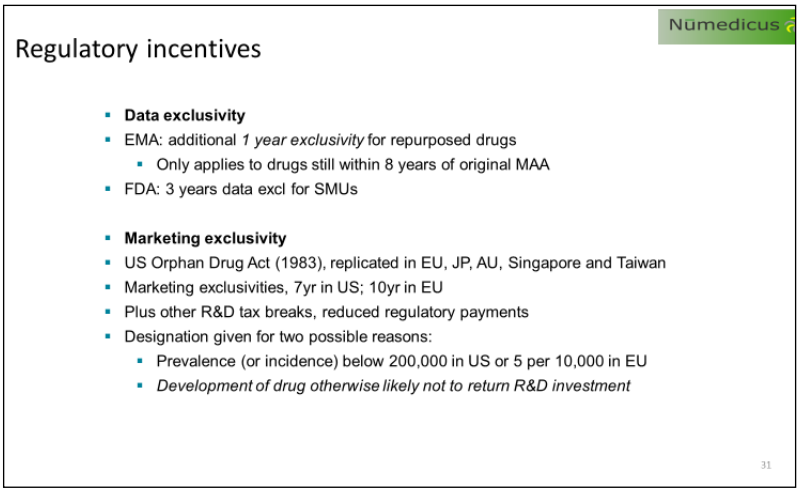
All these drugs — beta-blockers, calcium-channel blockers, and so on — and all of these cancers can be paired in various ways. There are too many examples to show you all of them in one slide. These are all situations where the administration of these drugs to people who do not have cancer has been compared with control cohorts and found to produce lower rates of cancer than would be expected in age-matched controls and so on. The conclusion is that these drugs are preventative. They may not cure cancer, but they seem to decrease the proportion of people who get it. In some cases — I mentioned earlier pancreatic cancer — the incidence is about one-quarter of what you might expect.

Potentially, from the healthcare payor's perspective, these drugs could be administered at the time of first diagnosis of cancer as a method to delay the requirement for the second line of therapy, the second line of therapy obviously being more expensive. The opportunity there is to save the healthcare system quite a large amount of money through this delay. This has not been done because of the second medical use problem we are addressing today.



And it does not just apply to cancer. There is a whole range of other conditions where retrospective evidence exists. One of them I worked on is cachexia, which derived from a cardiovascular trial where patients' weight was measured, and it was discovered, because weight is always measured in a clinical trial, that the administration of various beta-blockers diminished the proportion of

patients who developed cachexia in a heart failure trial. There are a lot of indications apart from cancer there.



Finally, I want to talk about regulatory incentives, and at the end of it I will come up with a proposal. The regulatory incentives that we currently have are based around either data exclusivity or marketing exclusivity. There are opportunities to get additional exclusivity for repurposing.

At the European Medicine Agency (EMA) there is a one-year exclusivity which can be applied to drugs that are still within the eight years of their original marketing authorization. It would not necessarily apply for old drugs which are generic because they would be outside the original eight years of their marketing authorization.

In the FDA you have a slightly different situation, three years of data exclusivity for second medical uses.

