Advancing Drug Development by Reducing Reliance on Animal Testing

Case Example: Pre-Clinical Animal Models in Lung Toxicology

Hybrid Meeting
Thursday, February 26, 2026 | 10am - 4pm (*eastern*)

Transcript

Welcome

Susan C. Winckler, RPh, Esq., CEO, Reagan-Udall Foundation for the FDA

Susan Winckler: (00:00:40)
Hello and welcome, everyone. Thank you for joining us both in person and online. It is just after 10:00 in the morning, so we are going to get started.

For those of you who I've not met in person, I'm Susan Winkler and I serve as the CEO for the Reagan-Udall Foundation for the FDA. For those of you who are new to the foundation's work, we are the nonprofit, non-government organization that Congress created to help FDA do more to protect and promote the public's health.

So today's meeting is part of that work. We bring together experts from across sectors to explore various issues. It's a meeting about shared learning, which can help inform the agency's work. It's not a meeting about regulatory decision making. The foundation does not engage with FDA on regulatory decisions.

But I have a few housekeeping notes before we get into the content, and I assure you in the... It's a mere hundred and some slides that we're going to get through in our day together.

I want to note to everyone who's in the room and online, we have about 50 people here in the room and a few hundred who are attending virtually. So we will be making sure that both all of you in the room and online can see and absorb the information.

Because of the size of the meeting, our virtual attendee cameras and microphones will remain off throughout the event. And if you're attending virtually, please use the Zoom Q&A function to pose any questions to speakers. For those of you who are in person, there are some note cards with the team that you can use to write a question on and hand it up to me.

We are recording this event and we will post the recording, the transcript, the slide deck on the foundation's website next week. The slides are already available on our event page and there are some paper copies available as well.

I'll note that with the paper copies, I know you will be stunned to learn that some of our speakers had last-minute changes to their slides. And so those are not reflected in the printed copies, but they are reflected in the version that is available online.

For those of you who are present in person, I ask you to not join the Zoom meeting just for risk of A/V conflict and to more importantly, embrace the dynamic that you are here in person engaging with your colleagues.

So I also want to thank each of our speakers for investing so significantly in preparing for today's event. We appreciate all that you have invested and explored in preparing your presentations.

We also thank Aer Therapeutics, Avalon Pharma, BIO, Charles River Laboratories, Endeavor Biomedicines, Ionis Pharmaceuticals, and VIDA for sponsoring today's event.

So let's talk about what we're going to do today. This morning, we're going to ground ourselves in the current realities of preclinical lung toxicology approaches and requirements, including the roles and limitations of animal models. We'll then hear some industry perspectives on how those expectations are playing out in practice.

After lunch, we'll shift toward solutions and the opportunities, including emerging alternative methods, human-relevant models, and what each player in this ecosystem might do to pursue our dual goals of improving product development for patients and reducing our use of animals in that process.

I'll note that most of our conversations today are above product, with the exception being those case studies that illustrate the specific dynamics. And our goal overall is to surface practical insights and opportunities that can help advance drug development while reducing reliance on animal testing.

So we'll open this morning with remarks from Dr. Steven Kozlowski, who will open our meeting. I'll invite Dr. Kozlowski to take the podium. Dr. Kozlowski serves as chief scientist in the office of the chief scientist at the FDA, where he plays a key role in advancing scientific and regulatory innovation.

Dr. Kozlowski, thank you for leaving White Oak and coming to DC to join us in person today. We're grateful for your leadership in this space and appreciate you sharing insight into FDA's overall commitment in this area.

Opening Remarks

Steven Kozlowski, MD, Chief Scientist, Office of the Chief Scientist, Office of the Commissioner, FDA

Dr. Steven Kozlowski: (00:05:10)
Yeah. Well, thank you, Susan, and thank you very much for the opportunity to be here.

I want to start talking a little bit about non-linear dynamics and about regulatory science. So there's an Earnest Hemingway novel, The Sun Also Rises, where a change is described as happening gradually and then suddenly. There's also a similar concept and an ancient parable about bamboo growth, which says bamboo requires a lot of time underground where it needs

attention and watering, and you see no progress. And then suddenly, when shoots form, it grows rapidly. So I think that concept that development and movements can happen very, very slowly and then very rapidly, I think is a very important model for what's happening with NAMs.

A little bit about regulatory science. So science obviously is fundamental knowledge, theory, discovery. There's applied science and translational science that are more focused on taking science and bringing them into inventions. There is regulatory science with the agencies very, very interested, and that is a science of developing tools and standards that allow safe and effective development of FDA-regulated products.

So there's also a term beyond invention, innovation. And in fact, it became very popularized with a concept of disruptive innovation. So what's the difference between innovation and invention? An invention is a new idea or technology. Innovation is when that idea gets broadly used, where it changes our behaviors, interactions, and the systems we live in. And ideally, we want to change inventions into innovations. And I think regulatory science, where it takes these ideas and technologies and allows them to be broadly used, is really an enabler for making innovation across the board.

So NAMs. They have amazing possibilities. And they really sit right now at the interface between science and regulatory standards, ready to move from invention into innovation. NAMs can include all kinds of in vitro systems, modeling, innovative platforms for drug safety, innovative in another way, and they are really about predictive accuracy of making decisions, including making choices about preclinical testing. We know that animal-based testing is not that helpful. 90% of drugs that go through animal testing end up not getting approved by the FDA. Probably around 30% of those are because of safety that was not predicted by the animal model. In addition to that, animal models may throw out products or drugs which do have opportunities because, again, they do not represent humans.

There's been a lot of work on NAMs. The FDA had a 2011 strategic plan in which NAMs were mentioned, a 2017 predictive toxicology roadmap, and a 2021 FDA report advancing alternative methodologies. This is not a new issue. There have been many working groups, a toxicology working group, a model and simulation working group, alternative methods working group. There's been targeted funding. In FY23, Congress gave FDA $5,000,000 in core funding for this, and there's been some additional funding, legislative change. The FDA Modernization Act in 2023 changed the definition of non-clinical test to allow for alternative methods. FDA has had guidance on reproductive toxicity, phototoxicity, modeling, and qualification, and there's a qualification process envisioned by the 2016 Cures Act, which is a multistep public approach to publicly qualifying drug development tools. There have been over 50 NAMs in the ISTAN, the innovative science and technology part of that program, including liver-on-a-chip, but currently none of them are fully qualified.

So what I would say is there's been a tremendous amount of effort, but progress is slow. The bamboo is not yet sprouting. We've invested a lot in watering it. We've spent a lot of time on it, but what is going to happen? And this idea of gradually then suddenly, there are many examples of this. Monoclonal antibodies. Discovered in 1975, there was one product in 1986. Really nothing happened until the mid to late '90s when immunogenicity was solved by genetically engineering antibodies, either chimerics or humanized, and then suddenly the field explodes.

Relating to animals, biosimilars, there's been debate since the beginning of biosimilars that animal studies are not necessary because you have all this structural comparative information. Fedora in 2022 made that change allowing for non-clinical testing to not be animal studies, and really very little animal testing is asked by the FDA now for biosimilars. So years of discussion about this and then change.

Interchangeability for biosimilars is an area, huge amount of discussion, and then suddenly we've really changed our guidance that switching studies are no longer necessary. So really, how do we move the gradually into the suddenly for NAMs? And I think the FDA is taking this very, very serious. The roadmap of April 2025 really says we need to push this faster and further.

And I think names matter. NAMs is something where the acronym has had a long persistent life, but what it spells out has not. New Alternative Methods, New Approach Methodologies. And to me, the roadmap picking New Approach rather than Alternative really suggests it's thinking about NAMs in a completely new way. That it's not just a one-to-one correspondence, how do we replace what an animal model does, but how do we really explore the powers of these new technologies?

The roadmap talks about integrating many, many different methods, really combining them in silico together with cellular and organ-on-a-chip methods. I will mention the National Center for Toxicology Research has recently combined liver spheroids with an AI/ML method, which got 15% better concordance for liver toxicity. So there's huge opportunities to get even better by using these models together.

So how do we get there? So the roadmap has a phased approach to integrating NAMs into the process. Using NAM data alongside with animal data, leveraging databases. One particular thing mentioned in the roadmap was reducing the duration of certain animal studies and monoclonal antibodies were mentioned as a possibility. And already the agency, as of December 2nd, issued a draft guidance, which eliminates most six month non-human primate toxicities for monoclonal antibodies using three-month data and weight of evidence approaches.

Obviously, to do this, we're going to need new ways of thinking about validation, and this may look at retrospective analyses of what we've done, standardization across approaches. And again, I reiterate this idea of new approaches, that we really need to think about this differently than just doing an animal study in a different way. To facilitate this, FDA's developing more guidance documents, it's going to provide more examples. Recently, CDER published two papers on agency experience with NAMs, and also created a website on December 29th, integrating many of the different possibilities for use of NAMs in drug development.

I think we also need to invest in training for our staff to make sure they are as familiar and comfortable with NAMs as animal models in review. This also depends on many partnerships, including within the government. So certainly FDA's working with many partners, ICCVAM, the Interagency Coordinating Committee on Validation of Alternative Methods, joint funding initiatives. I will mention that FDA and NIH had a workshop on July 7th of 2025. FDA signed an MOU with NIH on complimentary and its validation qualification network to support development of these in August of 2025. And recently, in December 24th of 2025, the FDA commissioner, along with FDA co-authors and NIH co-authors, published a paper really discussing long and short-term goals and concepts of NAM validation.

So as noted in the roadmap, FDA needs to assure that any new method that replaces an animal is equal or superior to the animal test it replaces. So this is a non-trivial question. And I think one of the keys to this is understanding practically what that means, is that overall baseline predictivity. Studies have used different data sets, approved drugs, drugs and animals. There's drug studies at both animals and humans and drugs only studied in animals that never made it into the marketplace. So we don't know human data. How do we leverage this in understanding what the comparator is? Because replacing an animal is about really understanding how much value an animal does or does not provide. What organs or systems need to be covered? Do they need to match literally every single adverse event in every single system in a one-to-one way, or is it possible that NAMs will actually miss some things animals do, but they will capture many more things and overall will lead to better predictivity?

And then also, when we look at safety, are we concerned about every adverse event that we predict or only grade three or four adverse events? Are we really concerned about adverse events that impact clinical development?

So to me, those questions become fundamental in thinking about that really super high-level goal, which we want to achieve of replacing many of these animal models.

So I want to close with the fact that this is really a time for change. We spent a lot of effort in this, and I don't think it's wasted effort. I think we were watering that bamboo, growing roots under the ground, but the question is, is it time now to really see that bamboo sprout and grow rapidly and really become innovation and not just the set of inventions which have limited use?

So I really want to thank all of you for participating in this meeting, because I think this is a great opportunity to push the science in the world of NAMs for very particular purpose, innovational toxicity, but one that is extremely important and really look forward to out of this meeting coming some ideas that really take us practically forward in moving toward this ambitious goal.

So thank you very much.

Use of Animal Models in Pre-Clinical Lung Toxicology Safety Studies: Current Expectations and Limitations

- **Matt Reed, PhD, DABT, Principal, Coelus, LLC**
- **Jeff Tepper, PhD, DABT, Consultant, Tepper Nonclinical Consulting**

Susan Winckler: (00:17:00)
Dr. Kozlowski, thank you so much, not only for the remarks, but I love a good metaphor. So let's just understand that bamboo is going to come up a lot today. So we really appreciate that framing [00:26:30] and helping us as we start our day.

Now let's turn to our exploration of our case example, where we want to focus on the use of animal models in preclinical lung toxicology safety studies. For this, we're going to turn to doctors Matt Reed and Jeff Tepper to ground us in the current science by examining the historic value, the limitations, and the translatability of animal models in predicting human safety and pharmacology for pulmonary drugs.

So I want Dr. Reed, if I could have you come on up to the microphone. Matt is a principal at Coelus LLC and you have our first deep dive.

Matt Reed, PhD, DABT, Principal, Coleus, LLC

Dr. Matt Reed: (00:17:55)
Deep dive. Here we go, right? Make sure I get everything straight here.

Susan Winckler:
Hit the big button. [remote control]

Dr. Matt Reed:
Big button? Big button in the middle? No, not the big button in the middle. Wait. That's not the big button in the middle.

Susan Winckler:
That didn't work. Here, let me... Why don't you just... There we go. You got it?

Dr. Matt Reed:
I think so. We'll see where we go from here. I really just want to thank the Reagan-Udall Foundation, all the organizers here, the backstreet components that really take place to bring a meeting like this together. I think it's wonderful to have regulators in the room. It's wonderful to have industry in the room and some hardcore scientists as well. It gives us an opportunity to potentially [00:28:00] look at things a little bit differently than we have in the past.

