Techtopia with Chitra Ragavan

Episode 16: Dr. Robert Pearl & Joanne Silberner

Chitra Ragavan:

Ever since the disease was recognized more than 100 years ago, patients with Alzheimer's, and their families and caregivers have longed for an effective drug for this brutal, and tragic disease. But last month when the FDA finally approved a drug named Aduhelm, for use as the first Alzheimer's drug in 18 years, there was little rejoicing.

Chitra Ragavan:

Instead, a big uproar from critics both outside and inside the FDA, who say that there's no clear evidence that the drug has any benefits, and that it could actually have serious side effects, including brain bleeding. And at $56,000 a year per patient and counting, they say, "It not only will break patients and their families, but stress Medicare to the brink." That's the federal health care for the elderly and disabled.

Chitra Ragavan:

Hello, everyone. I'm Chitra Ragavan, and this is Techtopia. Today I've invited two wonderful guests to help us understand what just happened at the FDA, the implications, the fallout, and what happens next. Dr. Robert Pearl is the former CEO of the nation's largest Medical Group, Kaiser Permanente.

Chitra Ragavan:

His latest book is called, Uncaring: How the Culture of Medicine Kills Doctors and Patient, the proceeds of the book go to Doctors Without Borders. Dr. Pearl also co-hosts with Jeremy Corr, who happens to be my wonderful executive producer, the popular podcasts, Fixing Healthcare and Coronavirus, The truth.

Chitra Ragavan:

Also joining me is my very dear friend and former colleague, the award winning health and science writer, Joanne Silberner, she is currently a freelance journalist living in Seattle. Silberner has covered the FDA for decades while at the US News and World Report, and an NPR where she worked for 18 years.

Chitra Ragavan:

Joanne has written a piece on how Aduhelm came to be approved, published today in the online media outlet, STAT+, and it's a fascinating look at how the FDA responds to pressure from drug companies and patient groups, very relevant for this story. Dr. Pearl and Joanne, welcome to Techtopia.

Joanne Silberner:

Thank you.

Dr. Robert Pearl:

It's a pleasure to be here, thank you for hosting.

Chitra Ragavan:

Dr. Pearl, this disease, what makes it so terrible, and why has there been no drug for 18 years?

Dr. Robert Pearl:

This is a terrible problem, it accounts for 60% of dementia cases, currently affects over 6 million Americans, and likely to increase in the future with the aging of the population. Once diagnosed, it has about a three to nine year life expectancy, which is a significant decrease, and in all depends upon at what age you develop the symptoms.

Dr. Robert Pearl:

What you see is progressive memory loss, it begins short term, and often is hard to differentiate from the type of memory difficulties older people can have, but it then progresses to the point where the individual becomes unable to even remember events from long in the past, or take care of themselves.

Dr. Robert Pearl:

And I think the real terribleness of this disease, why people are so afraid of it is that you lose complete control. I mean, the fact that as your memory goes away, you don't realize it's going away, it puts you totally dependent upon others, inflicts hardships on families, inflicts problems on the society overall.

Dr. Robert Pearl:

So this is a terrible problem needing an answer, the challenges scientists still don't fully understand its origin. What we do know is that in a large number of patients, there's a protein called amyloid beta that accumulates, and it's felt that this may interfere with the brain functioning.

Dr. Robert Pearl:

The challenge, of course, is that there are some people who develop Alzheimer's disease without having these brain plaques, and there are other people who have brain plaques that can be identified, on various radiologic studies that don't have Alzheimer's disease.

Dr. Robert Pearl:

So no drugs are there because we haven't figured out exactly what causes it, and all the drugs that might be available, we have no evidence that they are significantly

efficacious, although there are a couple on the marketplace that do seem to slow the disease ever, ever so slightly.

Chitra Ragavan:

Joanne, you've covered drug approvals and the FDA for decades, but you also have a deeply personal lens into this Alzheimer's drug because of your dad's own struggle with Alzheimer's, and I watched you go through that over several years.

Chitra Ragavan:

And you've been through what millions of families are going through, in dealing with parents or siblings or relatives with Alzheimer's. What did that teach you, and how does it inform your coverage of the story?

Joanne Silberner:

Well, I would say that it inspired me to really pay attention, because there's such real world effects to the prospect of a drug, to a prospect or treatment. When you're going through this with anyone you love, you're just so desperate for something, or something that works, for something that will help.

Joanne Silberner:

And the idea that an agency like the FDA would come out and say, "Here you go." With something that doesn't [inaudible 00:05:29], here you go. I mean, when you watch someone you love deeply lose their intellect, their memory, their sense of who they are, I think Dr. Pearl talked about that, and you see their pain, and confusion as they kind of recognize their loss, they know something's going on, they're frustrated.

Joanne Silberner:

And then when they finally die, you don't know whether to mourn their death, or to celebrate that they're not suffering anymore. And if you do mourn their death, you have to remember that you're actually mourning someone who died several years ago.

Chitra Ragavan:

And so when you look at what happened with this drug, and how it was approved, and you probably had to deal with other drugs that you were able to give your dad, what do you make of what happened here?

Joanne Silberner:

Well, we gave him, Memantine or Namenda, actually it was called when it came out the brand name drug, the day it came out, we knew it was coming out. I had followed things closely enough, and I'd read the data, and I knew that it wasn't a cure, and that it might slow things down a little bit, which is what it turned out to do.

