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**Speaker 1:** The *BioWorld Insider Podcast*.

**Lynn Yoffee:** This is the *BioWorld Insider Podcast* and I'm Lynn Yoffee, *BioWorld*'s publisher. In an industry always driving to speed drug discovery, clinical development, and commercial success, government regulation can sometimes seem staid and slow-moving by comparison. Even a brief look at regulatory highlights from 2021 shows nothing could be further from the truth. From COVID-19 and cancer to FDA advisory committees, so much has changed. Leadership changes and retirements at the FDA created new questions about what priorities might prevail in the US next year.

What about post-Brexit UK and the push for innovation by China's top regulatory agency? We've asked Peter Pitts to help us put it all into perspective. He's the president of the Center for Medicine in the Public Interest. He's a former member of the United States Senior Executive Service and was FDA's associate commissioner for external relations. He's now a visiting professor at the University of Paris School of Medicine. Today, he's joined by *BioWorld* managing editor, Michael Fitzhugh. Over to you, Michael.

**Michael Fitzhugh:** Thanks, Lynn. It's great to have you here, Peter. How are you?

**Peter Pitts:** Oh, my pleasure. Hi, Michael. It's going to be a good conversation.

**Michael:** Yes, I'm excited. I want to start big picture. If you had to describe the general tenor of the US regulatory landscape in 2021 in a word or two, and which is challenging I know so take as long as you want. Peter, in a word or two, what would you pick?

**Peter:** I think the word of the day is gemish. There's a lot going on. Everything is in flux. People are paying attention. Maybe that's the biggest difference between now and 18 months ago, is that people realize that regulatory issues really have a profound impact on moving healthcare forward, and not in the US but around the world.

**Michael:** Why do you think people are really getting that now in a way that maybe they didn't before?

**Peter:** COVID-19 has changed the way we think about a lot of things. It's also changed what we're thinking about more regularly. Obviously, before COVID-19, the general population didn't think about the FDA, they didn't think about emergency use authorization, they didn't know what mRNA meant. Maybe they thought it was Eminem when they went to the movies. They didn't think about supply chain issues when it comes to pharmaceuticals and diagnostics. They didn't think about diagnostics at all. They assumed that every diagnostic was 100% accurate, and every drug was 100% safe. We've learned a lot from that.

I think that's an opportunity moving forward so that people recognize that regulatory issues aren't just some boring red tape government thing, that it also has the opportunity to expedite innovation and improve health care because of itself rather than getting in the way. For example, FDA, rather than being viewed as a bureaucratic roadblock to innovation, FDA is now being viewed, and I think appropriately so, as a facilitator of innovation, as a partner with the industries that it regulates. I think complicated concepts, but at the end, a good conversation to have.

**Michael:** That newfound appreciation that is developed of the complexity I think has been accompanied by an appreciation or a greater appreciation for the personalities, people involved. There was a large change on that front at the agency this year. There's a contentious path to change the guard at the top with the eventual appointment of Robert Califf as the agency's next commissioner.

Turnover in the Office of Vaccine Research and Review after there was some dispute around evidence for COVID-19 vaccine booster shots. Even some struggle in terms of saying the agenda with the White House. Tell me a little bit about how you're viewing the leadership changes and power dynamics around the agency right now.

**Peter:** You've teed up a lot of things. Let me pick the juiciest,-

**Michael:** I'm sorry. [laughs]

**Peter:** -which is politics. Obviously, there's always been an undercurrent of is the FDA being driven by political agendas. I guess it's important to say upfront since we're talking largely about diagnostics and biologics and drugs, that in those three centers, in the centers for devices at CBER and CDRH, every single employee from the director on down to the newest secretary is a career public health official. There are zero political appointees, Schedule C appointees inside those centers. When people say that these are political decisions, I would have to disagree with that. The FDA has done a very good job maintaining its scientific integrity.

The problem has been from the White House, from the Trump White House and from the Biden White House. They both made significant faux pas, in my opinion, trying to dictate what the agency says, trying to predict what the agency is going to do when what they should really do is sit back and let the FDA do its job and then comment on the decisions that the FDA makes. For example, when President Biden says that, oh, the FDA is going to do this shortly, he shouldn't be saying that because those decisions haven't been cited on yet. That's bad. It basically says that science is back only so far as we want to be in track with our political agenda.

Clearly, when President Trump stood up and said things that were wrong, that were counterproductive, similarly, people lose faith in the process because the guy sitting in the Oval Office is the boss, and people take cues from them. I think what you've seen certainly in the office of vaccines within CBER is people being very upset with the Biden White House trying to predict what the FDA is going to do and saying that publicly. That's not the way the system should work. I think that system works best when you let career government scientists do their jobs and then support those decisions.