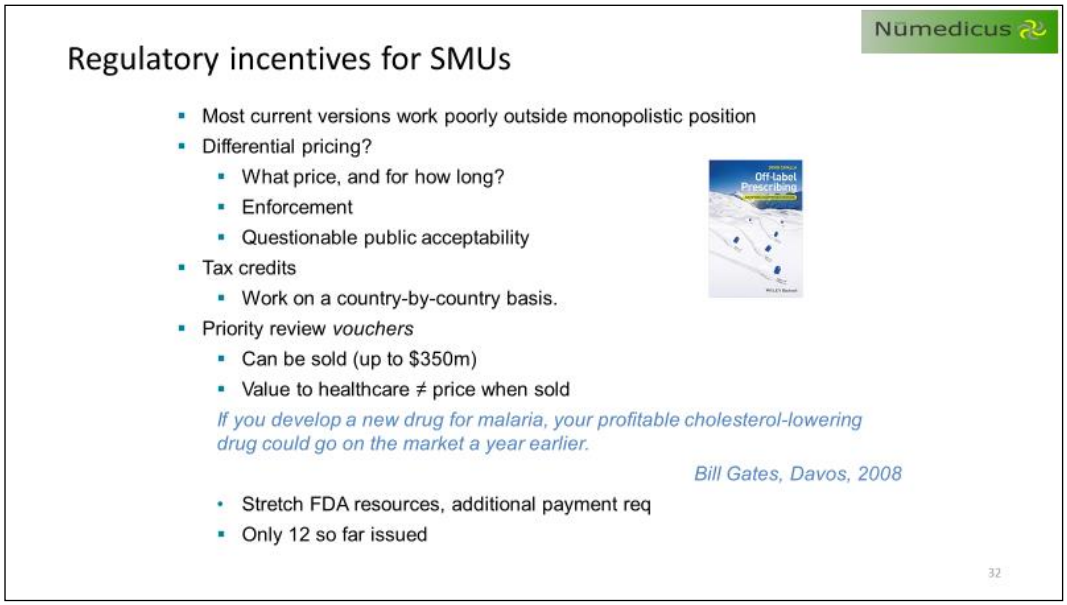
And then you have the Orphan Drug Act, which I think by common assent has been remarkably successful at generating new product applications. It is based on a mixture of marketing exclusivities and fee waivers and so on. One thing which we have not really talked about so far is that there are two possible categories of drugs which can be given orphan drug designation.

One is where the prevalence, or in some cases incidence, is below a certain hurdle — in the United States that is 200,000 and in the European Union it is 5 per 10,000. That is where you have a very rare condition.

There is also the provision both in the FDA legislation and in the EMA legislation for orphan drug designation to be given in circumstances where the development of that drug would otherwise likely not return the R&D investment. Now, it was not specifically set up for the situation we are facing at the moment, but that is the second category.

Those two italicized bits maybe we can come back to later.

The regulatory incentives for second medical uses — like the one I talked about earlier, the EMA one-year additional exclusivity for repurpose indications that have been applied for within the first eight years, or the three-year exclusivity in the FDA — do not really work particularly well outside a monopolistic position.



So what are the alternatives? I have three possibilities here:

• Differential pricing we have talked about in various ways. Ben Roin talked about it, and he has made a proposal for this which is similar to one I made in a book I wrote,[2] which was to have differential pricing or differential reimbursement rates for drugs which are repurposed for particular conditions.

The questions are: What price should apply and how long should it apply for? How do you enforce it? And then, third, the point I mentioned earlier, the public acceptability of substantially different prices for what is effectively the same product. This is still an interesting proposal. I think with some work it could be quite attractive. However, there are some issues which need some care.

The two other things I am not so sure work that well.

• One is tax credits. The problem here is it works on a country-by-country basis and pharmaceuticals are an international business. The only country that I think could effectively offer an R&D tax credit which is meaningful for the vast amounts of money that need to be spent on developing a drug would be the United States. In the United Kingdom it is difficult to see a situation in which that could be attractive.

• The other concept, which has been used with some success in the United States, is that of priority review vouchers. Here if you develop a drug for a certain rare condition or for pediatric use, you can then apply that priority review to a different drug.

In some cases, the priority review voucher can be very valuable. The situation here was that United Therapeutics developed a drug for a pediatric condition which was very rare but it then sold the voucher to AbbVie for $350 million. AbbVie then applied it, or is going to apply it, for the development of a major blockbuster.