Joanne Silberner:

I think, more than slowing things down, it elevated his mood a little bit, and sort of made him except where he was, and that was a big difference. I mean, it didn't reverse the disease, but it made all of our lives a little easier. But the approval on that one, everybody kind of knew this isn't that great, didn't cost all that much money.

Joanne Silberner:

It did at the time, I mean, it seems to me, I can't remember the price because this was 2003. It was certainly not $56,000 a year, that's for sure. And the committee had discussed it that it was clear, to me at least that the FDA had listened to the committee, in this case, on a committee of 11, 10 voted the drug down, the 11th didn't vote.

Joanne Silberner:

Now, when you cover the FDA for a while, the end of every story, when you cover a committee hearing is always, the FDA usually but does not always follow the advice of its committees, but I've never seen anything like this, I never saw anything where the FDA just said, "Oh, okay, you don't like it, that doesn't make a difference to us." Three committee members have quit since then saying, "If you're not going to listen to us, why are we here?"

Chitra Ragavan:

So let's talk about this drug from Biogen, its efficacy, its side effects, what we know to date, and also what's not known about potential side effects, and what's known about potential side effects, and whether this drug actually works, Dr. Pearl?

Dr. Robert Pearl:

The short answer is we don't know, which is why the whole conversation is being had about the FDA approval, because the FDA's job is not to approve drugs that don't work, whether we don't know whether they work, is to approve ones that actually do work that have minimal, or no consequences, in addition to the efficacy they provide.

Dr. Robert Pearl:

So let's look back at what happened in 2017, Biogen started [inaudible 00:08:35], it was called phase three trials, these are large numbers of individuals being looked at, they were specifically selected to be early in the Alzheimer's process, and the endpoint, and researchers when they do a scientific study before they begin, they're required by good scientific protocol to define what success looks like, and they defined it as a slowing of the memory loss.

Dr. Robert Pearl:

Two years later, now we're in March of 2019, they find that in one trial has absolutely no benefit at all, and the other trial does the smallest amount of potential positive impact. And when that happens, most researchers assume that the slightly positive study, is just how chance happens in a new research design, and the company stops pursuing the possibility of getting FDA approval.

Dr. Robert Pearl:

Lo and behold October of 2019, the company announces that they've done a new analysis, and they've found that at the high dose level of patients, that it had a somewhat positive response, although still in the other study, there is no major improvement, this kind of post hoc analysis is almost always used to then do another clinical trial, when you now have a different hypothesis, a different study group, and you look at that.

Dr. Robert Pearl:

The challenge [inaudible 00:10:21] is that there are side effects, brain swelling, and even brain bleeding, and it's particularly likely to happen in people in high doses, which is exactly the group that they're finding is the one who might be responding.

Dr. Robert Pearl:

It's still very, very vague, but the company now announces in the fall on October 2019, that they're going to be submitting a request for approval, based upon this small subgroup from one of their studies, that's finally submitted in July of 2020.

Dr. Robert Pearl:

The advisory group, as Joanna mentioned, meets in November of 2020, it in no way supports the moving forward, and then finally, in June of 2021, the company announces, sorry, the FDA announces that it's going to give it this accelerated approval for the medication, much to the shock of the scientific community, and certainly the members of the advisory group.

Joanne Silberner:

And I'd like to add something in the side effects from the family point of view, which is that, patients need to get this every four weeks from the doctor's office or hospital, and then just before, and then I think after the seventh dose and the 12th dose, they have to get an MRI.

Joanne Silberner:

And if you've ever dealt with somebody who has Alzheimer's, at least everyone I know who's had, it's moving them about, moving them into a medical situation, it can be really terrifying for them, it's very, very stressful for them. If you happen to live in the northeast where my dad was, you've got the winter to contend with, to getting people back and forth on the roads.

Joanne Silberner:

And then my father had been a physician, so he got very confused when he was in a medical situation, like he thought he was supposed to be working. But I think for anybody, it's very stressful to go into an MRI machine, and for people with Alzheimer's especially. So it's not actually a side effect, but it is something that you have to contend with.

Chitra Ragavan:

Yeah, even my dad, as you know he didn't have Alzheimer's, but he had really bad dementia towards the end as you know Joanne, and getting him out of the house to a doctor was proving impossible.

Chitra Ragavan:

I mean, I don't know what these people who have approved this are thinking, that you're going to be able to get these patients in and out of their homes, for this regular monitoring, they have no idea what do you have to go through as the as a family member, getting your dad, or mom, or a sibling out of the house, to actually get that that kind of preventive surveillance.

Joanne Silberner:

Well, and the treatment itself, the treatment itself is an infusion, and stop me if I'm wrong Dr. Pearl, but I think it needs to be done in a pretty sophisticated doctor's office, or in a hospital.

Dr. Robert Pearl:

Usually it's going to be given in a diffusion center, which could be a standalone or associated with a hospital, and you're right, it takes about one hour to administer the medication safely. The administration safely, the consequences is a different question.

Chitra Ragavan:

Yeah, so Joanna, you've done a lot of reporting on this whole accelerated approval process, and the use of whatever proxy biomarkers and surrogate endpoints, and all these fancy hoops that the FDA can, and has jumped through to get this drug, and some other drugs through the pipeline.

Chitra Ragavan:

And you have a new story in STAT+, that looks at this from the early days of HIV and the AIDS epidemic, when activists were fairly, I mean, literally in at the FDA is doorstep if not in it, pushing hard to get access to experimental drugs.