**Michael:** Do you think that the pandemic has diminished the agency's overall reputation, or is the level of things that I'm asking about here inside baseball that really only touches the perceptions of a few like us who are paying closer attention to it?

**Peter:** All of a sudden, everybody is an epidemiologist. All of a sudden, everybody is a regulatory expert. If I'm playing tennis, people want to talk to me about mRNA technology. They don't know anything about mRNA technology. I'm all for people wanting to get engaged in the conversation, but the truth is that there are no easy answers to complex questions. Politicians hate that. Politicians want easy answers to complex questions that can happen quickly. A lot of issues certainly when it comes to COVID-19 will be with us for quite a while. People say to me, "What? I thought once you’re vaccinated, you couldn't get COVID-19 like polio." I don't really think anybody said that.

That may be what you heard, it may be what you want to be true, but science is tough. The last time most people touched science was in high school where there was a right answer and wrong answer, and we were dissecting frogs. Regulatory science has tremendous nuance and a lot of gray zones. You really need to understand that, for example, the plural of anecdote isn't data, and that data takes time to collect and analyze.

When you look at the tremendous successes of Operation Warp Speed certainly with the bringing diagnostics and vaccines and therapeutics to market in amazing time through emergency use authorizations, you recognize that there's a degree of flexibility in what can be done and what can't be done. You can bring products to market through new ways, but that they're fully approved, that doesn't mean you can stop collecting data. People need to recognize that drugs are not 100% safe, that vaccines are not 100% effective, that there's a degree of understanding that needs to be had.

We can't really move forward on issues like health equity which is the buzzword of the day until we move forward on health literacy. The health literacy in this country and around the world is abysmal. I think one of the things that we've learned is that regulators need to speak in plainer English to explain people exactly what's going. Giving people certain equations with Greek letters of them is unhelpful when it comes to educating the general public.

**Michael:** That outreach or education aspect is really interesting. Tell me more about how you think that that could unfold or an effective avenue through which it might be prosecuted? You're right, there's clearly a gap between the way people perceive regulators and the way that they actually operate. That's really interesting.

**Peter:** I think one of the benefits, for example, the president finally nominating an FDA commissioner-designate and that person been Rob Califf, who I think is a fabulous choice, is that Rob understands the value of speaking to the general public about issues rather than simply speaking to his colleagues in shorthand. That's clearly something we all suffer from. We all understand these incredibly complicated, nuanced regulatory issues. We speak in code, people look at us like we're speaking a foreign language, and we are.

I think what Rob Califf understands is that if you want more people to be included in the conversation, you have to change the way you speak and the words that you use. Sometimes, like Einstein said, if you can't explain a complicated concept, simply you don't understand it. I think Rob Califf gets that. I think that was probably one of the strongest reasons that President Biden moved forward on his nomination.

**Michael:** One of the other interesting aspects of all this nuance coming to the fore during the pandemic has also been a recognition that sometimes there's discord between the FDA's advisory committees and its reviewers. Like very recently around COVID-19 vaccines, again, with myocarditis concerns, and even more notably in the eventual approval of Biogen's Alzheimer's disease therapy, Aduhelm. Are we just seeing reasonable people disagree or there's something else going on?

**Peter:** Let's talk about advisory committees. When I was at FDA, I was the senior official in charge of advisor committee oversight. It was still a pretty esoteric event at the time. Now they're televised and they're dealing with hot topics and lots of people are watching them. What they're recognizing is that it's neither all for or all against. There are always issues that are going to be out for future discussion. That's the first issue, so it's a risk-benefit calculation.

Then the fact that advisory committees are in fact advisory, that the FDA can move forward in agreement with those committees or contrary to the advice of the committees, and that each advisory committee is de novo onto itself. The past does not necessarily predict the future, even though the FDA generally follows the advisory committees until they don't.

I think what we found, certainly, relative things like vaccines is that there are open questions. It's good to air those questions and to air them publicly, but that doesn't mean that at the end of the day the FDA shouldn't move forward in emergency situations certainly to allow the use of many of these products.

When it comes to Aduhelm, that's very interesting. Aduhelm is a drug for Alzheimer's disease. It was approved through what's called an Accelerated Approval Pathway. A lot of people inside the division that reviewed this product felt that the risk-benefit analysis wasn't robust enough, that the signals for benefit were squishy. Then advisory committee voted against having the FDA bring this drug to market, to approve the application. The division however decided that in a therapeutic area where there are very few treatments, it is not a well-populated therapeutic armamentarium, that this was an advanced significant enough to approve. I happen to agree with that decision.