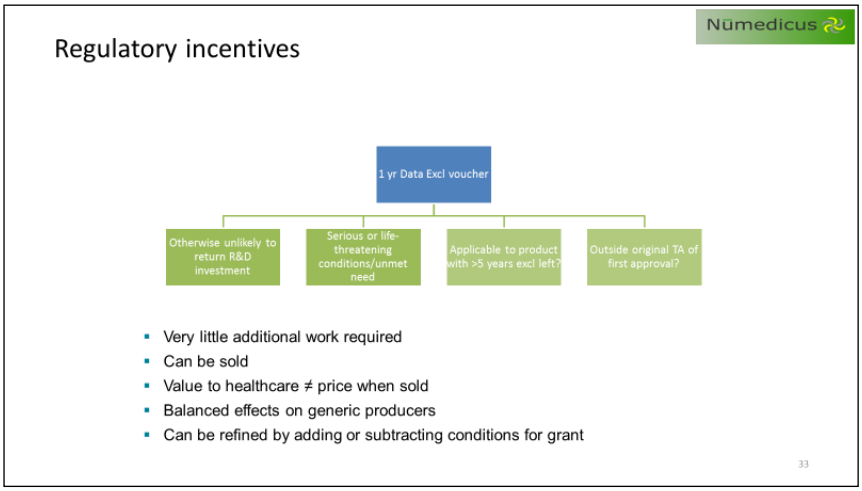
---

[2] DAVID CAVALLA, OFF-LABEL PRESCRIBING: JUSTIFYING UNAPPROVED MEDICINE (Wiley 2014), *available at* https://books.google.co.uk/books/about/Off_label_Prescribing.html?id=YBnWsgEACAAJ&redir_esc=y&hl=en.

As Bill Gates has said, "If you develop a new drug for malaria, your profitable cholesterol-lowering drug could go on the market a year earlier" (Davos, 2008). Actually, the priority review only gives you about six months, but nevertheless it can be very valuable.

There are some problems with that. It stretches the regulatory resources, and nowadays you also have to pay an additional amount for the priority review. It has been done to a limited extent.

But the crucial thing is the transferability of the benefit from one company to another, from one product to another.



What I would like to propose for discussion is something similar to that, not a priority review voucher, but a data exclusivity voucher. For the sake of argument, let's say that is a year-long data exclusivity.

• First, it could be, or would be, only applied to secondary medical use approvals or developments which would otherwise be unlikely to return their R&D investment.

• Second, it should only be for serious or life-threatening conditions or things where there is a serious unmet need.

• Third, when it is then used it could only be applicable for certain types of products. You would not really want it being applied too widely to drugs which already have an extensive period of exclusivity left to them.

• The last property of this incentive I suggest should be that the redevelopment is outside the original therapeutic area of the first approval. What I am trying to do here is avoid situations where you might get an original development in, say, schizophrenia which was then repurposed into bipolar disorder or something which has marginal innovative import.

The advantage of this approach is that very little additional work is required. It does not give rise to the kind of uneven workload that the priority review voucher requires because it is something that has already been approved in any case.

Because the voucher could be sold, the value of the data exclusivity voucher does not correlate with the value of the repurposed product, and that is a good thing and a bad thing. The problem we are facing with repurposed generic

products is that they have little commercial value in and of themselves. They have great healthcare value, but they have little commercial value. By dislocating those two things, I think there is an advantage in terms of providing an incentive for the repurposing of generics, even though the economic value of the voucher may not correlate to the healthcare value of the repurposed generic.

I think it has a balanced effect on generic producers because the current situation leads to a decreasing amount of small molecules being developed. In the "fourth problem" slide earlier, I talked about how many more of the molecules being approved are of biological origin, and that is a problem for generic producers in my view, as the business of generics is still largely based on small molecules.

The last point is all of these refinements or conditions for granting of the voucher can be either amended, excluded, or added to do in order to accurately incentivize the kinds of things we think intuitively are good to repurpose from the healthcare perspective rather than things which are just examples of gaming the system.

MS. TAYLOR: Thank you very much.

Let me introduce Peter Neumann from the Center for Evaluation of Value and Risk in Health at Tufts Medical School and get his take on this and any other issue in the payor's perspective.

PROF. NEUMANN: Thank you, Nancy.

Good afternoon to all of you. Thank you for inviting me. I have enjoyed the day. I have learned a lot today and I am certainly happy to be here I will say I am not a payor, and also I am not a regulator or a lawyer. My background is in health economics. I direct a research center. We focus on measuring value.

I want to make two points. I want to pick up on the characterization somebody made this morning, that you could think of this as a pricing problem and not just a patent problem — that is, the problem is the lack of price discrimination — and I want to pick up on indication-based pricing as a possible solution, which, as we have been discussing today, offers some benefits, has some real advantages, but does beg questions about how we would measure value for and implement an indication-based pricing system.