So what are we doing here? Not looking at llamas, or alpacas, sorry. All right, that's the wrong one. We need some technical help here.

Production:
That's okay. If you want to just- Just say, "Next slide," and then I'll take care of this.

Dr. Matt Reed:
Can you do this? All right, cool.

Production:
So just say, "Next slide."

Dr. Matt Reed:
Next slide. This is the wrong deck, but next slide. Perfect. Next slide. There we go. So, outline of discussions today, really looking at pulmonary delivery from a human standpoint, understanding dose, understanding exposure is hard, very difficult on the clinical side, but it's doable. Pulmonary delivery in animals, we use a lot of those same concepts that we look at for pulmonary delivery and understanding what pulmonary delivery means in a human situation. And then a couple of my thoughts on regulatory interactions and then also some other components here.

So next slide again. Next slide. So what are we looking at from a big picture standpoint? So again, it's a we're all breathing air. We're all breathing air tidally now. So delivery to the respiratory tract is really we're breathing through a nose, we're breathing through our mouths. Think the air that we're breathing, that atmosphere that we're breathing transects and moves down through the respiratory tract, past the nasopharynx, into the trachea, and then moving down into the larger airways, down to smaller bronchials, conducting airways, and then into the alveoli. That breathing is for gas exchange.

We have to understand that impacting from a disease standpoint can happen anywhere along the respiratory tract. So whether it's treatment or whether it's understanding toxicology or hazard assessment, we have to understand what human exposure means. We have to understand what dose means so that we are understanding how we impact disease and then how we impact hazard assessment and potentially safety as well.

Next slide. So an old slide from a good book. So if anyone wants to know where this came from, it's not AI-generated, but if we look at, again, human dose assessment, particles, droplets, these are the aerosols that clinically we're going to breathe into the lung that give us an opportunity to treat. Again, transecting the respiratory tract, moving down through different areas. People talk about targeting lung, tracheal bronchial area, so airways into conducting airways in the alveoli as two parts that we want to look at.

Then there's mechanisms in the biology that we can generate from NAMs, that we can generate through animal models, that we see in clinical trials as we assess people. Those health effects can either be good or they could be bad. But in the end, it's really about what that person, what that animal is breathing, what that atmosphere looks like, and then how we assess dose. That's the top line for moving into, especially in the toxicology space, where hazard meets safety, where safety meets risk. And then how do we apply that to people?

Next slide. So pulmonary target areas, this is a transition slide that wasn't meant to be a translation slide, but we look again at the larger airways. These airways move out to the periphery of the lungs. The gamma statistic figure that where we're actually looking at, at lightly labeled particles and where they go into the lung, whether it's central area, whether it's out to the periphery. So understanding as you transect what cell types are involved, as you move through the respiratory [00:31:30] tract, as you move through the alveoli, helps us understand where things go and then what unit surface area disposition looks like. So very much different in larger airways, what they look like in terms of unit deposition as you move into the smaller airways.

Next slide. This should be a transition, yeah. So tracheal bronchial ends. And then next slide. There you go. Pulmonary is another area that we're trying to target. So you'll hear lots of times about targeting, whether it's a non-animal model or whether it's an animal model [00:32:00] or whether it's human, what does that really mean from a big picture standpoint?

Next slide. So this is a busy slide. On the Y-axis, you're looking at deposition of particles. On the X-axis, you're looking at particle diameter. This is aerosol diameter. In the grand scheme of the pharma world, we're really looking at the right-hand side of this slide. These are bigger particles. Everything below one is something that you probably see from an environmental perspective. Everything above one is our pharma area from a drug delivery side of things.

So P equals pulmonary, that's what we just saw on the other side. So those conducting airways into the alveoli. TB is tracheal bronchial. Those are the bigger airways. And ET would be upper respiratory tract in this particular model. So the little yellow line that you see as you move across, that's where things start to transect. So ET and TB and P. So TB, the tracheal bronchial and the pulmonary region really transect in terms of particle size at around three to three and a half microns in this model of tidal breathing based on the ICRP. So what it really tells you is you think about that exposure that you have, there's differences in deposition in the respiratory tract, differences from a unit standpoint on where those aerosols go and what cell types they interact with. So to give an example, TB is at a surface area, the tracheal bronchial area. These are ballparks of around 2 meters or 2,000 centimeters. If you look at those pulmonary, conducting airways into the pulmonary region, we're looking at something more like half a tennis court area size. So big differences, same deposition as they cross lines percentage-wise, but very much difference in particle per unit surface area. Next slide. Go ahead and go to the next slide as well. Perfect.

So what are we talking about treating here? Examples of respiratory disease indications you can see on the left hand side of the slide. Anything from asthma and COPD down to systemic indications like migraine, diabetes, and other systemic. So the route of delivery, treating either systemic disease or from a top line standpoint, what's really going on in the lung. We have different ways that we can do this. We have formulations that we can use across the board. Nebulizer delivery, dry powder inhalers, meter dose inhalers. You have differences in the interaction with a patient and then what those different types of devices will actually do. So a nebulizer, an active device. Advair, if you will, capsule-based devices, those sorts of things. Use pulmonary pressure that's delivered from the patient, and then that delivers the medicine to the lung.

You have active, like an MDI where you have to breathe in, but you also have active generation. So there's components and parts and pieces of this that really, really get in back to that dose function that we were talking about earlier. And they're very different potentially and much the same in many cases across these different device technologies. Next slide.

So platform of delivery, what do we do from a kinetic standpoint? How do we use a nebulizer? Well, just breathe like we're breathing in the room now, right? DPI, forced inspiratory, hold our breath potentially. Same thing with an MDI, but you have to coordinate with the activation of that device. And so how do we determine dose from a clinical perspective and a chemical manufacturing control side of things? Well, we have to characterize particle size. So on the top right, you see what looks like a normal distribution, a mass function on the X axis, particle size across the bottom. And you see this normal distribution. Those are the kinds of things you want to see so that we can predict or potentially predict where those particles will go into the respiratory tract.

Again, you see a picture in the middle there on the right-hand side. That's that ICRP model that we just looked at. That's a modeling of where particles go using a certain type of breathing pattern that you'd see in people. And then we have methods and ways that we can do that from a modeling perspective and then measurements that we're going to use on the chemical manufacturing control site again to really understand where things go in the respiratory tract, like the gamma scintigraphy picture you see at the bottom and the right side. So next slide.

So what does this really mean from a take home standpoint? Super complicated, right? So it's super, super complicated. But what we've been able to do across the field, if you will, is really understand what kind of doses we're giving, where those doses go. And the figure that you see here, we look at the amount of drug that you may have delivered to the lung. These are real case examples from Andy Clark and reproduced by Jayne Hastedt as well. They look at the different device types along the X axis and then the types of different formulations and different device combinations that we use. So we really can understand where things go in the respiratory tract, where things are interacting from a cellular standpoint to really get at what human dose looks like. So I think that that's important for the audience to understand today for you guys online is we have the ability to accurately assess dose in human beings across technologies and across formulation of different types.

So from a toxicology perspective, that's the tenet where we want to start. Where is that exposure? What does that exposure look like? And then what does dose look like in a human setting? Next slide. So how do we use those kinds of technologies in an animal world? So we use very, very much the same kinds of techniques that we use to assess aerosols in the human side in an animal setting. And we've been doing this for a long, long time. So I think we mentioned 70 years of the use of animal models and inhalation toxicology. It goes back beyond that. A good friend, George Box, we hear about statistician, inhalation toxicologist as he started out. So it's been a long time. We've got a lot of data that's sitting there for us to utilize and to understand. We have the ability to go back and transect that information.

So delivery from an inhalation standpoint in the animal model systems, we almost always use tidal breathing. So same techniques, many of the same techniques, almost always tidal breathing in those situations. So a little bit different depending on how things translate from one model to the next. Next slide. So particles flying in a lung, what does this mean from a translational biology standpoint? So we talked about humans a lot. See the size of that human lung on the left hand side. We do inhalation toxicology studies down to the size of mice, if you will. So a difference in the size of lung, that tubing, where particles go. So if you look at what happens to a particle as you breathe it into the lung, it's flowing. For most of the pharmaceutical aerosols you see, you have two different mechanisms of deposition within the respiratory tract that are primary drivers.

So that particle can fall out over time. Sedimentation as it flows through and loses velocity moving through the lung, so it falls out, or it can impact onto the side of airways, essentially, as you move down the respiratory tract. The smaller those tubing sizes get and the bigger the particle. So if we're in a size range that I can breathe, that you can breathe, may not be exactly where we want to be for a mouse, just because of the difference in size, that changes where that particle deposits in the respiratory tract. So next slide.

It's a busy slide again, but what it shows you is that, again, we've been doing these things for a long time in rodent systems and larger animal models, we understand sort of the dynamics, the types of systems that we need to use, how we need to generate aerosols, what size those aerosols need to be in, and how to actually make this happen from a toxicology perspective. So on the left-hand side, you see a rodent system, you see a large animal system on the right. What do we use? A generator, some type that may be a clinical nebulizer. It may be some sort of dry powder generation system that goes into a mixing chamber and then is delivered to the breathing zone. Again, atmosphere, it's going to enter into the lungs of those animals just like it does into people.

So understanding what that atmosphere looks like, characterizing from a chemical standpoint, characterizing it from a size standpoint is very important. But we can do this. Again, we've been doing it for a long time and just like on the people side, it's possible. We understand what dose looks like. We're learning more about what dose looks like in these animal models, and we can apply that from a translational biology standpoint back to people. Next slide.

A couple of words on regulatory convergence and divergence potentially. So I think there's a lot of things that the rest of the world, that different divisions of the agency are currently using from a top line standpoint to look at regulation. Those are sort of tenets following ICH guidance and other. What's not always clear is sort of this clinical dose estimate as one component of that. And then you'll hear a little bit more about dose estimation and non-clinical models from Dr. Tepper here in a moment as well too. So I think understanding what the pulmonary division potentially does, so DPAC specifically versus the rest of the world versus other divisions within the agency is important from a top line standpoint to kind of understand the big picture. So use of NAMS in regulatory, we had a great talk on that from our previous speaker. So next slide.

So Matt's words on NAMS. So to sort of set the stage, I think as we talked about exposures on the clinical side, we talked about exposure on the non-clinical side and assessing hazard. So these toxicology studies that we used to, and then pushing that back to risk. How can we use animal models and NAMS from a top line standpoint to kind of really come together? I think it really depends on the question. And so, we have to understand what things look like on the exposure side. We have to understand where deposition, what those cell types look like, where toxicology may take place, and then understand the metric that we're using on the exposure. So that could be unit surface area, that could be gram lung weight, it could be other. So really understanding how that animal model or that NAMS may reproduce what you're seeing on an animal model side or the clinical side from a metric of dose is super, super, super important as we understand hazard.

So using animal models, we've got different types that are available. We're going to hear a lot about that this afternoon in silico, other, AI. Just remember, if you will, use AI, but do your spot checks as you transect the big picture from a modeling standpoint. And then I think it's really about the question. So it comes back to what the question looks like. How do we use that model to either with or replacement for animal models? Next slide.

So what do I recommend to this audience and to the public is, look, we have the ability to predict human dose. We have the ability to predict animal dose and we need to incorporate NAMS on a case by case basis to really get back to hazard assessment, toxicology, and then risk assessment for our patients and for the public.

Susan Winckler:
All right. Thank you so much, Dr. Reed. Even with technical difficulties on time and helping us now, we've got our bamboo example and our plumbing example to help us think about it. One of the questions that came in had to do with that you were talking about the lungs and not the nasal region, and that was because that's the focus here we're looking at this model. Is there any intersection where we cross? And here, I'll hand this to you since I'm asking you a question that you didn't expect. That's all right. So just when is the upper respiratory tract in the nasal region incorporated?

Dr. Matt Reed:
It's a great question. So if you look at most of the clinical delivery systems that are currently in use, it's oral delivery. So use the respiratory, the respiratory entryway is the oral cavity. And so when you look at it from a nasal perspective, you can have a face mask. So integration of a face mask into a nebulizer setting where you're breathing through the mouth and through the nose, that's where nasal toxicology can become important and important from a translational biology side as well too. There's also intranasal delivery, which is a little bit different, uses particle sizes that are way to the right of the graphs that I was showing you. So very large particles so they don't get to the lung is the idea. And we can use animal models to try to mimic that as well in certain ways.

Jeff Tepper, PhD, DABT, Consultant, Tepper Nonclinical Consulting

Susan Winckler: (00:36:00)
Great. Thank you. And we'll turn now to our second piece here, Dr. Tepper. If you would give us the second part of helping us understand the current use of these models. Jeff Tepper is a consultant at Tepper Nonclinical Consulting. So Dr. Tepper, take it away.