Chitra Ragavan:

And tell us what you kind of found in the course of that reporting, especially, how this expedited drug approval process works, and how it's kind of gone so wrong?

Joanne Silberner:

Yeah, because it's one of those things, on paper it's a great solution to problems of difficult diseases, like HIV and AIDS, HIV when there was no treatment for it, and Alzheimer's now, muscular dystrophy has had some drugs that have gone along with it, that have come in under accelerated approval.

Joanne Silberner:

Cancer, you want accelerated approval, because people are dying now, but the difference with cancer actually is you can usually tell pretty quickly if the drug is working, when you go and do the subsequent studies. But let me take you back to the beginning, which was in 1988, where there was this enormous demonstration on the doorstep of the FDA, that it come on top of other incidents people were throwing fake blood at government officials, saying, "We want experimental drugs now."

Joanne Silberner:

And they were faced with something that was decimating some communities, and there was nothing to do, but there were all these chemical entities out there who theoretically might work. So in 1988, the FDA started with giving expedited approval to drugs, where there wasn't really enough information, but saying, "Okay, go ahead."

Joanne Silberner:

They started using markers like CD-4 counts, which turned out not to be great, but eventually they looked at viral load, which actually, how much virus is in the blood, that was a better marker. But it got too fast too quick, even for some of the AIDS activists, there was a split in the HIV community, when the accelerated approval came in, in '92.

Joanne Silberner:

Where you had some of the activists who had trained themselves in statistics, and actually were very good, coming in like [inaudible 00:15:52] my story, saying, "Whoa, if we approve all this when we don't know if it works, we're never going to find out if it works, we've got to find ways to collect the data."

Joanne Silberner:

And all the years since, with accelerated approval getting more and more of a foothold, I think something like 13% of drugs are approved this way, that hasn't happened for a number of reasons. One is, you've really got to pick the right surrogate marker.

Joanne Silberner:

And this is... So for cancer, a lot of times it's been tumor progression, and that's actually turns out not to be a great marker, because when you look at mortality overall, when you have the time to let things run out long enough, until people either die or survive, with tumor growth for some cancers, you may be able to arrest the growth, but you're not extending people's lives, just because that's the way cancer works, and they've had that trouble with those drugs.

Chitra Ragavan:

Let me interrupt for a minute for people who don't understand, why are they using so called surrogate markers, what's the alternative, and why are they going with those surrogate markers, in the case of expedited approval?

Joanne Silberner:

Great question. Because it's fast, like with Alzheimer's, if you have to wait, the disease progresses fairly slowly, and if you have to wait, by the time, you can see an improvement, it might be three or four years down the line. So if you can find a mark or something that happens early on in the disease, with an antibiotic, can you find the bacteria, or virus or whatever it is in the blood anymore?

Joanne Silberner:

And even that's not a great surrogate marker, actually, in my story, I quote Jerry [inaudible 00:17:36], a physician at Harvard, who has written widely about drugs, and he was up in arms about a tuberculosis drug that was tested, that it did, it slowed the growth of the tuberculosis microbe in blood, when you tried to grow it out of serum.

Joanne Silberner:

The people who got the drug, yeah, it slowed the growth, or actually stopped it in some cases, so isn't that great, you got to figure that's going to help. Well, that was great, until you actually looked at the data for survival, and survival was lower, and the people who had gotten the drug. Either because of the drug side effects or some other reason, but the drug didn't help with survival.

Joanne Silberner:

But you had to wait a little bit, it's much faster to just go and say, "Can you culture this microbe out of the blood?" And in many cases, that is a fair enough marker, but not in all cases. So you'd say, "Okay, fine, the idea is approve the drug, based on the surrogate marker, and require as accelerated approval does require, that the company do subsequent testing.

Joanne Silberner:

But the problem is that the FDA hasn't turned around and said, "Okay, make it timely, and make it now." For Adulhum, they've got nine years, which is an enormous amount of time, and I just saw something today in the pink sheet, which is an industry newsletter, that the Adulhum time is longer than a lot of other drugs have been.

Joanne Silberner:

There's the muscular dystrophy drug that I talked about in the story, the drug was approved in 2016, 2015, they have until 2026 now, because the FDA approved because it increased very slightly the amount of protein in the blood, of kids with muscular dystrophy who are lacking a certain protein. But they didn't wait to see, does it keep them walking longer than a group who didn't get the drug?

Joanne Silberner:

Now they've gone ahead and approved it, and this drug is actually $300,000 a year, and these trials won't be done till 2026. Now, I've been talking to the company all day to day, because they were upset that I was criticizing them for that long approval.

Joanne Silberner:

It turns out that they actually were due to have the results from a longer study that looked at kids ability to walk by 2021, but the FDA wanted them to do some safety studies, they wanted them to increase the dosage. So they're sort of saying, "It's the FDA is fault that it's taking us this long."

Joanne Silberner:

But really, these studies should have been started as soon as they tested the drug. In fact, with almost all these drugs, the plan for the subsequent trial is within the application for approval. The only reason it wasn't in, not the only reason, it wasn't in Biogen application is because they didn't apply for accelerated approval.

Joanne Silberner:

They applied for regular approval where you have to show effectiveness, the FDA switched him over to accelerated approval, and for some reason, and I can't tell you, I don't know why, their plan for subsequent testing, Biogen plan for subsequent testing, didn't get into the original approval.

