Wow! Or Yeow?! 2026 Post-Session Chat Transcript

Zan Fleming (00:00):

That was just over the top in terms of high quality, very valuable discussion. I can't thank the panelists enough, but nothing for me to say other than thanks to our panelists. Maybe, Thomas, you've been watching the audience and the chat. Any quick takes from that?

Thomas Seoh (00:32):

Well, there's an active chat, but I think what we could try to do for a couple minutes is maybe go over some of the lightning round questions, because I think those are things that people are curious about, and Pediatric Vouchers was one of them. I guess one question for the pundits on our panel is, when will it pass? I think people are waiting for that. Is it going to be this spring? Is Congress all tied up with other things, war powers, impeachments? I have no idea. ICE? Or do we have to wait until September 2027 to see Pediatric Vouchers and other things with the PDUFA package?

Frank Sasinowski (01:16):

Are we with the audience still? Thomas?

Thomas Seoh (01:21):

This is the informal part, and we have a lot of people who are just hanging around waiting on your words.

Steven Grossman (01:32):

There are 80 or 90 people still on, so let's give them something to listen to.

Zan Fleming (01:37):

We covered Pediatric Vouchers pretty well.

Frank Sasinowski (01:40):

Yes.

Zan Fleming (01:41):

We might just say it's likely to happen. Will be soon. [In fact, pediatric vouchers were renewed on February 3, 2026 as part of the Consolidated Appropriations Act of 2026.] I'm interested in the panel's thoughts about the so-called National Priority Voucher Program and its sort of rough start, in my opinion. They've got a couple of selectees that have not proven to be ready to go, but maybe, what are your thoughts, Frank, about this National Priority Voucher Program?

Frank Sasinowski (02:17):

It is kind of, I'll go back to what I referenced earlier, in that Peter Stein was the first person who publicly announced that the FDA was going to be implementing the 1997 law with the new guidance where they're going to recognize confirmatory evidence as a way to confirm the findings of a single positive, adequate and well-controlled study. But that information, from talking to Peter,

all of that work, there was maybe a 10-year process internally to get to the point where Peter was able to stand up at the Willard Hotel in September 2019 and show his slides, which I still have kept copies of because they were so, you know, kind of trailblazing. But what I'm getting at is, that shows a process that works bottom up that both Peter and Steve talked about, being a bottom-up process, and where we have this top-down process that isn't taking into account wisdom that's inherent in the institution, it's a different process.

(03:30):

We used to call things like Peter talking “podium policy,” but we knew it was podium policy because it was being spoken from podium, but it had everyone's input inside the agency behind it. Today we might call, instead of “podium policy,” we might call it “podcast policy” because it is like when people are going to come onto a podcast and say, "I've got an idea," and then it hasn't been internally worked. To give you an example, when I referred to the Plausible Mechanism pathway, which came out in November, I was at the National Press Club at a meeting and I took, I won't say who, it was an office director in the Center for Drugs. I went up to the office director and I said, "By the way, can you tell me something a little bit more?"

(04:18):

And the office director said, "Frank, you know as much as we do, because you've read the same New England Journal article as we've read." So, both Peter and Steven have spoken to this, and they've spoken much more eloquently to this than I have, but I just want to say it's emblematic of how things have changed. And I'm just saying they changed because I did applaud the concept of a Plausible Mechanism pathway. I want to help Dr. Makary and Dr. Høeg and Dr. Prasad and Dr. Thanh Hai and Kumar. I want to help flesh that out so that it can help patients, but it's not being delivered to the public as a fully-formed concept. And I think that's the same thing with the Commissioner's National Priority Voucher Program.

Zan Fleming (05:16):

Yeah. Well, and another podium policy is the, and we'll ask Peter to comment on this, the so-called one trial makes all, will be sufficient for approval. Peter, is that really a thing? Is that going to make a difference in chronic drug therapy approvals?

Thomas Seoh (05:44):

And Peter, just state the policy we're talking about for the audience, please.

Peter Stein (05:49):

I'm not sure there really is an enunciated policy, but I think the idea was whether the typical approach that has been instantiated for many years based upon appropriate reading of the statute, which talks about the need for investigations that, it's been interpreted. And I think the prior congressional discussions on this made it very clear that the intent was to require two or more adequate, well controlled trials to meet substantial evidence. But as you know, in 1997, that was changed to one and confirmatory evidence. And Frank, as much as I'd like to suggest that I somehow instantiated policy, the truth of the matter is, confirmatory evidence has been used since the statutory change. It's just that guidance was developed by some terrific people in the policy office at OND – Dr. Pippins and others who put together with broad OND- and CDER-wide input, a guidance that articulates and clarifies and I think perhaps better characterizes what would be acceptable types of confirmatory evidence.