Dr. Jeff Tepper:
All right. Let's get this in the right space here. Okay. So my talk is entitled... Can I see it down there? Yeah. IRA demystified and next... Oh, I have the opportunity to do that. Let's see if that works. Nope.

Susan Winckler:
Other side. There you go.

Dr. Jeff Tepper:
There we go. IRA. What is it? All right. We're in business now. Okay. Well, it's not the Irish Republican Army and it's not an individual retirement account. It's something much more exciting. It is inhalation risk assessment. I know that's got you all excited now. By the way, if you happen to notice on that first picture of Matt and I, we didn't decide to wear the exact same shirts today. That was a coincidence which I noticed. I said, "Yeah, we do have other shirts, believe me." So the outline of my talk is, I really can't see that down there, is to talk about the 2005 FDA guidance and compare that to determination of starting dose for inhaled drugs. I realize that I'm getting down into the weeds that's going to really speak to my inhalation tox brethren here, but I hope you bear with me.

And thanks to Matt for providing a great introduction into what we do, how we do it, and maybe why we do it. Overall, my goal is to improve flexibility, transparency, and harmonization across regulatory agencies in determining first in human doses. My recommendation, in case I don't make it all the way to the end, and they boot me off the stage, is that the use of non- clinical data should be used according to the MRSD 2005 guidance to determine starting doses for clinical trials and allow clinical data to determine tolerability and maximum dose, in fact, in clinical trials. Put that into perspective. The conservative approach that is used by the pulmonary division in terms of determining clinical dosing is a common concern among drug developers and a major reason for initiating development overseas. And indeed, I was thinking back and in 40 years of doing this, I can't remember a single first in human dose actually initiating in the US.

So I'm going to go through the 2005 guidance. I hope some of you are at least familiar with this. This is the maximum recommended safe starting dose. Starting dose, make that in quotes there, for clinical dosing for first in humans. We start with an NOAEL, a no adverse effect level. We justify how we scale it. We convert to a human equivalent dose extrapolating between animals and humans. We select the appropriate species. Usually we test two species and usually that's the most sensitive one, but there can be justification for the more appropriate species. We include an uncertainty factor as it is in the guidance of safety factor, but I prefer the term uncertainty factor because it makes you specify what we don't understand, and that allows for further research to improve that. And when we divide that by that uncertainty factor, that gives us a starting dose according to the guidance.

And sometimes that's modified by a PAD, which is a pharmacologically active dose, but in my experience, I've never seen that used for an inhaled drug. In contrast, the pulmonary division has a new algorithm to determine the maximum clinical dose. Let me emphasize that it's not the starting dose. It is the maximum clinical dose that's being used for first in human. It starts out the same with a determining the NOAEL, and then we convert that by looking at deposition, which Matt kind of talked about, and I'll further discuss to come up with the pulmonary deposited dose. Now, I think that is a good thing. We should be talking about the dose that in fact is associated with toxicity, and the best way to do that is to have the dose at the target area of where the injury occurs. After that, we choose a scaling factor for animals to convert it so we can compare humans and animals. And for the pulmonary division, that's usually body weight or lung weight. And we'll talk about that a little bit further.

We then divide the animal dose NOAEL [00:50:30] at the pulmonary deposited dose with the nominal dose. Now, the nominal dose is the dose you put in a device. So we're not really comparing apples to apples here, and we come up with a margin. And that margin has to meet a certain criteria, which is different for different species. And if we reach that criteria, then that determines what our maximum dose is. If we don't reach it, and then in fact, we have to go back and lower the clinical maximum dose, and then we have to come up with a dose below that to actually start dosing.

So I'm going to now break down some of these concepts that I talked about in that comparison. The first one is the NOAEL, which is the no adverse effect level. And this is the primary output from a GLP toxicology study, and usually, as I said, in two animals. And the NOAEL is the highest... It was defined in the 2005 guidance as the highest dose level that does not produce a significant increase in adverse effects in comparison to the control group. Now, note that it does not define what adverse is. In the 10 years subsequent to that guidance, there's been a lot of work done on adversity by the pathology, various societies in both Europe and the US. It's a really nebulous concept what adversity is, and there's no globally accepted definition, but as I said, there's a lot of work that's been done on it.

The European Society of Toxicological Pathology defined it more as the results are the impairment of function to maintain homeostasis or maintain the capacity to respond to an additional challenge. This provides some narrowing of the scope of what adversity is, and it focuses on function, and that is a critical point. So we often infer function, we don't actually measure function in many cases, but we infer function from the pathology changes. And so that's important to helping us define what adverse actually means. The US Society of Toxicological Pathology maybe took another step further, and they defined adversity as indicating harm. Now, harm is equally as nebulous as adversity. However, what it really did was

focus it on... Its related to the test animal and the test animal only within the constraints of the study design. Meaning NOAEL should only refer to the specific studies, and it should not refer to include speculation about the origin of that lesion, the potential pathogenesis of the lesion, theoretical human patient extrapolations, clinical non-monitorability.

All of those should have nothing to do with the NOAEL. They should be uncertainty factors. And unfortunately, in the algorithm that I showed you for the pulmonary division, there really is no place to put those factors. So we need to consider how we separate the NOAEL from other factors that may influence the starting dose. I'm not saying that those aren't important factors. I'm just saying that NOAEL, the determination of NOAEL should have nothing to do with those factors. So let's talk a little bit about dose. As I already mentioned, the nominal dose is the dose you put in the clinical device. Now, we all know that what goes in the device does not all come out of it, and that has been in the clinical testing of aerosol devices is called generally the emitted dose. I prefer that term. I want to talk a little bit about terms rather than presented dose because presented dose often gets mixed up with delivered dose and inhaled dose, and that causes confusion among discussions about it.

Now, once we have a device, and now as Matt showed you, the device is not what goes to our animals. In fact, it goes through a bunch of tubing, and into an exposure chamber, and into another tubing and comes out at the animal's breathing zone. And as toxicologists, we typically refer to this as the delivered dose. My preference would be to actually call that the inhaled dose because delivered dose and deposited dose, the next category, are constantly mixed up by people and causes a lot of even more confusion. So I'd like us to talk about it as the inhaled dose because the inhaled dose is more descriptive of what we're actually talking about, the dose that the animal breathes in and doesn't get confused with the deposited dose. Now, the pulmonary division uses the deposited as the pulmonary deposited dose. And indeed, that is probably the measurement that we should be looking at, as I already indicated, because it is the dose at the target area where the toxicity occurs.

However, there's a little bit of a problem with that term also, which is the pulmonary dose generally refers only to the alveolar region and not to the tracheal bronchial region. Now many of our drugs, as you know, in fact, are meant to target the bronchials such as bronchodilators and mucolytics. So we need to kind of set that definition straight. There also is the systemic dose. And as you can see, it's an inverted pyramid, meaning less and less aerosol gets to that particular compartment. And I'm not going to talk about systemic dosing because mostly my talk focuses on a targeted dose to the lung to treat local lung disease. So how do we calculate dose? There's an equation to do that. Essentially, we can measure the aerosol concentration at the animal's breathing zone. We know the time we start exposure and end exposure.

We can also measure minute ventilation, although we typically do not do this. We estimate it from an equation that was determined by the Association of Inhalation Toxicology, which I'm a proud member, so as many members here that are in the audience. But what I really want to talk about is the deposition factor. And the deposition fraction is that portion of the nominal dose that actually gets into the lung, as I've kind of already described. And the pulmonary division's look on that is there are default numbers that describe what that deposition is. We also then scale it, and typically that's scaled in milligrams per kilogram. It can also be scaled in lung weight. It can also be scaled into surface area. The common ones are lung weight and body weight, and that's to do extrapolate between different animals and humans. So here are these default standard values that are set apart in their discussion of how to determine safety margins.

And for humans, as I indicated, 100% of it is considered to be deposited. Now, we all know that that is not true. That is a conservative approach, and we'll discuss that. For non-rodents like dogs and monkeys, 25% of the inhaled dose is deposited in the lungs in the alveolar region. And for rodents, 10% of that is deposited. There are no default values for things like rabbits, mini pigs, ferrets, and sheep. And so that leaves it up to the sponsor, in fact, to come up with some rationale as to what their deposited dose should be, which is somewhat problematic also. So here are the values that are shown from this guy, Tepper, he's in this stupid paper that... And for mouse, rat, guinea pig, monkey, dog, and human. What I want to point out here is the values for the mouse, rat, they can be used in terms of determining, using those as reasonable estimates for deposition if you're doing efficacy.

Do not use the human values. Those are conservative values in one sense and less conservative values in another sense in terms of body weight and lung weight. And I'll talk about that in a quick second. So only use those for safety margin calculation. So this, like what Matt showed you in the ICRP model, this is a paper from my colleagues, Ron Wolff and Michael Dorato in 1993, where they took data from this paper by Richie Schlesinger, another colleague of mine in 1985. I can't quite read that.

And what you can see is that there is clearly an important relationship between particle size and pulmonary deposition on the Y-axis, particle size on the X-axis. And that's for differences between species, rat, dog, monkey, and humans. And if you look at a particle size of one micron, in fact, it's about 10%, which from that previous chart is what the pulmonary division uses as their default value. And for dogs and monkeys, it's pretty close to 25%. However, if you go to where most pharmacological aerosols are, which is in the two and a half to say maximum of five microns, in fact, now the rat is about half that at about 5%. The dog and monkey are now about 15%. And you can see this is about the peak for human, and it's only about 50%, not 100% as in the nominal dose. So best case, at least according to this particular plot, is that we're at least a twofold difference in terms of deposited dose.

So why are we doing this? Well, that data was basically 50 or more years old. We can do better now. We have in silico models, the Multi-Path Dosimetry model, MPPD model, which can compute deposition factor for humans as well as five laboratory species. Unfortunately, not dogs right now, but that could be easily remedied. And this is from the Applied Research Associates. The EPA has recently, or as of, I believe, three years ago, endorsed this as the primary tool to determine deposition between species so we can compare apples to apples on the same background.

So now let me switch the topic, going to talking about scaling and safety margins. So for inhaled drugs, scaling using body weight or lung weight is usually the most common. And actually... Oops. Nope, try that again. Well, scaling between body weight and lung weight actually shouldn't make any difference whatsoever because body weight and lung weight scale isometrically, meaning they're proportional. If you look at the equation for scaling lung weight, you can see on that line below that, in fact, it has an exponent of 0.99, which means that it scales isometrically and not allometrically, which is usually to the 0.67 or the 0.75, which has more to do with metabolic activity. However, it matters a lot in terms of determining safety margin. And the default body weight for the pulmonary division is 60 kilograms. That is conservative. That's about 130- pound person. And if we scale it using that equation, in fact, that gives us a lung weight of about 653, I think, something like that.

On the flip side of that is that the default value for lung weight is 1,000 grams. That's less conservative actually, and scales to a person about 92 kilograms, which is about 200 pounds. So that makes the 60 kilogram determination, using that as a very conservative measure. And this explains why lung weight always provides a greater safety margin. And of course, clients want to have the largest safety margin possible. And why is that? It's because there are required safety margins that you must meet to in fact do clinical dosing. And the safety margin, just to remind you, is the pulmonary deposited dose, NOAEL, that's the deposited dose versus the nominal, the dose that goes into the device as the highest clinical dose. And you take the ratio of those, and if it's tenfold, then you can start a clinical trial in rats. If it's sixfold, that's okay in dogs and fivefold in NHPs.

So let's play this out. Okay? Here's a comparison of the MRSD, the maximum recommended safe starting dose by different scaling methodologies. We'll take the case example that the NOAEL and the studies that were done is 10 milligrams per kilogram with the rat being the most sensitive of the two species tested. So what are the uncertainty factors and where do we end up with a maximum recommended safe starting dose under the four scenarios? To the left are the factors, over the columns are the four different ways that it could be divided. The first two being more related to the 2005 guidance, the second two, according to that terrible paper by Tepper, which reminds me, I did not write the part on that. That is my dear colleague, Luqi Pei, who was the senior tox reviewer in the pulmonary division.

So as you can see here, the 2005 guidance for a safe starting dose, the default factor, and it can go up or down, is about tenfold. And so if we have a tenfold factor on a 10 milligram per kilogram dose, in fact, 10 divided into 10 gives us 1 milligram per kilogram. A default 60 kilogram person would be able to get 60 milligrams. Clear? All right. The other option in the 2005 guidance is used to use the body surface area. Indeed, that is a little bit more conservative. Body surface area scales better with metabolic function. And if we do that, that adds for the rat another 6.2, so giving us a total of 62. And now we can dose about at 10 milligrams for the same characteristics. Now let's take in the pulmonary division algorithm as it's currently designed. Well, now we still have a 10-fold difference, because you're required to have a 10-fold difference between your maximum starting dose. We don't really have a scaling factor here. We have a 10-fold difference because we do have a deposition factor. We also have a 2-fold difference because we're comparing, remember not apples to apples, we're comparing the NOAL at the pulmonary deposited dose versus what is added to the clinical device for the nominal dose. And then at best, again conservatively, it's the maximum dose. So we have to start lower than that. And typically that's a 2-fold dose. So if we have only two doses in our first in clinical trial, that drops it by another 4-fold. Altogether, that results in an 800-fold safety factor there and giving us a dose of 0.75.