Joanne Silberner:

All that got into the original approval was the FDA saying, "Okay, you've got nine years to tell us if this works." Which is nine years of millions of people facing this difficult choice with not enough information.

Dr. Robert Pearl:

So there are really two sets of issues, in terms of the listeners. The first one is the question of this whole accelerated approval process, and Joanne's absolutely right, that in the 1980s and 90s, we're approving about 10 drugs a year, overall through the FDA, and now it's 40 to 50 drugs a year.

Dr. Robert Pearl:

So the requirements to move through the process, seem to have dropped significantly, in terms of the rigor that's been required. But there's a second question that to me is fascinating about this particular approval, which is that this science upon which it was approved, is so challenging and problematic.

Dr. Robert Pearl:

First of all, because these amyloid beta plaques are not yet proven to correlate with the disease, to cause the disease and reversing them, or impacting them, isn't necessarily going to be positive. But I found it fascinating over the past month to compare the requests by Pfizer, that wanted approval for a third booster for COVID, against this particular approval.

Dr. Robert Pearl:

Now, we may be getting a little bit off track, but the Pfizer data says that antibody levels in the blood clearly dropped, we know that antibodies are effective at attacking viruses,

and so the data that might otherwise drive the process, and certainly the risk of death in the short term, is such that you're not going to wait to see in a very long time period.

Dr. Robert Pearl:

What happens is so much stronger, and yet the FDA steps forward, and says, "Absolutely not, we're not going to approve this." Even before any kind of full analysis is done, and in contrast, when it comes to this drug for Alzheimer, they say, yes, despite as Joanne said, the essentially unanimous opposition to doing so, I think the interesting question is, why did the FDA in one case, approve a drug with almost no scientific basis showing that it is efficacious, and another one chose to say, "No, I think we're not going to look deeper under the covers, at what's going on inside the organization."

Chitra Ragavan:

So I mean, that's absolutely irrelevant in this case, I was thinking about the same thing, you look at COVID, and the clear life saving benefits of Pfizer's drug, and Moderna's drug, and Johnson & Johnson, and then you look in this case, and the FDA is delay on the Pfizer one is fascinating.

Chitra Ragavan:

But looking deeper under the hood, Dr. Pearl, what do you make of that? I mean, what does it say about the culture of the FDA, or the way this, these types of drugs are approved, I mean, the people are scratching their heads about this?

Dr. Robert Pearl:

As you said, the book that I recently wrote, Uncaring: How the Culture of Medicine Kills Doctors and Patients. I wrote a piece on Forbes this week actually, about this decision, and pointed out that the FDA's esteem, cultures about respect and esteem and value, it really came out of the 1960s.

Dr. Robert Pearl:

When it chose not to approve a drug called thalidomide, when the European regulators said, yes, and the consequences were horrific amongst children born without arms and without legs, as a consequence of this thalidomide drug. And its reputation was based upon the fact that, its number one priority was minimizing danger and risk to patients.

Dr. Robert Pearl:

And I think what we're seeing now is a change in how the FDA gets its respect, and esteem, and rather than being the protector of the patient against the horrific consequence, it now is being judged by how fast they can move drugs forward, regardless of the science that might have been required in the past.

Dr. Robert Pearl:

As Joanne said, regardless of the cost that's involved, even looking sideways around the issue of the risks, they're obviously not going to prove something with proven

absolute risks, but the shift in this culture, and I think that that's what we're seeing, of course, they're going to be political forces there, they're going to be lobbying forces there, they're going to be a lot of backstories, but to me, they fall into this cultural realm.

Dr. Robert Pearl:

And I think the FDA has now moved beyond where it should be, with a good balance point is going to be an approval is now, what it needs to do the gold standard for its success, which wasn't its original creation reason. And we're now seeing this, which in retrospect, I think almost everyone would agree was a bad decision, with the exception of the families of patients who have Alzheimer's disease.

Dr. Robert Pearl:

And understanding how motivated they are for anything that might work, because this disease is progressive, and they want anything that can happen. And at some point, the science has to say, "The data is saying your chances are so small, that it's not worth it." And then the economics has to ask, what are the other consequences that happen as a result?

Dr. Robert Pearl:

This money can be used to support families, and helping to take care of the individuals with Alzheimer's disease, it could be used for prevention, for saving lives for a variety of ways that those dollars could have a major positive impact on those specific families, as well as on others.

Dr. Robert Pearl:

And all of that is getting lost, and we can talk about the price tag, which experts looking at the question of what is the proven value against the cost, have said that this drug should cost between 3,000 and $11,000. And, as is true for the entire pharmaceutical industry in the United States, which is equally problematic, or even more so, what we see is that the price tag is arbitrarily set by the company.

Dr. Robert Pearl:

With the FDA approval, at least in the past, Medicare and Medicaid have had great difficulty saying no to providing the payments for it, and it becomes a guaranteed cash cow for the company. And I'll add one last piece which Joanne said earlier, yes, there are phase four trials, yes, they take at least nine years.

Dr. Robert Pearl:

But more importantly, they're not going to prove anything. Because the FDA did not say doctors can't administer this drug to people who do not meet the requirements, doctors can still give drugs for 'off label' approval, and if you're someone with someone in your family who has Alzheimer, are you going to go into a drug trial, where half of the people get placebo, or are you going to find a physician who will administer the drug? I think the latter is most likely what's going to happen. And we'll never know what this drug does any good or not.