(06:59):

But confirmatory evidence has been used for many, many years before that guidance came out, before I said anything at any podium. In terms of the one trial, I mean, you should realize that, if

you look at the substantial evidence guidance, one trial is already in there. The issue, if you think about it, a lot of the background for the two or more trials came from the recognition that back in the sixties and seventies and into the eighties, many of the trials that were submitted to the FDA were little teeny trials. They were trials with one or two sites, ran a trial with 20 patients, not necessarily with the best designed or conducted trial. And so one of those trials didn't mean very much, and the statute really evolved based upon that understanding of how drugs were being developed back then. Now of course, fast forward now to the last two decades where drug trials are generally global or sometimes are US only, but often they're global, multinational trials and very large trials and much better powered.

(08:04):

The guidance that came out just a couple years ago on substantial evidence articulated the three pathways that were already understood and used. One is two or more trial well-controlled trials. Another is one trial and confirmatory evidence based upon the change of the law in 1997. And the third is one trial that provides the same evidentiary threshold as would occur with two or more trials. And so what does that mean? It means that a trial that is consistent in its primary and secondary endpoints, across its different sites, across subtypes, and typically is a trial which is focused on a significant morbidity or on mortality, but that is in statute and it has been used. There are approvals already with one trial that is a very, very rigorously done trial with very convincing p-value and consistent findings throughout all of the primary and secondary endpoints.

(09:08):

And so it's not necessarily a change. I think we have to recognize, we can say, well, "Let's move to one trial," but we should also just recognize, what do you give up when you do that? Well, one trial with a p-value of less than 0.05, I'm not going to go into, I think most people know what a p-value means, but it certainly doesn't necessarily mean that the drug works. When you have two trials, both of which show the same outcome, then you have a much greater surety. I think the question really comes down to, and this is what the Commissioner has to consider as he's pushing these kinds of changes, are we okay with more mistakes? I'd say more drugs that actually don't work but have one trial that suggests they do work. I mean, I think that's an important consideration that we have to think about, is what do we give up when we do that? And again, I would go back to the point that one trial is already used. The one trial approach has already been used for a number of approvals, but that trial has to meet the criteria that are articulated nicely in the substantial evidence guidance.

Steven Grossman (10:19):

Peter, maybe you could respond to a position I've taken that I'm not sure I'm right on. So I'm sure I've overstated it in writing, which is that the current state is, two are required except when you can show that there's justification for something that is either confirmatory in terms of the second or in size. In other words, I like the standards you set up, that if you have two trials with lots and lots and lots of exceptions, where one trial, however formulated is sufficient, that it's hugely different than a standard that says, "One is required, and we'll tell you when we need a second one." I think that the message change is just awful.

Peter Stein (11:14):

I would agree because then one trial with a p of 0.049 is sufficient. Now one trial with a p of 0.0001, that's a large trial with consistent endpoints and consistent findings across sites for a very serious disease where needing and doing other trials is very challenging. That may be sufficient, and that's what the guidance currently allows. But I completely agree with you. The standard is lowered to one trial, well, there'll be approvals of drugs with a p of 0.046, and those drugs probably work. And again, the statistics would say they work, but they certainly don't give anyone the assurance that the current standards do. And just to pick up on something else that you've

mentioned, which is something that I think is really an important sort of philosophical point in the confirmatory evidence guidance is that the confirmatory evidence is not a sort of single thing.

(12:08):

It can be a range of different aspects and evidence, all of which has to be meaningful and scientifically valid. But you can put together confirmatory evidence with multiple components. But moreover, the strength of confirmatory evidence isn't the same in all applications. If you have one really strong trial, adequate well-controlled trial, with a strong p-value, the burden on confirmatory evidence is lower. And on the other hand, if you have a trial that has a more marginal p-value 0.04, not the most robust evidence, then the strength of confirmatory evidence has to be much greater. And so really the one trial approach has been instantiated more often by using confirmatory evidence to increase the probability that the one trial gave the right answer, and I think is the approach that is much wiser and much better than just saying, "Hey, one trial," because what you're left with is no other evidence that really could be mounted to support the probability that the drug works.

(13:13):

And then you're left with one trial that gives you some confidence, but not a very high level of confidence. If you ask me what I would want to give to my children or my wife or my family, would I give a drug that was proven with one trial with a p of 0.04? My answer would be no. I would give a drug that has two trials that have established that the drug works, has properly characterized safety. And that's a drug that I think we can trust. And I think we all know that even the phase 3 programs that are currently done don't characterize drugs fully. And there's much we learn after drugs are approved, both about their efficacy and about their safety, and I can only imagine situations where one trial is sufficient, and you're ending up with learning much more afterwards. And on some of the things I suspect would be learnings you wouldn't want to have afterwards. So I'm not in favor of changing things because I think the public deserves to be sure that a drug works and is safe. And I think the change would change that formula to being not so much sure, but better than even odds, which is not good enough from my perspective.