One thing that has not been mentioned today that I want to pick up on, and something that what I spend a lot of my time doing, is measuring cost-effectiveness as a way to measure value. We can think about the value of these second uses in terms of the cost-effectiveness they bring and argue that we could at least bring to this discussion the idea that we can measure value through cost per quality-adjusted life years (QALYs).

There are some limitations to QALYs. Some people do not like QALYs. I know there are people from NICE here in the audience who have long experience in using QALYs and appreciate their pros and cons.

In the United States we have begun to, I suppose, tiptoe our way into this debate. We have a relatively new organization called ICER, that I'm sure some of you are following. ICER stands for the Institute for Clinical and Economic Review. Not coincidentally, ICER also stands for incremental cost-effectiveness ratio, but they use it in the other way. ICER has been estimating cost-per-QALY

ratios for new technologies, mostly drugs. Cost-per-QALY analyses, as we know from longstanding work, have some pros and cons.

The great advantage is it gives you one number as a proxy of value, one number that combines morbidity and mortality. That is a powerful construct for reflecting relative value, to provide a benchmark for value. As second uses come in, even before we have data, we can model potential cost-effectiveness and value as a way of thinking about future costs and future benefits and future value to populations, recognizing all the uncertainty that would come with that.

There are also some downsides to using costs-per-QALYs, and these have been well studied and well argued — e.g. one number does not capture everything that patients may care about, and there are some strong assumptions underlying QALYs — but it is conceptually appealing and it gives us a framework to think about value with relevance for indication-based pricing.

As people have been saying throughout the day — I think, David, you said as well — as new uses come they will likely bring different value than the existing uses. But we need some way of measuring that value, and formal cost-effectiveness is a useful way to think about it. In fact, ICER has come out with a report on indication-based pricing which I think is worth looking at if you have interest in the topic.[3] In the report they address pros and cons.

Point one that I want to make is we should think about second uses and their value with some quantification through cost-effectiveness, which I believe will be a useful addition to this discussion.

Point two is, having said that, there are all kinds of challenges that we will face. Most of these have been brought up today and I do not want to spend a lot of time rehashing them. Except to emphasize that I think these challenges may be more important in the U.S. context where we have hundreds and hundreds of payors. We have large payors/we have small payors; we have for-profit/not-for-profit payors; public payors/private payors.

Trying to think about indication-based pricing arguably is more difficult in a system like this where you do not have a single payor, such as the National Health Service (NHS) or a government-led payor. There are probably advantages, maybe obvious ones, to the drug industry of having this kind of decentralized, fragmented U.S. payor landscape — namely, that there is not one purchaser negotiating prices and less leverage of for existing payor to do that.

But I think it does make it more difficult to have a well-functioning indication-based pricing system. Why? One reason is the administrative burden. Second, there may be more opportunities for arbitrage, which somebody mentioned today — that is, it is harder to separate and pay for different indications across the same drug.

There are also some very interesting other alternative options here that you, David, mentioned in your last slide, which I hope we can come back to.

---

[3] INSTITUTE FOR CLINICAL AND ECONOMIC REVIEW (ICER), INDICATION-SPECIFIC PRICING OF PHARMACEUTICALS IN THE UNITED STATES HEALTH CARE SYSTEM, A REPORT FROM THE 2015 ICER MEMBERSHIP POLICY SUMMIT (March 2016), *available at* https://icer-review.org/wp-content/uploads/2015/03/Final-Report-2015-ICER-Policy-Summit-on-Indication-specific-Pricing-March-2016_revised-icons-002.pdf.

I would just leave you with two points — and I look forward to the Q&A — (1) we should think about measuring value of repurposed drugs in terms of cost-effectiveness and, in particular, costs-per-QALYs; and (2) we should recognize this will be challenging — maybe not insurmountable, but I think this will be challenging for the foreseeable future, particularly in the United States.

I will stop there and look forward to the Q&A. Thanks.

MR. NAPOLITANO: Thank you very much, and thanks a lot for inviting me here. I am very glad to speak at an event organized by the UCL, where I studied, at Georgetown, such a fantastic university here in the United States.

Before a couple of remarks on the presentation and on the issues that we have been discussing today, I have to make a couple of clarifications.