Joanne Silberner:

Where they found that with the HIV drugs as well, that you can't get people to go into a trial, if you're going to trial, it's because you think the drug has some chance of working. And with a desperate disease like Alzheimer's, and there is a drug, you're going to try to get that.

Joanne Silberner:

But I want to bring one other price factor that I didn't consider in my story, and that is an important part of the equation, and that is that since 1992, drug companies have paid for their own reviews at the FDA, an act went into effect, the Prescription drug user fee act.

Joanne Silberner:

And what had happened was the FDA was just getting pounded by Congress, for not approving drugs more quickly, for not getting to the root of food outbreaks, food disease outbreaks more quickly, they were just getting pounded and pounded and pounded. And they didn't have the money to do it, they didn't have the staff to do it. And they weren't allowed, I can tell you I know how the Department of Health and Human Services works with its employees.

Joanne Silberner:

If they're called before Congress to testify about something, they are not allowed to complain and to say, "We're not getting the money, we need more staff." They're not allowed to say that. But it was true, and somebody finally recognized it, but the response instead of giving them more taxpayers dollars, they said, "Well, why don't we let the drug companies pay for this?"

Joanne Silberner:

The drug companies can pay for their own reviews, which is true, but a lot of the consumer groups were saying, "Wait a minute, that's going to create a problem." And I think it really has. And I don't know that I can put numbers to this, but subtly or not, the upper level folks at the FDA know that the money to run the agency is coming from the drug companies, which gives the drug companies a tremendous voice with Congress as well, where they can go in and say, "We're paying for these reviews, and they should be done in a certain way." And it puts a pressure on the system, that I don't think should be there, and I don't think it's good for consumers or patients.

Chitra Ragavan:

There's so many layers of conflicts of interest, and potential conflicts of interest in how these things are structured, it's just mind blowing. I mean, first of all, Joanne, from what you said, going back to the AIDS epidemic, and all of the activism around it, the FDA as you pointed out, is just not good at responding to pressure from consumer advocacy groups, from patients, patients families.

Chitra Ragavan:

And then you've got from all the reporting that's out there, by the Washington Post and The Journal, and yourself and the New York Times, this really cozy relationship between the FDA and Biogen in the months before the approval. And is that unusual?

Chitra Ragavan:

I mean, and how has the FDA fared in other similar situations, if there has been these kinds of cozy relationships, in terms of joint studies or joint presentations, and those kinds of things, which again, create another layer of conflict of interest?

Joanne Silberner:

I think that the level of cooperation is unique to Adulhum, there has been a cooperation that has made sense over time, where the companies can go to the FDA, and ask them, what kind of proof do you think will be necessary, especially with the more conventionally approved drugs, but even with the accelerated approval drugs, they can say, "What are you going to need for you to say that this works?"

Joanne Silberner:

And I think that's fair enough, and the FDA can say to them, "Well, we're going to want to see this, if we're going to want to see this, we're going to want to see that. Fair enough. But the level with Adulhum, I have never before heard of what STAT has reported, with the company doing the joint presentations, with FDA people, I've never heard of that. And that just the level of cooperation does seem to be out of hand.

Joanne Silberner:

But one thing I want to say is the biggest critics I've talked to, were all just really sad, I mean, they've seen this with other drugs with smaller populations, I mean, the muscular dystrophy drug for example, but that's a population of 10s of 1000s, very active patient groups, but a smaller population.

Joanne Silberner:

And the cancer drugs as well, when you divide it out that the groups are smaller, so this is a big, big group, but they all say, "This could work." If we had a system, where the companies weren't involved in paying for their own studies, where the surrogate markers were clearly agreed upon by the medical community, and the medical community doesn't really believe as a whole, that these proteins that clog up the brain, if they disappear, that Alzheimer's will go away.

Joanne Silberner:

So it's not good surrogate marker, they feel like if there were real rigor on the surrogate markers, and if they were real requirements, for example, if you were allowed to market your drug under an accelerated approval, Joe Ross at Yale was saying, give them a year, give them two years for the confirmatory trials, and if they're not done at the end of two years, boom, you drug is out until you have those trials.

Joanne Silberner:

Give them nine years. And when you do give them nine years, there are a lot of examples of the FDA not demanding that they meet their deadlines. In fact, I'm not even sure I could tell you how often they do mete out any kind of punishment.

Joanne Silberner:

They've done it actually with a couple of cancer drugs, they've pressured the companies lately, a few of them have pulled drugs for certain indications, although the drugs are still on the market for other purposes. But the point is that it could be done well, and it's not, and there's a legitimate reason to do it, but it's in the execution that it's not working.

Dr. Robert Pearl:

All right, as you say Joanne, and I wrote about in the Forbes piece, so this week, we could have a maximum time period, particularly when the FDA goes against the advisory groups, whether it's two years or three years, I think there should be a requirement to involve external people like the NIH, in overseeing the scientific rigor, because this is not a company just doing research on its own planning to submit a request for approval to the FDA, they've already received it, but on a temporary type basis.

Dr. Robert Pearl:

And that's where I think the FDA could be saying, if you want this approval, you've got to repeat your studies, you've got to document that everyone who receives the drug falls into the criteria set up by the FDA, which in this case would be only very early people with Alzheimer's disease.