Finally, if we use lung weight, and as I showed you, because of the default value being a little less conservative, in fact it gives us a scaling factor that actually increases the dose using a default value. And that's 0.36. And that will get us up to two mgs and dose. So that's close to the end and I'm about two minutes over, but I'm going to finish up quickly. I know this is a minor point, but it would really avoid a lot of confusion if we could standardize our terms. That would be nice. I'm not going to go further on that. We should be using the best science to determine deposited dose. And we should be using the same comparison in humans and animals, not some artificial comparison between a conservative dose and actual dose in the lung.

I would argue that we should only use the NOAL to talk about the specific study and the characteristics of that study and not include any other factors in that, such as potential concerns over pathogenesis, clinical relevance, and uncertainty. I'm sorry, and non-monitorability. Those are things that can be important. And I'm not disregarding that. I'm just saying they don't belong in the determination of the NOAL. Overall, what I would suggest is that we return to the MRSD guidance because that's what's used around the rest of the world. It's also what's used in most divisions of the FDA that I'm familiar with. Maybe some don't use that. And it allows that we determine the clinical starting dose from the non-clinical data and let clinical data determine what is a maximum tolerated dose and a maximum clinical dose before moving on to treatment of patients and further. Thank you.

Industry Experience in Current Environment

- **William Thelin, PhD, Senior Vice President, Aer Therapeutics**
- **Per Åberg, MSc, Senior Director, Clinical Pharmacology and Safety Sciences, AstraZeneca**
- **Jorrit Hornberg, PhD, MSc, Vice President, Global Head of Safety Sciences, AstraZeneca**
- **Aidan Curran, PhD, Principal, Curran Nonclinical Consulting**

Susan Winckler: (01:00:00)
Thank you. And good news, you and Matt coordinated just enough so we ended the session exactly on time. Yes, I do need that back. So let's pivot. We wanted our prior presentation to speak to what is the current requirement and then to look at some comment about how this affects and is applied in specific examples by industry. So we're going to turn first... I'm going to introduce actually everyone, but let me do the forward, back. Ignore the big button in the middle as I should have. So we're going to hear first from Dr. Bill Thelin, who's senior vice president of drug development at Aer Therapeutics. Then we're going to turn to colleagues from AstraZeneca who are joining us virtually, where Doctors Per Åberg, who is senior director of clinical pharmacology and safety science, and Dr. Jorrit Hornberg, vice president and global head of safety science, will give a tag team overview. And then we're going to close out the session with Dr. Aiden Curran, who is principal of Curran Nonclinical Consulting. But Dr. Thelin, take it away.

William Thelin, PhD, Senior Vice President, Aer Therapeutics

Dr. Bill Thelin: (01:01:10)
Thank you so much. I really appreciate the Reagan-Udall Foundation for working so hard with us to organize this workshop. So I'm going to start this session today with essentially a case study that's very focused on the program that our company Aer Therapeutics is developing. It highlights some of the challenges that we run into when one species has very different outcomes than another. But also how we really work to interpret data across multiple species to have mechanistic understandings and try to integrate modern clinical imaging and monitoring into a program and what this really means for innovation in respiratory therapy.

So to start with some background, COPD is a severe disease. We understand this well. It carries a really high morbidity, mortality, and an enormous healthcare burden. And one of the things that has more recently emerged in COPD and other mucus obstructive diseases are the presence of monitorable mucous plugs. These are in the conducting airways. And if you look on

the left, you can see by CT image the presence of these mucous plugs. And these are important. These are not subtle pathophysiology. These are physical blockages analogous to like a blood clot. And so what we've understood about mucous plugs and looking at large cohort studies in asthmatic and COBD patients is that the presence of these tend to track with disease severity. So if you look at some of the panels, the first is looking at different GOLD status, which is ranking the severity of COPD patients.

And as you get into the highest and most severe forms of the disease, GOLD-3, GOLD-4, you see a much larger number of mucus plugs present in those patients. Similarly looking higher mucus plugs tend to be associated with lower lung function, lower quality of life, higher exacerbation rates, and even all-cause mortality rates. So it's a really significant target within a very severe disease. And I think that part of the case that we'd like to make today is that for something as serious as this, as we consider the regulatory paths forward, we need to balance the risk proportionally and with evidence as we go forward.

So a little bit about our compound to start this. So AER-01 is the drug that we're developing. It's currently in Phase 2 clinical trials. It's an inhaled thiol saccharide. And essentially what this does is it targets the disulfide crosslinks that form within the mucin subunits in the lung. So if you look at a mucin, these are normally tethered end to end disulfide crosslinks into a large polymer. But in the presence of pulmonary inflammation and oxidative stress, those disulfide bond crosslinks rearrange and form aberrant links. This causes the mucus to go from a more flowable gel to something that becomes a really viscoelastic solid and forms the basis for a plug. And essentially what our compound does is it breaks those disulfide bond crosslinks. And I don't know if the AV team can click on the first black box to show you what this does.

So this is actually cystic fibrosis sputum. You can see it is really nasty and viscous. And it stays bound inside the tube. If you click the other video, it's the same sample treated for 12 minutes with our compound. You can see it liquefies the mucus. It's breaking down the mucins, and it's restoring it back to a flowable state so that it could be cleared from the lungs. One important thing that I want to point out is as we're developing this drug, there is a predicate compound, an acetylcysteine, that was approved in the 1960s by the FDA. And we have decades of human clinical experience with this drug safely. So we're not dealing with a drug that has a new class of toxicology. This is a known class of drugs.

Next slide. So to establish our target clinical dose. Initially we used a number of assays, including things like rheology, to look at the dose dependent change of our drug on the viscoelastic properties of the mucus. That allowed us to establish a minimum effective concentration. We used things like deposition modeling to estimate how much drug will we actually need to put into a nebulizer to achieve that effective concentration in our target airways. We even did this with modeling that factored in mucus plugs. And then finally, we took this into some in vivo animal models that our COPD likes, so they have mucus plugs. And we were able to show that the drug reduces the mucus burden, improved survival in the animals, and also reduced pulmonary inflammation. So at least mechanistically, that allowed us to anchor a target clinical dose that we will want to achieve to be able to evaluate efficacy in the clinic.

So from there, we went on to conduct initial GLP toxicology studies. So we did two-week studies in both the rat and the dog. And we identified no NOAELs in both species. And if you look at the image here, the green nebulizer indicates our target clinical dose. The blue box around there gives the dose range that we'd hoped to go into the clinic with initially. And then you can see

the no NOAELs listed as a human equivalent dose for both the rat and the dogs. So they're both well above the target clinical range that we want to evaluate. So with this, and as Jeff mentioned, we actually went to Australia to initiate a Phase 1 clinical study. There were economic advantages to doing that. And so we started there.

We evaluated 96 healthy volunteers in a single ascending and a multiple ascending dose study. We evaluated all the way up to four times over our target efficacy dose in the clinic, and essentially saw no real safety signals. So spirometry was stable, lung function was stable. There were no systemic or other lung findings associated with this in the healthy volunteers. Our pharmacokinetics was dose proportional. So this was reassuring that we achieved higher than our target dose very safely, very cleanly in Phase 1.

So where we had a divergence in our program was when we went into longer term toxicology studies. So we go into the 13-week tox studies in rat and dog. And the dog we identified NOAEL and that outcome was very positive. However, in the rats, we observed mild to moderate pulmonary inflammation with protein accumulation. And these findings were mechanistically consistent with what we understood about the biology of our compound and potentially a direct effect on the rat surfactants. So in this study, we did not achieve NOAEL. And at this point, this becomes a regulatory sticking point for the company. The findings in the rat were not progressive. They showed evidence of reversibility. But yet, it leaves a small company like ours in a conundrum or a confusing place with how we go forward.

I want to address a couple things and some understanding that we've developed over time as we've thought about the outcomes in the rat. And the first point that I wanted to make is that the rat lung is not just a small human lung. It is anatomically and physiologically different than a human lung. So on one level, rats have a very simple branching pattern in their lung compared to the dichotomous and much more complex human airways. Another issue is that rodents have much slower mucociliary clearance from their lungs. So you're looking at a scenario in which aerosols might deposit at a higher level in the alveolus and also clear more slowly. So they may be biasing towards a higher exposure in this case. And we're looking at this and wondering, are we really looking at some universal aspect of the toxicity of the drug in the rat lung, or is this really something that's species specific?

Another important point is that historically, any findings that are histologic in the lung are deemed by the regulators as non-monitorable. And we're working towards helping make the case that, in fact, we can monitor for some of these things clinically. So on the left is actually an image of the rat histology from one of our studies. And it is showing protein accumulation in the alveolus, which was one of the dominant signals in our histopath. But on the right is a human CT image looking at ground glass opacities that measures deep lung inflammation, and really protein accumulation in the lungs. So it is to say that the rat findings actually have a radiographic correlate in humans that we can take advantage of and use that in our clinical trials.

So the way that Aer advanced this program and has been working on this, we established a weight of evidence argument for our program. So we utilized our non-clinical data, the aspects of the mechanisms of the tox that we understood, our Phase 1 data, as well as I think a fairly innovative way to do clinical monitoring to ensure that we don't have these types of issues as we go forward into clinical trials. So with that, we advanced our program into Phase 2a. We did this outside the US. So we have done this in Australia, New Zealand, the UK, and had no regulatory

issues in bringing this weight of evidence argument to those jurisdictions. We're waiting right now approval for being able to start the protocol in the EMA as well.

And so what we did with this is in our Phase 2 study that is ongoing, we're enrolling 100 patients with severe COPD. We're going up to that 90 milligram dose that was our target dose against the placebo and looking at, on the efficacy side, pulmonary function. So FEV1 is the primary endpoint. But we're also using CT imaging to look at mucus plugs. And we are further using that CT imaging to also look at safety. So we use it to quantify emphysema as well as ground glass opacities, and established a very set stopping criteria in our trial. So if we saw an increase in the ground glass opacities that looked like the correlate to the rat, we would stop the study. And to date, we've gotten through the first 25 patients without seeing any evidence of that. So it suggests that the rat's actually not predictive of the human in this case.

So in the end, this is really a challenge that extends just beyond the science. What happens when these regulatory blips come up or aspects of the program is it slows the development of needed medicines from reaching patients. But it also has economic and policy implications as well. So in our example, we sent about $30 million worth of clinical studies outside the US. So this is money that we're not spending here internally. And it really highlights the challenges that we get when we over rely on one species, but also brings up these concepts that maybe we actually can monitor for some of these findings using modern clinical imaging techniques.

So to wrap up, I think it's really important that we respect things like the rat toxicology signals. We're not trying to argue that they're not relevant, but they should not necessarily automatically disqualify a program from going forward. And I think this has been an issue, not just for things that we think about at Aer, but for a number of the companies I've worked with. And a lot of people in the room have had similar types of issues. So we would argue for the regulators to really think through accepting weight of evidence arguments, where we might have one species that is an outlier for a particular reason, maybe it's related to the actual drug itself, but to really consider that and allow some of these promising therapies to go forward. Thank you for your time.

Per Åberg, MSc, Senior Director, Clinical Pharmacology and Safety Sciences, AstraZeneca

Susan Winckler: (01:14:40)
Great. Thanks so much, Dr. Thelin. And in particular for helping us just see the application, both in the challenges that you run into as well as some of the creative solutions that you're exploring. This is the point where every moderator of a hybrid meeting gets incredibly nervous because we're turning to virtual presenters. So I'm going to wave a magic wand that I hope works and say, let's turn to our presenters from AstraZeneca, specifically Doctors Åberg and Hornberg.

Dr. Per Åberg:
Hello. Can you hear us, hear from Sweden?

Susan Winckler:
We can. Please proceed.

Dr. Per Åberg:
That's great. Many thanks for inviting us to the session. We really appreciate. And it's a really useful topic for us. So I'll see if I can move the slides. I will describe a case example here on an

inhaled drug candidate where we had lung histopathology lesions in rats that limited doses in humans. And we experienced differences in risk assessment between different health authorities. But then also we want to take the opportunity to briefly describe how we work with in vitro models and to assess and prove our drug candidates, and also present work we have done with the lung safety biomarker initiative. And Jorrit will talk about those two topics.