Zan Fleming (14:25):

Such an important point. And to emphasize that it's relatively easy in many cases to show efficacy, but to be able to assess safety typically takes more than would be the case for just demonstrating a therapeutic effect that's desired.

Peter Stein (14:47):

Yeah, no, I completely agree, which is why the implications of it are limited because in general, what drives the need for two trials or certainly the size of the overall program is the need for adequate safety exposure and characterization that supports labeling. So I think you're quite right.

David Fox (15:04):

We don't have anything resembling an articulation of the new policy, so it's hard to opine, but what I understood, where we might be headed directionally is not one trial full stop, but one trial plus confirmatory evidence, but opened up to a broader range of products than the serious or life-threatening disease category.

Peter Stein (15:31):

Oh, can I correct you there? There's nothing in the statute that refers to the need for confirmatory evidence to be in serious, life-threatening, unmet needs. It doesn't say that.

David Fox (15:41):

Yeah, no, I understand that. I'm saying that the way FDA, from a policy perspective, through guidance, has interpreted the statute, is they have tended to limit the use of one study plus confirmatory evidence to particular cases, serious, life threatening. And what I understood, that the Commissioner may be headed directionally, was to open up one study plus confirmatory evidence as a more general approach than the more limited approach it has been historically. And I think one of the interesting things to think about, I totally agree with you, that the heart of this is how much uncertainty is the public willing to bear? That's critical. But it is interesting to think about, the issue with one study is, was that the result of chance? And the question is, do we have more analytical tools available to us and more visibility into the disease pathway to get a higher sense of confidence that what we saw in that experiment, the passing study, and I don't want to talk about marginally passing studies, but a clearly passing single study, can we get to a higher level comfort that that was not a false positive through using other tools, other sources of evidence, rather than repeating the study, doing it a second time.

(17:15):

Doing the study twice, yes, that was an old way of reaching a higher level of statistical confidence. But I think if you push the policy in that direction, it could actually have a very favorable effect on innovation and science because there'll be incentives to develop new tools to gain confidence that what we saw empirically in the one experiment, we can say with confidence was not the result of chance.

Peter Stein (17:45):

Yeah, I mean, just two quick comments on that, I just want to make one is that you're absolutely right that confirmatory evidence can be very compelling. And because there can be multiple sources of it, I think it can complement a single trial that's itself reasonably convincing ,to provide a package that certainly would meet substantial evidence. I think the thing that we should recognize in common diseases, and Zan I think commented on this, typically, you still are going to need more than one trial anyway just to get the safety.

David Fox (18:20):

Absolutely for safety, yeah. Safety is a whole different issue. Yes.

Peter Stein (18:24):

But I do think, and so really where it applies is where it's been applied, which is in rarer diseases, where doing two trials is more challenging, I think because the statute already allows for this. Again, the statute doesn't say "in serious diseases," it basically says "at FDA's discretion" essentially, or "secretary's discretion," or whatever.

(18:43):

But it doesn't say that there are particular criteria where it can or cannot be otherwise applied. It's more where appropriate, and I think this doesn't therefore require statutory change. And I think a company could itself just say, "Look, we have enough patients in this one trial, and we have preclinical evidence." We have real world evidence. As to John Jenkins' point, we have mechanistic data and PD, pharmacodynamic data to give you a compelling case that the results from the trial that we're going to conduct are indeed showing that the drug is effective. And would you, FDA accept it?" I think a company that pressed on that point could potentially be successful because there's nothing in the statute that would undermine their argument other than the fact that it is discretion as to where this is used. But I think, truthfully, to your point, a very strong scientific basis where you understand how the drug works, the molecular target in the pathogenesis of disease, and you have evidence from preclinical and clinical data that, all told,

gives you a compelling case the drug works, and then you have a positive trial, I think that gives you the same level of evidence essentially as two positive trials.

(19:54):

So I completely agree with you, and I think that's on the table. I think companies could push on that point where they felt that it would make their program more streamlined.

Zan Fleming (20:04):

Boy, we could keep going for hours and hours. And I do apologize to Jodi and Ricardo for getting into the weeds of drug and biologic development. Boy, what terrific additions they were to this panel, and likewise, everybody else was just stellar, could not have been more valuable. The only problem is, as usual, we left a lot of stuff on the table, and we'll have to come back to those offline.

Steven Grossman (20:39):

Or maybe do a midyear edition instead of just doing it anually.

Zan Fleming (20:48):

Yeah, there's just too much to cover in a single annual version. So thanks for that.

David Fox (20:56):

Whoa! or Yo?

Zan Fleming (21:00):

With, holy cow, we got to bring it to a close. I know everybody's got to get on other calls, and so, thanks again. It was just wonderful. I've learned more than anybody.