Dr. Robert Pearl:

And you've got to work with independent scientists from the NIH, under strong conflict of interest, non disclosure agreements. And then after two to three years, we will have rigorous science, and if that happened, I think most people would be very sympathetic to giving this type of, I'll say less than scientific approval, but as it stands right now, as you said, it's nine years, who knows if the science is going to be any good, by that time, people will have forgotten it.

Dr. Robert Pearl:

And unless there are terrible consequences, which we will regret, significantly, the chances of reversal are so small, and the consequences of the cost, this drug is projected potentially to cost as much as all of the other drugs provided through Medicare. And as we know, Medicare is likely to run out of money sometime in 2024, and this could speed that up by a full year, if not done well.

Chitra Ragavan:

That is just absolutely astonishing. And the fact that the agency's own Acting Commissioner, Dr. Janet Woodcock, at least from what I've read, says or wasn't involved in the approval process, is that normal?

Chitra Ragavan:

And now she's asked her internal watchdog, the FDA inspector general to investigate how this approval took place. I mean, that seems even more bizarre, do you have any insights into that?

Joanne Silberner:

I wish I did. And I would STAT, and the New York Times they've both been doing terrific coverage, but it doesn't seem to make sense. It would be unusual, but I think Time will tell.

Dr. Robert Pearl:

Yeah, no, to me it's not believable, that a decision of this magnitude, these dollars going against the unanimous thought to not approve this drug by the advisory group, would not require at least a conversation with the acting director.

Dr. Robert Pearl:

I just can't believe that somehow this decision was made at a much lower level, it would never happen in any agency, any company, when you have this type of very visible, public, inevitable conversation and criticism, that decision always involves the most senior person, which in this case is the acting director.

Dr. Robert Pearl:

I don't know why she says that she's not involved at all, it's just not even imaginable to me, whether it would be in an agency of the government, or in a business and corporation.

Joanne Silberner:

I imagine the Freedom of Information Act requests are flying.

Chitra Ragavan:

Yeah. And why is there no full time commissioner in place yet? And would that have made a difference? I mean, do we know who that might be?

Joanne Silberner:

The two leading contenders are Dr. Woodcock and Dr. Josh Sharfstein, who was Baltimore City Health Commissioner for a while, he was at the FDA for a while, and he is known as a reformer, very consumer positive, and the drug companies don't like him. And they've made no secret about that, it's been discussed... Actually, it's not a secret, they may not be talking about it, but it's widely known that the drug companies do not like Josh Sharfstein, they do like Janet Woodcock.

Joanne Silberner:

It's fascinating to me, this is the longest I remember of the incoming president not having ahead of the FDA names, this is a very long time with a lot of key issues in front

of the agency, moving from emergency use approval for the vaccines for COVID, this drug, a bunch of other issues going on, it's a little scary to me that we don't have a full time commissioner, who is a permanent full time Commissioner.

Dr. Robert Pearl:

I think it speaks to this internal politics, and once again, I think it speaks to this culture, a culture now that is valuing the ability to move drugs forward, and other people who think that that's not the right role for the FDA, that it should have a lot more caution.

Dr. Robert Pearl:

And it should behave a lot more like the European FDA equivalents, that are going to be looking at the true efficacy, and tying that in with the price, and leading around to some of the negotiations that are happening now in Congress, around the role of the government being able to figure out the right price to pay for a drug, based upon its likelihood of doing good.

Dr. Robert Pearl:

And all of that is now caught in this political turmoil, and I think that that's why we don't have a full time commissioner right now, because that's getting sorted out at even a higher level than the acting commissioner.

Chitra Ragavan:

So how do you see the FDA as a doctor, and drugs that might be approved by this agency after this particular debacle, Dr. Pearl?

Dr. Robert Pearl:

I, as I said, believes that we need more science, and I think we've drifted away from science, when it comes to the entire pharmaceutical process to say nothing about the FDA approval, we saw with hydroxychloroquine, during the early phases of COVID-19. There are there is science that should be applied, and there needs to be a lot of transparency, and right now we don't have either.

Dr. Robert Pearl:

One could justify a lot of decisions, if they have an associated, I'll say, braking mechanism to stop them or to move them, we have very clearly defined approaches to being able to test new drugs, to price new drugs, to require as an example, that we understand how much better they are than the alternatives that otherwise exist in the marketplace today.

Dr. Robert Pearl:

I think there's a lot of action right now in Congress, that both of you are aware of, looking at the anti competitive actions of the drug companies, the Biden administration has looked at that, particularly companies that are able to pay generic drug manufacturers for delaying bringing products onto the marketplace.

Dr. Robert Pearl:

This entire industry is now tilted against, what's my view, the benefit of the nation and the patients, and I, as a physician, just would say, we need more science, and if anything, we have less science now than we've had in the past.

Joanne Silberner:

[inaudible 00:42:17] this agency used to be the gold standard, it was the world standard. And I've been living in England for the last few years, and it's not looked... At least from Europe, it is not looked on the way it was, maybe 20 or 30 years ago. I think people over there think we've gone nuts.

Dr. Robert Pearl:

Well, there was a lot of pressure, the [inaudible 00:42:37] decision, I still believe was the moment of truth. And the commissioner at the time, came under tremendous attack from the drug companies at the time, saying this was a great medication, it should be approved rapidly, you're very unsympathetic to pregnant women for whom it was administered.