So to start with this... And just to comment, there's no right and wrong here regarding these things. It's all about judgment. And this molecule was eventually discontinued because we didn't really find a good differentiation versus already available therapies. So it wasn't the toxicology finding per se that hindered us to further develop this. But there were some challenges on the way. So this was a non-steroidal glucocorticoid receptor agonist. It was intended for combination treatment of respiratory disease, asthma, and COPD. In our rat efficacy models, we saw good anti-inflammatory activity, as shown on the graph to the left. And it was basically similar potency as a potent inhaled corticosteroids, fluticasone furoate. To the right is a graph where we looked at the systemic response to this, where we saw a rightward shift in plasma corticosterone suppression. Which is a typical indicator of systemic glucocorticoid effects. So this molecule, the rat data indicated a good therapeutic index. And even though inhaled corticosteroids are recognized as quite safe, we saw some opportunity here for improvement for patients.

And we did a one-month asthma trial, and we established dose-related efficacy at 360 and 720 micrograms. Our tox program, this was a dry powder formulation. Our tox program was done with one and six month studies in rats and one and three and nine month inhalation studies in dogs with a dry powder formulation. Prior to Phase 2, FDA raised concerns around a lung histopathic path finding in rats. And they required a dose cap at 360 microgram, which was the lower of our two doses. And that was, again, based on this approach that Jeff and others have talked about, the 10-fold safety margin to a no effect level, as we called it, assuming 100% deposition in humans.

This finding was not present in dogs in corresponding doses. And at the time we had a three-month study. Our assessment was that the lesion was not representing an effect of concern for the proposed doses, and there was no concerns raised by other health authorities. So we went ahead with a three-month Phase 2b asthma trial at 360 micrograms in US and 720 micrograms in the rest of the world. [inaudible] efficacy, and we did not see any safety signals of concern. Sorry, I need to... I think I clicked a little... Now I have a technical problem because I can't move my slides back. Sorry.

Susan Winckler:
Is that right?

Dr. Per Åberg:
No, it's the slide before the first one I spoke to. So maybe I...

Susan Winckler:
That one?

Dr. Per Åberg:
Yeah, this one. So what was the finding, then? It was described as alveolar eosinophilic material. And there's a tissue section here where you can see the pink deposits here in the alveoli. And

we did some stains and assessment and confirmed that this was surfactant. It was consistent with surfactant phospholipids and protein. It was low severity and it was reversible. And there was no associated inflammation and no damage to the blood-air barrier. And it was present at an estimate dose multiple, which basically was 10-fold, our high dose that we were proposing. And accounting for lung deposition that were estimated with quite good reliability it would be 19-fold. And it was absent at the 5-fold multiple of this 720 microgram dose. The concern from FDA was that this had not been previously been described with inhaled corticosteroids and expressed a concern that it could represent alveoli proteinosis, which is a severe human condition.

Let's see if slides are moving. Thanks. And this slide then... So as I mentioned, our molecule was very well tolerated in rats. So we had a better systemic tolerability. And since the doses that can be given by these type of molecules are limited by systemic tolerability, we could give significantly higher doses of our molecule. And this is basically what the graph shows, that we were very much on a dose basis above the inhaled corticosteroids. And still we had similar potency with this molecule. So it was reasonable to argue we had a much stronger pharmacological drive with our molecules in this rat study. And you can see the low effect level was basically exceeding the doses for all inhaled max doses in chronic studies, rodent studies with corticosteroids. And it's well known also that GR agonist, or corticosteroids, can stimulate surfactant expression. That's why it's also been used historically in neonates.

So we basically hypothesized this was just a high dose pharmacology that we shouldn't be concerned of at these levels. And next slide. So we're doing Phase 2b. We did an investigative package to support high doses globally. We used human alveolar cells to show at relevant concentrations. We had up-regulation of surfactant expression with our molecule and the corticosteroids. And then we also did short-term studies with local administration to the lung at levels that could be tolerated of those corticosteroids and could actually show that we had up-regulation of surfactant in the lung. Other supportive information we generated, because during this time we did the nine-month dog study. And when we actually looked at histopathology in the controlled dogs just exposed to air, we did see similar type of lesions in other species, but still similar type of lesions in healthy animals. Again, pointing towards that this is not really an abnormal pathology. And our assessment of the pathology phenotype was also that it was not consistent with alveolar proteinosis.

So the overall context for risk assessment here, this occurred at a dose that basically would correspond to a dose in humans of 7,000 micrograms. Which would be a massive dose of this type of molecule, which we wouldn't go ahead with. And that should be compared then to 720 micrograms delivered dose, and actually an estimated deposition half of that. Which actually is quite a big window there. And also no associated epithelial inflammatory lesions. And our investigative studies supported our hypothesis as we saw it. And we did also see some similar histopathology in non-treated dogs.

So for us, this 10-fold margin concept and 100% lying deposition assumption created a very high bar for this type of lesion and molecule. When we submitted this information, there were still concerns expressed for various reasons. But there was also a proposal to do a pathology working group, which we would have gone ahead with if we had continued this program. But as I said, we discontinued it for other reasons. And it would have been nice to work this through and resolve it. Which there could be a potential for, because I think we had good data. But I think it's a good example illustrating that I think a weight of evidence situation, looking at the

actual lesion rather than applying a generic approach to these type of things, is quite justified. And we do actually apply this way of thinking with a long dose calculation extensively whenever we see something we're really concerned about. So I think that it depends on the findings and the scenario.

And finally, I just want to show this slide because this is something... A couple of years ago, we collected the information that is published in the FDA approval package on inhaled drugs. And we plotted the NOAEL or the highest dose used in the chronic rodent studies versus max approved lung dose in humans. And the lower line here basically reflects the corresponding dose. The upper line, the dotted line is the 10-fold variant. And actually most molecules actually meet this criteria of a 10-fold multiple. You can see the inhaled corticosteroid, they group here and they would not meet this criteria. Which shows that in some cases it's not really valuable to apply that type of approach. And as you know, these are really important therapies in respiratory disease. So I think it's important to reflect around that. And I think with that, I will hand over to Jorrit.

Jorrit Hornberg, PhD, MSc, Vice President, Global Head of Safety Sciences, AstraZeneca

Dr. Jorrit Hornberg: (01:26:14)
Thanks, Per. And just checking, Susan and others, that you can hear me?

Susan Winckler:
Yes, we can hear you.

Dr. Jorrit Hornberg:
Perfect. So just want to build on what Per said. And I guess the ultimate question that we have today is what's the best way to predict human safety, right? At AstraZeneca we have a proactive integrated safety strategy, meaning that we aim to employ really alternative methods to predict human safety early in drug discovery already. And with that strategy, we have actually tackled most of the safety related attrition. But can we then use in vitro methods to predict lung histopath? So on the slide that starts with breathing lung-on-chip there. Yeah, thank you. So first I'm going to give two examples that I think hopefully inspire the discussion afterwards as well. So first case is an inhaled biologic. And we all know inhaled biologics cause a particular histology phenotype. And there's lots of debate in the field about what is adverse and what is not.

But for this one, we had two different formulations. And they each gave a very different pattern in terms of visible particle size upon reconstitution of the dry powder. And each also actually giving a very different pattern in the histopathology. So the first formulation gave adverse inflammatory profile, but the second formulation had no findings that were different from the controls. And we hypothesized then that this was due to an immunogenic potential of these larger particles that were caused by the first formulation. So we wondered, could we have predicted this using an in vitro model?

So what we did is we applied a lung-on-chip model, which this particular model contains both type one and two pneumocytes. So alveolar, epithelial cells, microvascular cells sit on a membrane that stretches with a pressurized system so it mimics breathing. And you can incorporate immune cells on top of it as well. And then you can measure various endpoints from the system. And indeed on the right-hand side of the slide there, you can see that as we

increased the dose, you could see that the drug induced a range of pro-inflammatory cytokines, but only for the formulation that actually caused that adverse inflammatory phenotype in vivo. So great hint that this model could actually potentially have predicted that. So we use systems like this now in later stages of drug discovery. It doesn't necessarily have the throughput or maybe the cost-effectiveness to apply across hundreds or thousands of compounds. But in earlier drug discovery, therefore we use a much simpler in vitro model. And on the next slide, I'd briefly talk about that.

So this is based on an imaging assay for occludin. So occludin is a tight junction marker. It's important to maintain the integrity of the epithelial barrier. And you can nicely see there that you can image this in a very simple 2D assay, so 2D cell line assay, and quantify the perturbations that you can induce by chemicals. So I've switched now to small molecules. And we validated that assay using a range of compounds from either our own collection or from the public domain. So the in vivo lung tox profile was known. And we saw that there is, although maybe not a perfect, but a pretty decent separation between the blue compounds and the green compounds there. So the compounds that were toxic to the lung versus the compounds that were not. So then on the next slide, we took that compound... took a compound from our active portfolio, and then what we did is we predicted the concentration in the epithelial lining fluid in the rat. So we used the PBPK model that we apply across our inhaled programs and usually obviously to predict for humans. But we can also use it to predict in rat with a few tweaks to the model. So each line in that graph, each blue line in that graph, represents the concentration over time in each kind of generation of the respiratory tract, so from the TB regions down the alveolar region. And if you animate just once, you can see on the top right there that the data from that occluded imaging assay for this specific compound.

And then what we did is we met the predicted ELF concentration across the X axis there of the in vitro assay. And what we found was the irritation phenotype that we saw in the rat histopathology occurred only at the locations where the predicted ELF concentration exceeded that red line kind of when the in vitro assay started to give a signal. So consequently, there was no histopathology if the concentration was at a level that was clean in the in vitro assay. I thought that was quite interesting. And, next slide, it suggests that it's worth discussing whether such predictions based on alternative methods could actually be used to predict human safety. Ultimately, maybe even set dose limits, because you can make it quantitative.

And I want to take that quantitative piece one step further on the next slide. You recall that graph from Per's presentation, that 10-fold margin, and it really hampered us there, right. And part of why that 10-fold is used is also because it's difficult to monitor the histopathology in humans. And the first speaker already talked about that as well. So what if we could link the rodent histopathology, if you could animate to easily accessible biomarkers? So, it's a challenging exercise, but we did a pilot to try that. And I'm going to just spend one slide on that. So we applied spatial transcriptomics, which you see here. And I just... One back. Sorry.

On the right-hand side, you see spatial transcriptomics is a schematic representation. So this is technology for those who are unfamiliar that provides you with a full transcriptome overview on each location on a histology slide. So it can basically inform you about the molecular mechanisms at play spatially resolution, right, with spatial resolution on a systems level. So you could interrogate that data and understand what molecular mechanisms were driving histopathology. This was a bit tricky to get to work for the lung, but we managed to do this. And

on the next slide then is the experiment. So on the left-hand side of that slide, you see the experiment.

So we had a compound that caused an inhaled pathology phenotype. So we collected... we did an inhaled study, we collected lung tissue, we collected bowel fluid, we collected blood, and then we kind of took a stepwise approach here from left to right here on the slide. So first, we used the spatial transcriptomics to understand which genes and which gene signatures correlated with the drug exposure, but also how they differed between areas where we saw the histopathology in areas that looked completely normal. So you kind of get an understanding on a gene level, on a gene signature level of what the drug... of the drug-induced lung toxicity.

So then we collected proteomics data from the bowel fluid and try and map that. And then ultimately from the plasma, try to connect that mechanistic signature from the histology to the biomarkers that we could measure in circulation. And this actually yielded 12 biomarkers, a set of 12 biomarkers that we could mechanistically connect to the lung pathology. And what I thought was interesting, and this needs to be looked into further, I think, is we confirmed that these biomarkers were, not all 12, but sets of the 12 were consistently dysregulated across a range of inhaled lung toxicants, so including drug compounds. And we also looked at environmental toxicants.

And even in a human disease like IPF, which has an inflammatory component, we found some of those biomarkers upregulated. So that alludes to a uniform mechanism, right. And so taken together, I think this work could potentially be a step forward towards identifying a way to monitor, mechanistically monitor drug-induced lung injury in humans that we identified in histopathology. And so if we could do that, could perhaps that margin of 10-fold come down. And obviously, that would take down a huge hurdle for the development of new inhaled drugs. And yeah, that would be tremendous benefit for patients suffering from respiratory disease. With that, thank you for your attention.

Aidan Curran, PhD, Principal, Curran Nonclinical Consulting

Susan Winckler: (01:35:10)
Great. Thank you so much, Doctors Åberg and Hornberg. And we will bring you back for the panel discussion after we have one more presentation here, and that's when we'll get to some of the questions that you've been submitting as well. So, welcome Dr. Aidan Curran of Curran Nonclinical Consulting to round out our presentations, and then we'll turn to our panel discussion. Did you get the... This is forward, that's back.