First of all, Medicines for Europe represents three categories of company members, which it is quite important to clarify. We represent generic medicines producers; biosimilar medicines producers; but also what we call value-added medicines producers, which is exactly old molecules gone off-patent, reformulated, reworked, repurposed, to create a value added for patients, for healthcare budgets, and so on.

A second clarification is related to the terminology "off-label" and "cross-label." We should not confuse off-label use and cross-label use. Off-label use concerns a case like the one that has been mentioned a couple of times today, the Avastin case, where there were two molecules, two different products, one of the two used off-label. It is cross-label use when we are in the context of second medical use patents and you have a generic product that is able to enter the market for one of the indications and it is not able to enter the market for the patented indication.

I think those two clarifications are quite useful.

Today I am giving very briefly the perspective of the generic medicines industry when it comes to second medical use patents, being aware obviously of the importance of having a fair and right protection of the patented indication for as long as it lasts and, at the same time, having generic entry when it comes to the indication which is off-patent.

The pregabalin case is very well-known and has been described several times today.

We know that generic companies, in general, can be considered liable for indirect infringement in the case of second-use patents for actions put in place by other entities, e.g. prescribers or pharmacists. Here there is obviously a risk of disincentivizing generic companies from entering the market *tout court*, which is something that obviously we want to avoid.

I think it is quite relevant to mention that generic versions of products that have second-use patents are being developed more and more. Twenty to 60 percent of the products where a generic version is developed have second-use patents. When it comes to biosimilars, this rate increased up to 100 percent.

We have seen earlier a list of global sales for biological products. In the context of the top-selling medicines, we have three of these — Adalimumab, Rituximab, and Bevacizumab — which have between three and ten second-use

patents each. So you can understand to what extent for biosimilars this might be an issue even more than for generic products.

Obviously, this has an impact in terms of legal uncertainty, but also in terms of cost of litigation. That is why — and we have been discussing this for a while now — we need to find balanced solutions. I think about balanced solutions obviously taking into consideration the importance of incentivizing investments in new uses, but also, at the same time, ensuring that there is generic entry for those uses that have gone off-patent. I think that is the biggest challenge.

As has been mentioned several times, for that we need on one side a holistic approach — systemic approach let's say — which is not only a patent-related approach; and, on the other side, we need targeted ad hoc solutions considering the peculiarities of the different national systems. Especially in Europe, you have basically twenty-eight — soon to be twenty-seven — different national systems with different pharmaceutical policies and practices, and any solution has to take into consideration this peculiarity.

Obviously, we have these national peculiarities on one side, but we also have broader uncertainties — or let's say incoherencies — especially when it comes to the regulatory system as it is and the impact that this might have in terms of patent litigation.

If you take, for example, safety profiles, there is a regulatory contradiction in the fact that obviously there is a general requirement to harmonize as much as possible the Summaries of Product Characteristics (SmPCs) and patient leaflets with the ones of the reference products. But at the same time, the generic company needs to carve out the indication from your label; otherwise you infringe. It is challenging to remove all the references to the patented indication without removing critical safety information from the label. I think this was also discussed in the context of the pregabalin case.

We know that there are several second medical use patents covering a safety profile. In the pregabalin case in the United Kingdom,[4] it was argued that the fact that certain safety profiles were in the SmPC was an indication of the intention to enter the market for the unpatented indication.

We know, obviously, that there is also a requirement on the part of the EU regulatory authorities to include safety information in the SmPC, which is also needed for product liability. This incoherence is an example of what should be fixed at broader regulatory level.

Again, a systemic approach is necessary. Ad hoc solutions need to be taken. We have seen today the case of Denmark, which has adopted a solution [*see* Session 1C]. It might be more or less appreciated, but it is a solution where

[4] 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.

we know more or less who is liable for what and where responsibilities are shared clearly among the players.

To conclude on the voucher proposal, there are several proposals which can be taken into consideration.