Dr. Robert Pearl:

And the director said, "No, we need to make sure the science works, and protect patients against it." And it turned out to be correct, as I said, as against Europe, which is why I think the Europeans still look at this as being the golden moment for the agency. That day is long passed, unfortunately, and we've gotten a lot of politics, and a lot less science.

Joanne Silberner:

I'm waiting for the payers to come in, we've seen it really now for the first time, in a big way with Adulhum, with Medicare saying, "Whoa, we need to take a step back." And the insurers are evidently doing that too. Because the insurers, the health insurers are the payers, it used to just be a [inaudible 00:43:38] drug prices went up, they just raised the rates for that insurance, they just passed the rates on.

Joanne Silberner:

But with this, people aren't going to be able to afford insurance that covers drugs anymore, given their costs. And I think it'll be interesting to watch in the next few weeks or months, whether the insurance and the payer start to play a bigger role in some way.

Dr. Robert Pearl:

Everyone is stuck in a unsolvable problem, when the FDA makes a decision like this, as you said, almost always Medicare and Medicaid follow exactly in the process that's been recommended by the FDA, and then the insurers fall back behind the government. Everyone goes lockstep, and the cost of care just rises as a consequence.

Dr. Robert Pearl:

But almost always, there is an offsetting economic benefit, and the challenge in this particular situation is a drug that you're going to take for the rest of your life, and one for which the benefit is not yet determined, that's very different than as an example, when there was the hepatitis drug that was very expensive, probably also much higher price than it should have been.

Dr. Robert Pearl:

But at least it was a one time, or a set of one time administration, and it avoided future costs. None of that applies in this situation. It was a block buster type medication as the hepatitis one was, that actually solves the problem, everyone would be saying, "Whatever the cost, it's worth it, thank you very much."

Dr. Robert Pearl:

But to have a drug that even on the pharmaceutical companies testing, show that one of the arms had zero improvements, and the other one, a small, minimal one, and another price tag of 56,000, there's something absolutely absurd about this whole process.

Dr. Robert Pearl:

And I think it's coming to roost right now, and again, I keep going back to Congress, because Congress is debating this, they'll be interesting, some of the senators, and representatives coming from very pharmaceutically positive communities are going to have to decide, are they going to continue the processes of the past, of pushing the agendas of the drug companies, or this time, are they going to stand up and be counted?

Chitra Ragavan:

So we can't end the story without asking, where's the Alzheimer's Association? And all of this? Where I mean, what's their role? And are they protecting patients interests, or not?

Joanne Silberner:

Well, they pushed really, really hard for this, they showed up at the FDA committee hearings, they've been talking about the sell off, they've been talking to legislators, they've been making their views known to the FDA, they pushed very hard for this drug. And the little bit of backtracking they've done, they have come out and said, "Well, gee, we don't think it should be so expensive."

Joanne Silberner:

But they really wanted this drug. Is that serving their population, or is it fulfilling a goal that the association had, that maybe have lost its meaning when the drug didn't test out so well, I think it's the latter.

Dr. Robert Pearl:

There's also the fact that the drug company is a major contributor to many of the patient led groups, that they'll become part of the national organization, and stopping that donation certainly has economic consequences.

Dr. Robert Pearl:

I teach in the Stanford Graduate School of Business, and we study financial incentives, again it's hard to imagine that that is not weighing in on the process, when a significant amount of your funding is coming from the same organization, that's pushing for an FDA approval, that's potentially going to benefit your people, and your doubts tend to become less powerful, less visible than they might otherwise be, if you could have a purely objective viewpoint.

Chitra Ragavan:

I wonder in the financial planning space, you have to show fiduciary, you have to show, are you a fiduciary as a financial planner, and people can go to those planners who have an exercise, their fiduciary right to put the client's interests before their own, in terms of making commission's on recommendations of what financial products they should buy.

Chitra Ragavan:

And in the case of trade associations, there are a number of instances where this kind of funding from the groups that, like the drug companies, or other groups, can really sort of color their decision making, and it seems almost like there has to be a fiduciary responsibility in all of these Washington trade groups that they should follow. And I don't know if that exists or needs to exist, but I'm seeing more and more of that gray area when it comes to trade associations.

Dr. Robert Pearl:

When there's a lack of transparency, your first thought is something's being hidden, and I think that that's what's going on right now, when you look at the dollars that are being given, acknowledge what they are, you should be proud of taking the dollars, and using it well on behalf of people who are at risk of health consequence.

Dr. Robert Pearl:

Why not make it easily publicly available, and again, we could go in a broad conversation, whether we're looking at the hospitals right now, or some of the insurance company issues, or in this case at the pharmaceutical world.

Dr. Robert Pearl:

Medicine today is a very closed environment, there's this blue wall of silence that people talk about, no one wants to disclose this information. We're now in 2021, the time has come to make it easily available to everyone who wants to look at it. If you're embarrassed, you probably shouldn't be doing it, you should be willing to show the information with pride, because you should believe it is the right thing to do.

Dr. Robert Pearl:

I don't know exactly where we are, whether it's 80-20 or 20-80, but we're certainly as far away from what should happen from a moral, ethical, scientific, economic, you can go down a list of terms, perspective.

Chitra Ragavan:

So in closing, who would you say are the big winners and losers in this fight over Aduhelm?

Joanne Silberner:

Well, Biogen is the winner, and I think everybody else is the loser.