Dr. Aidan Curran:
Okay. Thank you. It's a pleasure to be here today. I want to congratulate the organizing committee and the sponsors for putting together such an interesting session. So what I wanted to do today was talk a little bit about the experience, the real-life experience of small pharma. The companies that I worked for and that I now represent as a consultant don't really have the heft and the mechanism and the funding to really develop a lot of novel mechanisms or novel approaches. And so what I wanted to focus on today is where we are today and how the roadblocks that companies, small companies, face today and how we can potentially improve our current situation.

And I'm going to be a little provocative in some of the things I say just in order to stimulate the conversation. And the approach I wanted to take as well was to issue some challenges to the broader community, to the experts here in the field biomarkers and NAMS folks to help us to use the data that we have. We generate a lot of data, and I don't think we use it in a way that's necessarily as useful as we could. So I'll start off with probably the first, maybe controversial thing that I wanted to say was that early development is dependent upon non-clinical data, animal data, and I think it's going to remain that way for a significant future period.

And so being able to use those data in an appropriate way, I think, is what I want to get at. I'm going to talk a little bit about the issues that we see going forward that the small companies find, things like individual findings in single findings in one animal. We've heard a little bit about that already. I want to talk a little bit about severity, NOAELs versus NOELs, things that Jeff and Matt talked about already. The safety margin calculations. Again, I'm going to retouch on that from a slightly different perspective from Jeff. And I think the uncertainty around these issues leads to a lot of real, serious roadblocks for small pharma.

Big pharma have the wherewithal and the heft to overcome a lot of this, but a lot of small pharmaceutical companies are really at risk. And a lot of the cutting-edge advancing science that's going on is going on in a lot of small pharma companies, and their entire future can be put at risk. And the other issue, we talked about this already. Jeff mentioned it that in 40 years, most early clinical studies are ex-US. I think that's true from my experience too. And not only does that remove them from this country, but it also gives FDA less oversight of these kind of studies. So these studies are going on outside of FDA jurisdiction.

And therefore, I think it's beneficial for us to bring these back to the US and make sure that we actually can see what's going on. Make sure I get the right button. Okay. This is my only graph with... my only slide with any sort of graphics on it. So I'm going to spend a little bit of time on this one because the rest of it's all just writing. But I wanted to talk about the safety margin calculations. And again, Jeff talked about this in great detail, and so I don't want to overdo it, but we obviously need to have safety margins. But how we calculate it has multiple layers, and there's an uncertainty in each layer and a margin in each layer that compound upon themselves.

And so, for instance, delivered dose. When we do this non-clinically, you can't have an animal take a deep breath and hold it, right. So you have to do this with tidal breathing. And so the delivered dose is determined by the aerosol concentration, the minute volume of the animal, and the time, the duration of exposure. And this is often an hour or in some cases up to four or six hours of exposure. We then estimate the pulmonary deposited dose. And again, as Jeff said, that's 10% in rodents as an example. And we don't assess any sort of pulmonary deposited dose in humans. We assume 100% of the nominal dose. Now, I find it interesting that, for instance, our CMC colleagues, when they're generating our regulatory documents, they have to very carefully determine their emitted dose.

They have to very carefully determine the fine particle fraction of that emitted dose. It's all very important to have in the regulatory documents. And then we don't use it at all in the clinical end of things when we're determining our safety margin. And so that's at least a 10-fold difference in terms of the pulmonary deposited dose between the clinical and the nonclinical. And then we require safety margins. Again, if we just take the rodent, for example, 10-fold safety margin, that can result in a difference in dose of over 100-old. Jeff calculated up to 800-fold difference, right.

So you're resulting in massive doses in animals, and then we're looking for subtle tox findings in these animals.

And one of the things I also wanted to mention is that these deposition fractions and the deposition fractions in humans are assumed based on I've written here data from research in the 80s and 90s. But I was corrected last night by Jeff and Matt that those papers were written in the 80s and 90s. The data were generated as far back as the 1940s and 50s. And the aerosol technology, the device technology, and the aerosol, the CMC technology has advanced so much that I'm not sure that these assumptions are even relevant in the modern world. And so if I move along to the next one. Yeah. So then if we're trying to generate these non-clinical safety margins, and I have here starting dose, but as Jeff pointed out, it's not a starting dose.

It's a maximum dose for inhalation, which is different than all other routes of administration. And we have to generate these very high margins in animals breathing tidally, and so we have to either dose them at very high aerosol concentrations for very long durations. And this risks, in my opinion, findings related more to the fact that we're shoveling huge amounts of drug into these animals' lungs rather than the effect of the drug itself. So, you can get lung overload, you can get mechanical effects with things like dry powders, you can get mechanical effects that are completely unrelated to the API itself. The other point, and I think Jeff made it, was the lung assumptions of 10% deposition in the rat are based on alveolar deposition.

And yet when we see findings in the upper airways and the larynx, we apply that 10% deposition factor to those findings. And so it's yet another layer of impediment to progress. So I think that a couple of challenges that we could pose right now, one challenge would be to regulators, and we could do this today, use the deposited dose in humans for safety margin calculation. That's a very simple fix right away. And we've talk... we've had speakers talk about this already. That could be done today, and that would really impact, I think, a lot of the difficulty that a lot of small pharma face. The other thing is these assumptions, the 10% deposition and the 25% deposition, again, as I said, these are based on technologies and data that are decades, decades old.

And we have folks that do a lot of modeling. Fluid dynamics folks. We have a lot of people that are probably paying attention to this, who have data, and a lot of them are probably screaming at the screen right now if they're online, saying, "I've published this data already. It's out there." But it's not being collected together. It's not being built into a data set that regulators can use because we can stand here and I can say, "FDA should take note of this." But it's up to industry as well to say... to pull it together and to actually make the effort to put a reasonable case forward. NOAELs, and again, I'm sort of rehashing a little bit what Jeff and Matt have talked about, but determining what is your starting dose based on an NOAEL.

Over time, I think what I've seen over the last 20 years of interacting with regulators is that we've gotten more and more and more risk-averse, and what used to be an adverse finding is now we're now worried about potentially adverse or of concern. And it's very ill-defined that the term adverse is ill-defined, as Jeff pointed out, but the response to regulators, particularly in this country, to what is it you're concerned about, I think, is becoming a little [inaudible]. And so we're ever pushing down the starting dose and increasing effectively the safety margin required based on nebulous findings that are not clearly adverse. The findings in the rodent larynx are a typical one, but there's also a lot of this term non-monitorable that everybody throws their hands up when we see it.

And the next challenge I'd like to cast out there is to all of our biomarker friends and our imaging friends, is there any really non-monitorable findings? We have excellent biomarkers. We have excellent imaging nowadays. I'm not sure what the term non-monitorable really means in this context. And I would go potentially even farther and say, if we can't find it, if we can't monitor it with all the current technology, is it worth monitoring? Is it really of that concern if it's so minor that we can't even see it, and we can't find it? So again, just to be provocative a little bit there. So I'll give you a little case example. I'm watching the clock tick down very rapidly here, and I'm conscious that I'm standing between everybody and lunch.

Susan Winckler:
No, there's a panel.

Dr. Aidan Curran:
Okay. All right. So here's... So again, as a consultant, I don't really have the access to all of the data of all my clients, but this is from a program that I ran in a previous life. 505 program, taking an IV drug, making it inhaled, essentially a rescue drug to be taken as needed for a systemic exposure. So this is not... this would be going into healthy lungs, otherwise healthy lungs in humans. And we knew the systemic toxicity. We knew what the limiting factors would be. It's essentially emesis, and this occurs also in dogs.

And so we knew essentially what the doses were going to be because we knew that the upper limit in the dog, we knew what that reflected in the human. And so we set our dog and our rat doses to achieve the same safety margins in order to progress. Well over 10-fold margins, probably something like 16 or 17-fold margins based on the conservative FDA approach. If you look at it based on the rest of the world approach, 20-plus fold margins. And the feedback that we got was that our data was not acceptable because we had a lack of findings in the rat study.

We didn't go high enough in the rat, even though we had, I think, from FDA perspective, 15 or 17-fold margins. We knew that the dog was our limiting species. We knew what our clinical doses were going to be. And so we had to make the decision. This was actually one of those studies where we were going to run a Phase I study in the US. We wanted to run it in the US, but we were a small company. We didn't have a whole lot of money. So we ended up having to run our study ex-US, affect our bottom line and our runway by having to repeat a study in rodents, which ultimately gave us a couple of 100-fold safety margin because there was no finding.

This was a very potent drug at a very low dose, and it had zero effect in the lungs. And so I think applying stringent rules of you need to have an upper limit in all the species, regardless of whether it ever, in real world, made any difference, I think, put us in a very difficult position and pushed the clinical study, another clinical study abroad. Other case examples that I can't really get into, but things like findings in the rodent laryngeal pouch, if a structure doesn't exist in humans, preventing progressive of a program.

Non-monitorable. The term non-monitorable is something that we see an awful lot. I think Matt and Jeff will agree. This is a very common response. Nebulous findings like epithelial alteration that are flagged as a concern without any understanding of what that actually means and what that would translate to clinically. I'll try to speed up a bit here because I see 30 seconds left. So I think this pushes a lot of small companies to the brink and forces studies abroad, as I said, that are not monitored now.

And so, another couple of challenges here that I would like to pose. We have incredible AI tools, large data management ability these days. We have multiple programs from large pharma and small pharma that have been through non-clinical and clinical. Is there some way that we can pull all of these data together? Companies are very reticent to release their data into any sort of a pool, but is there some way that we can actually use existing data to mine and see, do these findings ever translate into anything clinically?

And the other question I'd ask is, all of these studies that we move ex-US, is there any evidence that those patients are at increased risk relative to whether we ran those studies in the US? I don't think there is, but I think knowing that and pointing that out might help to relieve some of the stress to folks in the US and trying to develop these compounds. So, last slide. I think that the advances that we have in inhalation engineering and particle development can be used now to remove a lot of the uncertainty based on the current assumptions of things like 10% deposition and all that sort of stuff.

Conservative approaches to data assessment and risk mitigation by US regulators, I think we could ease that a lot. And quite simply, even what I said earlier with the assumption of fine particle dose in humans, I think there's a huge ability to advance the science with using the data sets that are already available to us from large and small pharma. And I think it would require a commitment both on the industry, but also on the regulator's perspective to work together to generate these data, and for regulators to agree that any outcome of that will be acceptable and will be implemented.

And I see a lot of folks here already who are involved in professional bodies, ACT, ISAM, AIT. I would hope that we can continue these kind of conversations, that today is not the end of the conversation, but the start of the conversation to try and advance these conversations through conferences and through sessions going forward, so that we can continue to build upon this because this is, I think, a really excellent start, but not the final outcome. So I apologize I ran a couple of minutes over, but...

Panel Discussion: Impact of Current Environment on Product Development and Patients

- **Teresa Barnes, Chief Executive Warrior, PF Warriors**
- **Karin Hoelzer, DVM, PhD, Senior Director, Patient Advocacy, Biotechnology Innovation Organization (BIO)**

Susan Winckler: (01:51:05)
That's all right. When you're way over, I move you off the stage. So, Dr. Curran, thank you. Let's... And if you take your seat on the stage. Dr. Thelin, we'll invite you back up to the stage, and Dr. Hoelzer to the stage. We are going to move now to a panel discussion to help us think through what we've heard and how we should be thinking about this. And as we do that, we'll also invite some virtual folks back to the stage. And so in particular, we will have Doctors Åberg and Hornberg return to the virtual stage, and we're adding two individuals to our conversation.

Now, let me note. Some of you may have been stalking the agenda for the last week, and you said, "No, you're supposed to have three people joining this panel." Unfortunately, Dr. Bruce Miller from the COPD Foundation had a last-minute conflict and will not join our panel today. But we have two members of the broader product development ecosystem who are serving as a

reactor panel to the presentations that we just heard. So in the room, we have Dr. Karin Hoelzer, who is senior director for patient advocacy with BIO.

And in our virtual discussion room, we have Teresa Barnes, who has my favorite title of the day. Teresa is Chief Executive Warrior for the PF Warriors. So, Teresa, welcome. So let me first... I want to give both Teresa and Karin the opportunity. Do you have any questions for our colleagues who just finished their presentations? It's okay if you don't, but if you do, I want to make sure that you get to ask those questions. I have a few to ask, and then we're going to turn to the commentary. So Karin, anything that you want to ask of any of our presenters that we just heard from?

Dr. Karin Hoelzer:
No, first of all, thank you so much for having me, and it is so exciting to see the future. I'm looking forward to the conversation, but I think I will wait with my questions until they organically appear.

Susan Winckler:
Okay, great. Teresa, anything from you?