I think the data exclusivity voucher is something a bit problematic in terms of how that could be used. We have some experience with the orphan regulation in Europe, and we know that orphan designation and orphan exclusivity has been achieved several times, but it has been also dropped in most of the cases. In Europe, around forty-three orphan exclusivities were dropped. Why? Because in these cases there was an SPC pediatric extension covering the patent, the whole product, for those medicines where there has been pediatric status, which lasted longer. Between the two protections, obviously, the IP covering the whole product, not only an indication, is favored.

My last point on these vouchers is the huge political debates about the cost of innovative medicines that now we are seeing in Europe and in the United States will be a real obstacle if you want to introduce or extend an exclusivity. It is very complicated to introduce something like this in any legislation. Healthcare budgets are finite, obviously, and paying more for one medicine in one field would leave less budget for other medicines in other fields.

The final point is that we should sit at the table, see what ad hoc solutions can be taken, and we are ready to do that as Medicines for Europe.

MS. TAYLOR: Thank you, Sergio.

Now I would like to introduce Erik Komendant, who is with Federal Affairs Association for Accessible Medicines.

We hope we have time left over to have some discussion.

MR. KOMENDANT: There is nothing better than being the last person to speak on the last panel of the day.

Thank you, Nancy. Thanks, everyone, for the opportunity to speak. I will offer a couple comments.

As Nancy said, my name is Erik Komendant. I am Vice President of Federal Affairs at the Association for Accessible Medicines, with the Rebranded Generic and Biosimilar Trade Association in Washington.

The foundation of the entire pharmaceutical industry is really predicated on striking the right balance between innovation and access. Nancy, when you worked on the Hatch-Waxman Act, you did a remarkable job in striking that balance, and I think we have seen a robust generics market develop in the United States as a result.

But that system only works when public policy does not favor one side of the access-and-innovation equation at the expense of the other; it only works when generic and biosimilar manufacturers are able to enter the market when exclusivity periods are intended to expire; and it only works when there is robust competition in the market and that there is competition is between drug manufacturers, whether that is brand-to-brand or between brand and generics, as well as competition between purchasers and manufacturers. We would argue that the patient-access side of the equation is in jeopardy due to a combination of

factors — and I think a number of them were addressed in the earlier presentations — but that balance is increasingly favoring the innovation side.

As we look at additional incentives on the innovation side, which are often well-intentioned to meet a patient need that the market is currently failing to meet, we need to make sure that we do so carefully and we do not further compound the problem of high drug prices or, as we have seen in other instances, create an incentive that can be abused or exploited in ways that were never intended.

So it is important that we ask ourselves what problem are we trying to address: is there an opportunity for the market to correct itself; and, if not, then what new regulations or public policy is necessary?

We will definitely say that without competition from generic and biosimilar medicines there is no ability for the supply chain to address this large conversation we have been having about prescription drug prices.

There are a number of challenges that we have in getting to market with new competitive products. We have seen, even with generics that have been on the market for a while, a challenge in maintaining profitability for those older products.

Martin Shkreli was mentioned earlier. Over the last three years we have had a national debate and he has been the poster child of this debate. "Pharma Bro" increased the price of Daraprim pretty significantly. That led to congresssional hearings, a bipartisan investigation, legislation.

When we considered the FDA user fee agreements last year, reauthorized for five years and passed in August, the one area that Congress chose to legislate was in dealing with these off-patent branded medications. We looked at all sorts of incentives for how to get more competition into this space. This included priority review vouchers, additional exclusivity periods.

It is a challenge often when we are trying to match the solutions with the problem. In my opinion, if we do not accurately assess that problem, we are going to continue to come up with solutions that fail to ultimately address it.

I am glad to conclude there and give us four minutes of Q&A.

MS. TAYLOR: Thank you very much.

I am a lawyer at Greenberg Traurig, and I am going to try something with this group. Give me five words about how you think the payor can most affect the price and the activity with drugs. Give me one sentence, each of you. You said vouchers. Give me one sentence.

PROF. NEUMANN: I would say that you try to move the system to value-based pricing where value is proxied by cost-effectiveness.

MR. NAPOLITANO: I think that is a reflection that has to be made, being aware that this does not have to have an impact or become a barrier for generic entry as soon as the patent expires.