Dr. Robert Pearl:

I would agree this is a company that's going to make a lot of money. I think the only way that... It had a totally losing hand, when it stopped it's phase three trials in 2019. This is an attempt to raise the sphinx from the ashes, to be able to now be able to generate a massive amount of dollars, literally, for at least nine years, administering this drug to six million people, although theoretically, a smaller number at the front piece.

Dr. Robert Pearl:

I think the only question is really going to be, how does this finish playing through, maybe the game's over, and it's all done, I just can't believe with the amount of negative press that's happening, and the progressive exposure of some of the ways in which corners were cut, potentially inappropriately.

Dr. Robert Pearl:

I think we still have more chapters to go, and I'm hoping that that's going to be the consequence, we need more scientific study. If this drug works, that is terrific, we should make it available, how we price it as a different question. And if this drug doesn't work, don't give false hope to families, let them face the truth, and use the same dollars who would have spent, in ways to give them the support that they need, taking care of their loved ones for whom this terrible disease is exacting a major, major pain and problem.

Joanne Silberner:

And the real losers are the patients and families.

Chitra Ragavan:

And do you think they should pull the drug back? Do you think the FDA can, and should pull back Aduhelm, till more more work is done on it?

Joanne Silberner:

Well, they pulled back slightly in that they've limited, instead of saying for anyone with Alzheimer's, which was not what the company has asked for, they've gone back to do it

on who the company tested it on, which is mild to moderate. Will they pull it back completely? Should they pull it back completely?

Joanne Silberner:

From my viewpoint not as a journalist, but as somebody who had this in their family, yes, I don't think the option should be there for families, it's too terrible position to put them in it.

Joanne Silberner:

When they're faced with an already difficult situation to put them in the position of saying, "We want to experiment on your dad, and you're going to have to pay a lot of money, and you're going to have to put them through all these tests. And we can't really say that there's a good reason to do that right now, except on an experimental basis." I just don't think that's a good place to be for families.

Dr. Robert Pearl:

Well, I'll go back to what I said before, that even though that's what the FDA [inaudible 00:52:57] gave its approval for, doctors could administer to anyone that they choose, so called off label administration of medication, often promoted, by the way by drug companies for different expensive medications that are out there right now.

Dr. Robert Pearl:

I think what we need is more science, and that to me becomes the resting place. As I said, I'd like to see this have a specific timeframe, that's far shorter than nine years, I'd like the NIH, or some other independent agency to get involved in doing it with the drug company, I'd like the data to be presented to be very, very clear.

Dr. Robert Pearl:

Because if I were a family, with a member with Alzheimer, I wouldn't like to just know this might work or not work. I'd like to have the data, the information, I think to be able to make this decision, yes, science is difficult sometimes, at the most detailed level, reading a case report out of a journal, but we can translate it.

Dr. Robert Pearl:

Journalists like Joanne and yourself, are experts of being able to take complex sets of information, and make it understandable by patients, I think we can promise people that we're going to start with the individuals who are most likely to benefit, we're going to make sure that they are the right ones chosen in line with the FDA's new approval.

Dr. Robert Pearl:

We're going to have a scientific study with data and great transparency, and we will have a definitive answer for families in a short amount of time, whether it's two years or three years, I think that's the best resting place. We're not going to go all the way back

to say this drug doesn't work, and at the same time, I think it's a big mistake, to give this type of carte blanche for next nine years.

Chitra Ragavan:

But leave it on the market till that study is done?

Dr. Robert Pearl:

Make the market be the study. So what I'm saying is shrink the number of people, for whom is going to be administered to the group most likely to get better, administer to them as part of a scientific study, not just as available to them anyone who wants it, and promise people that we'll have the definitive answer, by the way, exactly what we did with COVID vaccines.

Chitra Ragavan:

Great. Well, Dr. Pearl, Joanne, thank you so much for joining me on Techtopia, and for this fascinating conversation.

Dr. Robert Pearl:

Thank you so much for hosting it, and hopefully it will be educational, both of the families that are facing this tragic disease, and for the rest of the nation.

Joanne Silberner:

I second that.

Chitra Ragavan:

Hey, Joanne, it's great to finally get you on my podcast.

Joanne Silberner:

Great to be here.

Chitra Ragavan:

Dr. Pearl is the former CEO of the nation's largest Medical Group, Kaiser Permanente, and the author of a new book called, Uncaring: How the Culture of Medicine Kills Doctors and Patients, the proceeds of which go to Doctors Without Borders. Dr. Pearl also co hosts with Jeremy Corr, who also happens to be my wonderful executive producer, the popular podcasts Fixing Healthcare and Coronavirus, The truth.

Chitra Ragavan:

Joanne Silberner is an award winning health and science freelance journalist living in Seattle, and my friend, and former colleague at NPR. Silberner has covered the FDA for decades while at US News and World Report, and at NPR where she worked for 18 years. And for eight years Joanne taught young journalist at the University of Washington.

Chitra Ragavan:

Joanne has won multiple awards including the Keck Communication Award, from the US National Academy of Sciences, and the best cancer reporting award from the European School of oncology.

Chitra Ragavan:

She has written a piece on how as you Adulhum came to be approved, published last week in the online media outlet, STAT+, and it's a fascinating look at how the FDA responds to pressure from drug companies and patient groups, very relevant for this story. This is Techtopia, I'm Chitra Ragavan.