Teresa Barnes:
Yeah, I just want to say thank you to them and hurry up. We need the therapies, so thank you.

Susan Winckler:
Yes. Well, and I'll just reflect what I was struck is, and when we think about regulatory science, the regulatory science develops somewhat in parallel, but often following the science that's advancing, right, that you have to be thinking about how do you adapt to the regulatory structure.

So it actually makes some sense that our regulatory environment might be a bit behind, but I also appreciated in each of the presentations that we heard that you were illustrating not only the challenges, but also some of the solutions that might be pursued both on the private sector and on the government side.

So I do have just a couple of quick questions that I want to run through as we join into conversation. So this one. There was a fair amount of reflection and commentary that the data is old. So why haven't there been any new papers written and consolidated by industry? And it's okay if you say, "I don't know, it's collectively our challenge." That's a fine answer.

Dr. Aidan Curran:
Well, actually, I think that there has been. There's a lot of interesting literature out there. It's a matter of making sure it reaches a critical mass to a point where it's taken seriously. And this is where... this is part of my challenge to the societies and also to the regulatory bodies is start to pull these data together into... One paper isn't going to make the ultimate difference, but there's a lot of literature out there. And if we pull it together in a controlled way and we start to highlight it, that's how change occurs. I'm not-

Susan Winckler:
I'm going to take that out of your hand.

Dr. Aidan Curran:
No, it's easy from an industry perspective to say, "Ah, the FDA is too difficult to deal with." But you don't... it's the... you're like allegories, but it's the cruise ship, right. You're not going to turn... You can't do a handbrake turn on a behemoth like that.

So, you have to work on pulling together and everybody working together on this. And I think there is a ton of literature out there. We just all sort of fall back on 10%, 25% [inaudible] papers, Wolf and Dorado. It's very easy to just fall back upon that, and it's a large effort to fix it.

Susan Winckler:
Yeah. So it strikes me, actually, if we go back to Dr. Kozlowski's observation about bamboo, that there's some... there's papers, if we use that kind of emerging, but we haven't done the synthesis perhaps or pulled those together to have-

Dr. Aidan Curran:
Forest for the trees, right.

Susan Winckler:
Pull it together. Yes. Yeah. Okay. Go ahead.

Dr. Bill Thelin:
I think another issue, and I think this workshop is a fantastic way to start this, but getting companies to come up and share on their programs can be a challenging thing too. So I mean, I know so many people that have had programs die because of these types of regulatory interactions that never really make it the light of day, and they're held confidentially within the company. So being able to come out and talk about those and integrate them with the toxicologist becomes really important.

Susan Winckler: Mm-hmm. Right. Because that's a... I mean, our product development system is, at some level, built at the tree, and those trees that die, we don't often explore. See, oh, you're just going to send me to so many metaphors that I'm going to dial them all back. Let me ask one more question, and then we'll turn to more... Actually, two questions. This one is for you, Bill. Were you able to measure the drug in dog or rat lung to compare potential specific PK?

Dr. Bill Thelin:
Yes, we did do that. And we actually found that the PK could be relatively similar, but I mean, some of the data was different and it's challenging. So one of the challenges with the pulmonary drug is using systemic PK as your index. As Jeff showed on the funnel, that is sort of the lowest amount of drug.

So, as a small company, we did in our early studies, we would do lung lavages and actually measure drug, but that becomes extremely expensive and difficult to do that across, especially going into the dog and things where it's more invasive, and you really try to limit the number of animals. So we don't have a perfect comparison of that PK.

Susan Winckler:
Okay. Very helpful. And Per and your... I think you mentioned the Lung-on-Chip model. There was a question about is Lung-on... is the Lung-on-Chip, is that a validated model?

Dr. Jorrit Hornberg:
Yeah, great question. I think it's always debatable what you call validated, right. So it depends what you're looking for and to what extent can you test it. So I always make the comparison with validating liver toxicity predictions using in vitro models because there's so many compounds that have been in the clinic, that have been in humans, for which we know exactly what they do. It's so easy to validate them. For long toxicity, it is slightly more difficult. So the compounds that we've tested, 20 compounds, something like that, that's kind of our validation set.

So we call that sufficient. We've just published some of the data I just presented together with a company called AlveoliX, and so you can look that up and see what we have done. And then we can judge, is that validated? I would really like to take the discussion to the regulators and discuss what is validation. So in other areas where we have more advanced even microphysiological systems coupled with also quantitative systems pharmacology modeling, we can really accurately predict, for example, heme tox in the clinic.

So that data speaks for itself and shows that we have a validated system, right. But I think what is required is that regulators interact with us with the field, and then we are clear what is expected from qualifications, official qualification and validation for such models? But I think the way we use it is for our internal decision-making. And that already saves a lot of animal use, of course, but it also helps us speed up decision-making because, sometimes, these models are much faster than running in vivo studies.

Dr. Per Åberg:
And for that...

Susan Winckler:
Great. Thanks so much. Yep, go ahead, Per.

Dr. Per Åberg:
Yeah. And for that, we would say it's fairly well validated because we are reproducing findings. And then, of course, a key question is it's as progress so you ca... could replace one of the animal studies with it. We haven't come that far, really. But of course, it's maybe a question too useful to have actually to reduce the number of animals in development, but we're not there really to say that it's kind of... But at the end, also in vivo studies are not 100% predictive. We know that.

So you could imagine scenarios where you have one species, and you have a battery of assays, and you reason around low systemic exposure, and you assess the local risk. And then linking further, I mean, I think things like the deposition modeling, I mean, we should start to apply that for humans because we apply that from a clinical pharmacology perspective when doing device [02:10:30] bridging and predicting PK in humans. And I think we should use that also in this type of risk assessment we're talking about, because it could be all from like 20% deposition to 90. And of course, you should take that into account when you do a risk assessment.

Susan Winckler:
Yeah. Okay. So it's small V validated in use, and then kind of a broader question in broader validation. Let me turn... Let's bring you into the conversation, Teresa. So in your role with PF Warriors, you are thinking about how to improve the lives of patients with pulmonary fibrosis

every day. If you had to highlight what was the most important part of this morning's presentations for those patients, what would you call out?

Teresa Barnes:
I think I would call out the idea that we don't have perfection in models and that there are going to be challenges, and there have been challenges. And in our experience in pulmonary fibrosis as patient advocates, and I've had five people in my family die of pulmonary fibrosis in the last 20 years, which I don't have to tell anybody here what my risk might look like. And I have a twin sister, so I told her if we do a study together, she's the control. But the opportunity is that we don't have to settle on one. We need to find the models that fit the purpose. And I think that really is what some of these, in fact, all of them said. This model, you talked about your rats models, and your dogs. We study dogs in pulmonary fibrosis that get the disease naturally, so that might be an interesting model to look at as well. But we don't need perfection. We just need better. And after 30 failed drug trials or so in the pulmonary fibrosis space, I think we can do better. And I'm excited to hear what you're all talking about and what the future may hold for that.

Susan Winckler:
Great. Thanks so much, Teresa. Any thoughts in response to Teresa's observation?

Dr. Aidan Curran:
Only to the extent that I think we would have more trials, and more ability to move compounds forward, if we can improve our access to clinical trials. We have a lot of companies who are desperately trying to move their products forward and are running into technical roadblocks, as opposed to real safety or efficacy roadblocks.

Unfortunately, small companies don't have the... I don't want to jump on our AstraZeneca colleagues, but small companies don't have the resources to try out multiple different approaches, and to generate huge amounts of data. We're stuck with the idea of, "Let's try to get through regulatory, and get into clinic as quick as we can." That's the major road block from a small pharma perspective. Large pharma has the ability to generate a lot of really cool data. Hopefully move that, that trickles down to the rest of us at some point. But really, from my perspective, as a small pharma person, there's a lot of companies out there that are trying to get into clinic that are struggling, because of nebulous reasons. Non-monitorable finding.

Susan Winckler:
Yeah. Yeah. That's where shared learning can help everyone.

Dr. Aidan Curran:
Right, exactly.

Susan Winckler:
I'm not going to call them large pharma. We thank Per and Jorrit for sharing their experience.

Dr. Jorrit Hornberg:
We're trying to move the view forward, right?

Susan Winckler:
Yes.

Dr. Jorrit Hornberg:
But I do want to clarify, we face the exact same hurdles that you face in a small company. We have maybe more programs and then more programs run into that issue. We do generate a lot of data, but it doesn't always help to get around that hurdle. We very much recognize, and thank you for your presentation. It was fantastic. Totally agree with you there, what you said there.

Susan Winckler:
Yeah. Okay. So go ahead, Bill, and then I want to turn to Karin.

Dr. Bill Thelin:
Sure. We're in this paradigm where everybody runs rat and dog. We are straddled with these safety margins and what caps us at the top dose. But I think what we would want to advocate for is really to come in with this weight of evidence, regulatory review, where we really integrate the data. Maybe to a disease that for pulmonary fibrosis and where this gets interesting and a lot of other diseases, it actually turns out that sometimes the findings that you get in these normal animals look very different in a disease model that have preexisting inflammation.

Drugs can actually be anti-inflammatory in the disease models, but are pro-inflammatory in the normal animals. But that ends up setting the risk for the patients when it actually may be really advantageous. I think that being able to put this together in a really cohesive way and look at the data as a sum becomes a really important exercise for regulatory interactions.

Susan Winckler:
Karin, we've heard the insights from a couple of companies. In your role at BIO, how do you think about this reality for the industry writ large? I think you've already got some ideas presented today for what BIO might do next.

Dr. Karin Hoelzer:
Absolutely. And just to clarify, in my role at BIO, I'm really that intersection between the patient community and our member companies, which is a really fantastic place to be. As BIO, we represent the biotech industry, including our more emerging companies and our larger, more established companies.

Very much appreciate the discussion this morning around the diversity of perspectives. You mentioned at the outset the need for more data. We at BIO actually collected some case studies on NAMs which you published last year. It was not specific to respiratory, but I do think there are lots of themes that apply here.

Listening to the conversation this morning, most of our members are very excited about the opportunities here. And I think we heard a lot from the fantastic presentations about what is possible and how this can really help speed the path to the clinic and ultimately to cures, which I know so many patients are so desperately waiting for.

But we also know some of the challenges, regulatory challenges were already brought up, challenges with international harmonization, concerns around the added time of getting that validation study, and then really the concerns around how do you handle false negatives and false positives. I think we had some really great case studies this morning. I think we see tremendous opportunities here. Fully agree on the need to compile more of the data and to really walk that balanced approach.

The other thing that really makes us very concerned given the innovation ecosystem is really hearing the concerns around this driving more innovation outside of the US. We need a very strong biotech industry in the US. We've long been the leader in biotech. It's so important to our industry, to national security. That's definitely certainly important too.

Susan Winckler:
I hear you speaking then back to this tension of helping better understand the science, so then that can inform the regulatory science, because we do want our regulators to be performing their function and to help us understand what are the safety signals of import here. I have a question that came here that I want to follow up. It ties in a bit to what you just mentioned, Karin, and from other comments that part of the problem here may be the premature pivot away from animal testing without exploring that. Can an argument be made that the lab animal data provide important verification for translational approaches? Unless Per or Jorrit jumps ahead, Bill leaned back a little. Yes, it goes to...

Dr. Aidan Curran:
All right, so I'll stick on the being provocative.

Susan Winckler:
That's great.

Dr. Aidan Curran:
I'm a firm believer that safety assessments will, for as far as I'm concerned, continue to need animal studies. I think the animal studies are insufficient and there is so much more mechanism of action and specific findings that we can get from NAMs approaches that can streamline everything.

But the point I was trying to make in my presentation as I was running out of time was that we have an absolutely unfathomable amount of data that's available to us right now to do translational assessments of non-clinical and clinical. That that perhaps might negate the need for a whole lot of animal studies going forward, but we don't use it. It's sitting there in repositories and various companies under confidentiality and under people trying not to release data.

But if we could come up with a mechanism to use the data we already have generated, all the animals that we've used, hundreds of millions of animals we've used over the years or more than that, let's make use of those data now. Let's try to figure out, we have advancements in AI and data mining that we could apply that then to future development in association with NAMs and other methods.

The idea here is not to replace one with the other. I don't see this as a battle between animal research and NAMs. I see this as an attempt to reduce. How I would reduce animal usage is by making better use of the data that we have and that we generate going forward and including NAMs work and including all of the tools that we have. It's like trying to build a house, but only using half your tools.

You still need to have a crane and a hammer, but better tools make better work. I don't think it's one or the other. I don't think it's reasonable to set it up that way. Again, I'm not here to say, let's

not go ahead with NAMs, let's stick to the way we've always done it. The idea is let's improve the way we're doing it.