MR. KOMENDANT: I think they have to shine the light on the problem. Prior to my current job at the Generic Drug Association, I was working for the insurers. A lot of insurers have tried to reach out and establish these value-based purchasing arrangements with drug companies, and they have yet to really produce many results. It is a challenge both from a market perspective but also because there are barriers in place to doing it successfully.

MS. TAYLOR: I represent the actual payors. I represent the very largest purchasers of products. What they are demanding has been said here. But what they want is outcome; they want to know that the product will in fact work. The discussion around only reimbursing for indications that are proven safe and effective is absolutely what they want. Just be prepared for that.

Any questions?

QUESTION [Dr. Amitava Banerjee, UCL Farr Institute of Health Informatics, London]: My question is particularly to Peter, but any of the panelists can chip in. If value-based pricing is what we are going for, how do you see the reward structure working out in terms of an assessment afterwards, prospectively? And do you see that, for example, the pharmaceutical sector will be incentivized to think of the drug within the healthcare system, so it is incentivized, for example, to increase adherence and persistence, rather than to just think drug innovation and sell that drug innovation?

PROF. NEUMANN: There is a lot in your question. I am not sure if you are asking in particular about outcomes-based pricing models, but I will focus on that.

Conceptually, those models are appealing. We should all want to pay for outcomes and we should try to adjust prices to the extent possible based on post hoc realized outcomes. In practice it has been hard to do because the systems are not set up, because both parties are taking on risk which makes them uneasy, and because there may be some legal and regulatory issues, particularly in the United States, that make it hard to do.

We are starting to see some movement in this space in the United States, and I am sure overseas, some other examples of this. The recently announced arrangement between Novartis and CMS on the CAR-T therapies is one; there are some for diabetes, and other examples. For the near future, my guess is those will still be the exception, not the rule, and we will see where we go.

But I do think we can do more ex ante, and Arti Rai was talking about this [see Session 1F]. We could still try to move to value-based pricing, even without ex-post outcomes-based arrangements, in the sense that at launch we can model cost-effectiveness, try to price based on cost-effectiveness, and then adjust going forward.

DR. CAVALLA: How would that work with rare conditions?

PROF. NEUMANN: There is an important ongoing debate about whether rarity should be valued differently, if that is what you are asking; and, if so, on what basis.

Most health systems have decided rarity is something we value and we override the traditional cost-effectiveness thresholds because rare diseases deserve higher prices. Those debates go on. NICE has its own rules on this, and in the United States most rare disease drugs are getting reimbursed at much higher prices given health effects — that is, QALY gains and cost-per-quality ratios.

It is not easy. $500,000 per QALY has been thrown out by ICER as one benchmark for rare diseases. It is arbitrary, but the important point is that is higher than the usual ones.

MS. TAYLOR: One more question?

QUESTION [Chris Loh, Fitzpatrick Cella]: There seems to be a fundamental disconnect between the idea of pricing based on outcomes or quality and the R&D costs that go into developing these indications. How, if at all, do you bridge that disconnect, or do you use pricing at all to try to address simultaneously compensating the drug maker for its R&D costs as well as keeping the payors' emphasis on outcome in mind?

PROF. NEUMANN: I will start and others can weigh in. If you price based on R&D, you are creating all kinds of funny incentives — "I can raise my R&D costs as high as I possibly can to get a higher price, even if I don't bring good value"— we know that. So we should try to price based on value, not price based on R&D costs. You do not go into your car dealer and they say, "Here's a car, the R&D costs were very high, so the price is high."

That said, obviously we want to incentivize R&D too. So what do we do? Well, there are various options and we do pursue them: we subsidize research at the National Institutes of Health (NIH); we have tax credits; we can have other ways of doing it. We have to keep those two things going on parallel tracks.

MS. TAYLOR: Thank you very much for the opportunity to be here, and thanks to all of you.

MR. CORDERY: Thanks, everyone.

Drinks are served downstairs just beyond where you had lunch, another twenty meters and you will find them there. Those go for an hour or so.

Tomorrow morning at 8:30 assemble here ready to go, please.

Thank you all for your great questions and attention throughout the day.

We will see you at the drinks and then tomorrow morning. Thank you.

[Session adjourned: 5:31 p.m.]