And there's fixes in the short term that we can do with animal research, as we get better and better with NAMs. My fear with some of these models is there's different models being developed and there's not a whole lot of uniformity between them. Again, the industry coming together to start to streamline, what charging port are we going to use in our cars? Those kind of things. As the technology advances, things should get more clear.

Susan Winckler:
Bill, you wanted to jump in?

Dr. Bill Thelin:
Yeah. The three Rs to deal with replacement, but also refinement and reduction.

Susan Winckler:
Absolutely.

Dr. Bill Thelin:
That's where NAMs are really, I think, doing a great job. They can be used to help us cut down on the number of studies that we have to do or avoid having to do replicate animal studies in the event of the finding. I thought Jorrit's example was great for predicting what the animal outcomes were actually going to look like. That really helps you refine those studies, run the right dose groups, keeps you from dosing as many animals, which I think is a fantastic start towards the entire principle.

Dr. Karin Hoelzer:
And to maybe just chime in. It really comes down to that balance. We want to move towards NAMs, but we have a lot of data, we have a lot of evidence, we know it'll take time, and there are differences. I think the case studies this morning did a very good job talking about the nuances and the differences. And so really keeping that in mind, that this will be a process.

Susan Winckler:
Absolutely. Go ahead.

Dr. Jorrit Hornberg:
You want more comments or...

Susan Winckler:
Yes, please.

Dr. Jorrit Hornberg:
No, I just wanted to build. Of course, I agree with what's being said. We are very firm and heavily investing into NAMs because we do believe it will hit all of the three Rs. As we were saying, you send cleaner compounds into the animal studies that you still have to conduct because ultimately there is a requirement to do certain studies before you can bring them into the clinic, your programs into the clinic.

But the compounds that you put into those studies will have a much better safety profile. It hits all of the Rs. There are aspects of toxicology where our NAMs currently predict much better than the in vivo studies ever did. So we stopped doing those in vivo studies. We focus on the NAMs. But clearly there are areas where we're well behind the predictions of the in vivo model. We're trying to bring that field forward. We're not there where we need to be. But I would say there's definitely a place for NAMs, even in respiratory medicine, I think.

Susan Winckler:
I want to follow up, Aidan, on your recommendation about using the data that we have. I guess that the common challenge I hear for that though is that the data is siloed, that it's in individual sponsors data vaults or perhaps abandoned products. How do we think about, for our existing data, breaking down those silos and pulling it collectively? And then for future studies, you observed that there's... And actually it's from the earlier presentations, we have this conflict in terminology and nomenclature. It seems like there's an opportunity for thinking more consistently in future studies. I'd invite, if folks have some thoughts on how to break down the silos of the past data and then how we might improve future studies.

Dr. Aidan Curran:
Yeah. Sorry. I don't want to hog the entire conversation.

Susan Winckler:
Oh, you're not. Don't worry.

Dr. Aidan Curran:
But yeah, I think historically people don't want to release their data because it's their data and they've invested a lot in it. But we have the tools now to anonymize the data, to analyze the data without any release of confidentiality or release to human beings. We have AI that can mine these data for things that we never might've thought of in the past.

I'm particularly interested in how do these findings translate from non-clinical to clinical. We have a lot of conversations about 90% of drugs fail because it doesn't translate. I'm not sure that I necessarily believe those numbers, I think that's a generalization. A lot of drugs fail for a variety of reasons, oftentimes for commercial reasons or for... I think understanding, actually generating these data, we're making inferences and assumptions based on conversations without ever actually mining the data for what it's available for. And as I said, we've used these animals already. These data already exist for 40 years or 50 years of inhalation studies.

It's out there. It's useful. I think it'll take some sort of public private partnership to fund it. It's not going to be cheap. But if there's a commitment there to really advance the science, then there's no reason why we can't use the data to predict potentially... We have a lot of things like structural activity relationships that have developed over time.

I think we can advance that as well as things as simple as calling it deposited dose the same thing. That is a fact. That we still have different people calling different things different things. There's multiple levels to this. This is where the societies and the professional organizations can have a huge impact as well, in trying to create these standardized and create these partnerships.

Susan Winckler:
And Teresa, it strikes me, you've mentioned the challenges that you've seen in the area where

you work and the patients that you engage with. The question to you, I think, tell me what your [02:28:00] community would think about the opportunity to compile that data and learn from it more broadly.

Teresa Barnes:
One, I think we would love to have access to that. We have 30 or so failed trials, as I mentioned, we'd love to see why. Really understand why those trials failed. It's probably a lot of different reasons. But we need to learn from those. I think our patients are desperate. They're dying. We have three drugs and we're grateful to have them, but our patients don't survive.

They often die really fast. It's not a pretty sight. I have one patient who has pulmonary fibrosis and lung cancer. And guess what? Lung cancer is in remission because he had therapeutics that moved quickly through the regulatory process to help him. And his doctors said, "Great, we got the cancer, but too bad PF doesn't have any treatments to save you." We're really in a bad spot and the best thing we can do is move quickly with ideas.

The best way to speed drug development is to try every proven tool, whatever that is, including what FDA has done with new approaches and methodologies, NAMs and different animal models, it really comes down to being able to do so with speed. The pulmonary space is suffering. If you compare us to other spaces, it is not the same.

We have high death rates for every disease in the space. We can do better, but we also have to have strengthen in collective knowledge and understanding. We have to have journals that are willing to publish on new models and not just the standards. We need flexibility so that studies can be done in the US and we aren't seeing... Our patients miss out when studies are done outside this country, that we have patients internationally, but we have a lot of US patients. When they can't participate, that's a loss not only for the patients, but for the entire community.

I think we need more models. We need all of the successful models. We need to investigate them. We need to even go back and look at the models we have to see if they're really, really the right models. Let's really take a really close look at all of it. And then we need all hands on deck to move quickly to therapies for these patients.

Susan Winckler:
Thanks so much, Teresa.

Dr. Jorrit Hornberg:
Very powerful. I want to build on it because what you're indicating there about IPF and comparing that to lung cancer, this is a message that everybody in the room should hear. Because we've had molecules that were stopped because of toxicities and not necessarily pulmonary toxicities, but toxicities. The difficulty bringing such something like that forward in the respiratory space, the exact same mechanism, this was mechanism-based toxicity, the exact same mechanism does progress in oncology. This is a powerful message, and I hope everyone hears that.

Susan Winckler:
Yeah. We have time, I'm going to do one more question that came in, and then I'm going to give you each... You each get a final word, which means there will be six final words. But I first

want to ask, can the panel comment on the concept of most appropriate species or how to interpret two species tox? Bill gave me that smile that said he doesn't want to answer first.

Dr. Bill Thelin:
Two species can be tricky. There are lots of examples where that works out very well. There's a clear reason that we've historically, I think, looked at two species, although Aidan and the JFs and the toxicologists could probably answered that better.

The problem we run into is what if one of them says something different? What if it really ends up not being predictive of human? There are different physiologies and I talked a little bit about anatomy and things that sometimes just the way that the rat protein interacts with said drug that doesn't happen in humans or dogs, that becomes a problem. How do we overcome those challenges?

Susan Winckler:
Yeah. Everybody else is saying, "Good job, Bill." Let's go to, this is the question I'll pose to each of you and let me tell you, you order first. We're going to turn to our virtual panelists first. We'll do Barnes, Hornberg, Åberg, and then we'll do Curran, Thielen, Hoelzer. So you know your order. Karin, you get the very, very last word, but I'd like each of you to comment on where you see the greatest potential promise in improving product development and reducing reliance on the use of animal models. And I think within that, this component of how might we, as part of that, also make sure that we're bridging the gap for patients that are here in the United States and as well as the research enterprise in the United States. Where do you see the greatest potential promise? Teresa, would you pick that one up?

Teresa Barnes:
Sure. I think the goal is obviously to reduce the reliance on animal models, but traditional animal models we know have a role here. I think we don't want to move too quickly to get rid of those. But I do think having a look at all of these opportunities with NAMs, with organoids that are coming to fore, with AI's opportunities to basically help us make decisions better is going to be part of the answer. I think for our patients in the US, they would all be jumping up and down if they thought that there are more trials in the US could happen. And right now, some of the problems we see is that there's a cookie cutter approach on the regulatory side. Because one company did it one way and it worked, everyone wants to duplicate. And that may not be benefiting our patients.

And it's not the company's fault, it's a regulatory issue. Looking at more creative approaches for inclusion and exclusion and ways to do studies that are more creative and may hold better opportunity for patients, I think we need to keep options open instead of closed.

Susan Winckler:
Thanks, Teresa. Jorrit, go ahead.

Dr. Jorrit Hornberg:
I think it's important to also recognize, of course, regulators, just as we do, are aiming to protect human safety as well, so all good intent. Your question, I think I have in my presentation probably commented on it already, there are models out there and use them to take your decisions. One aspect I didn't touch on is you can use these models really to accelerate your drug discovery. And we have platforms using large scale omics data using AI to then do

predictions on certain toxicities, where in the old days you'd have to run repeated in vivo studies. Much faster than... Bringing medicines to patients faster. I [02:36:00] do want to say it's not just about alternative methods. I think that some of the speakers have talked about this, how we calculate margins is a topic we could tackle and we should tackle.

Susan Winkler:
Yeah. Great. Thank you. Per?

Dr. Per Åberg:
Yeah. At first I'd like to say it's inspiring to hear Teresa's comments. We are calibrated on this very conservative where very discreet findings may actually limit us and we may actually discontinue opportunities because of that. I think it's important to have this discussion and really think about risk benefit. But in relation to NAMs, yes, I agree with Jorrit. We do apply that already in a discovery context.

I think we already have concluded that we have deselected compounds that probably would be quite toxic in vivo, and that's what we actually set them up for. We're optimizing molecules in that way. If they are there to replace the regulatory test, I think, my example, we did a repeat of six month rat study just to titrate where we were on that finding that we were actually not concerned about.

And I think in those cases, we should be able to use NAMs and in vivo models to contextualize the finding. And by that, refining, reducing use of animals. I could even see scenarios if you have, like the one Jorrit presented, I'm not sure the rat study there really gave us much more than what the in vivo study and the predictions of exposure did. Maybe one species could be considered in some instances.

Susan Winckler:
Yeah. So then thinking what did we learn and where was the most value? And then thinking and applying that in the future. All right, let's turn to the room and you actually have three minutes total. Because I'm going to start with Aidan. Yes. So Aidan, you have one. Bill, you have one. Karin, you have one. Aidan.

Dr. Aidan Curran:
All right, I'll be super quick. I'd like to distinguish between efficacy and tox, first of all. I think NAMs right now probably predict efficacy better than a bleomycin model or something like that. That is really awful. As much as we're not happy with the tox situation, the efficacy prediction is terrible. That to me is where we start. We need to start really quickly moving and then refining tox models and reducing... I still believe we have to do tox, but knowing what we're expecting to see when we get in there, I think will hugely improve the situation.

Susan Winckler:
Bill.

Dr. Bill Thelin:
Yeah. I have two thoughts on this and one to really sort of agree with you and Per. I see the NAMs having a really big impact on early discovery. What people don't always think about is that you might run through 100 compounds to get to the lead that you take into the regulated studies. And you may be running animal studies all along the way to make sure that you've got

the right compounds so we can use NAMs to refine that on the front end. You might cut the number Oof animal studies tremendously.

But the other one, and part of what I talked about is also really utilizing and applying modern clinical medicine technology. Imaging, the development of biomarkers and things to predict the toxicity so that we could actually advance drugs into clinical trials to figure out if the mechanism is even valid for treating a disease. We're not iterating so many times to get the right compound, only to find out that it fails in efficacy studies.

Susan Winckler:
Thank you. I had thought when we were hearing the earlier presentations about the extraordinary value in development programs of better understanding the new approaches and how those might be used. Karin, official last word for the morning.

Dr. Karin Hoelzer:
Very much appreciated and what a fascinating conversation. I'm actually veterinarian by training, so this has been absolutely fantastic. I do come from the rare disease community. One thing that I want to bring up is that there are many patient groups that are actively working on animal models, on NAMs. There's a lot of excitement around tissue chips, et cetera, a lot of the work that NCATS is doing.

Just reminding us that these patient groups need to be part of the conversation and really incorporating them. I think to Teresa's point, what this morning has taught me is that if we get that balance right, if we move forward having that right balance, there's a tremendous opportunity to bring life changing, life altering treatments to patients much faster. And I know there's so many patients out there that are desperately waiting. I think that's a tremendous opportunity here. Thank you for having us.

Susan Winckler:
Excellent last word. I'll say, let's first thank this panel for helping us absorb. We're now going to break for lunch and we'll resume in 44 minutes at 1:15 PM Eastern time. For those of us who are in person, there's lunch outside the conference room. If you're joining us virtually, we will see you back at 1:15 Eastern.