A lot of people inside the FDA and outside the FDA felt this was the FDA willy-nilly approving drugs based on a biomarker of hope as opposed to hard data. I think at a certain point you need to say, "Listen, we need a lot of programs in this area. We need more tools. If you don't allow these drugs and therapeutics to reach the market, people are going to stop investing in them." That's the way the free market works and that can't be allowed to happen. I'm not saying that drugs be allowed to come to the market because we don't want to scare away investors, but we need to recognize that when a real therapeutic signal presents itself, we have to look at it in new and significant ways, again, based on risk and benefit.

When it comes to Alzheimer's, I think there's so many risks here that even benefits that are yet to be seen as significant, we need to look at them and understand what that might mean for the future. I think that recognizing that regulatory science needs to advance with the times, with the technology, but also based on the therapeutic area that we're talking about is now actually something that more people are having and that's a good thing.

**Michael:** Tell me about regulatory science as a thing. I often think I apprehend what's meant. I look at conferences about regulation or regulatory professionals get together and see all the titles, I'm like, "Oh, yes, okay. That's fine. This is a broad field." Tell us what you mean when you say regulatory science.

**Peter:** Regulatory science is how the FDA does business. How does it collect data? How does it design clinical the trials? How does it review the data? How does it create the label for the products, and that physicians can understand how best to use them or not to use them? I think a good example of that is the evolving use of biomarkers. Rather than simply looking at, did the tumor get reduced, did patient with Alzheimer's disease have better cognitive skills, we look at things like, for example, the Alzheimer's disease, amyloid plaque.

When it comes to Alzheimer's disease, there's a big debate about what causes the disease. One of the major theories, and it's a theory, it's a hypothesis, is at the buildup of amyloid plaque present itself in patients with Alzheimer's disease. If we can create products that reduce the buildup of amyloid plaque, the biomarker says that should therefore reduce the advance of Alzheimer's disease for any given patient.

I personally believe that's true, but again, it's a hypothesis. A lot of people have said we shouldn't base it on a biomarker, we should only base it on actual clinical results. That's very 20th-century thinking. The problem when it comes to science, like with many other things, is that the status quo is a harsh mistress. A lot of people inside the FDA go, "Look, that's not the way we do it, this is the way that we do it."

I believe inside the FDA from Rob Califf should he get confirmed on down to the leadership within the divisions, people are beginning to understand that 21st-century science needs to be introduced into the review system. That's harder than it sounds because you have a lot of people inside the FDA who've been there for many years, they're very qualified and very credentialed, and they don't want to do things in different ways. You really change agents within senior management at the FDA to drive things forward. I think that's actually happening.

**Michael:** Do you think Califf, should he get confirmed just going to bring those people into the upper management that can deliver that kind of change that you're talking about?

**Peter:** If Rob Califf gets confirmed, this is Rob Califf take two, part two because he's already been a commissioner and he was deputy commissioner as well. I think right now what Scott Gottlieb and Rob Califf during his last 10 years as commissioner and Margaret Hamburg before Rob and Andy Von Eschenbach before that, they really began to hire people and promote people from within the agency that had a more innovative dynamic in the way that they think.

That obviously initially presented itself within the oncology divisions, which has really done amazing things. The FDA can't just be innovative in oncology, it needs to be innovative across therapeutic areas. I think that is starting, but when you have somebody at the top who really understands and rewards this type of thinking within the review divisions things happen. I think the value of having Janet Woodcock having been acting commissioner since the end days of the Trump administration, since President Biden came into office is she is a firm believer in that, and that she has the faith and trust and friendship of many of the senior leadership inside the FDA.

I think a key thing about Rob Califf being commissioner and Janet Woodcock hopefully staying on once he is confirmed, and that's at least the gossip at the moment, is that the senior leadership at the FDA, the career leadership inside the FDA knows these people, it trusts them so that the best way to make sure your legacy is successful while you're there is that the senior staff becomes inculcated with that philosophy. I think that Rob Califf and Janet Woodcock understand that dynamic.

**Michael:** Interesting. I guess moving back from the leadership for a moment and maybe more down into the weeds, I want to ask also about review decisions that were delayed this year, mostly around the inspection of foreign manufacturing facilities being completed in not so timely fashion often because of travel restrictions and even resulting in complete response letter in some cases. Do you think that that's a transitory issue that the agency can get a handle on in the year ahead?

**Peter:** Quality is the third leg of regulation. We talk a lot about safety and efficacy, but the real issues here are safety, efficacy, and quality. You can't have any two without the third. A huge part of quality obviously is cGMP issues and inspections of manufacturing facilities. This is not a unique COVID problem. I think it became more evident during COVID because the FDA couldn't physically send people to plants. It was almost a convenient excuse, but I think it's important to remember that even before COVID when it came to foreign inspections, there was a cue.

Even before COVID-19, the FDA recognized it would have to move to what's called risk-based inspections, which means aiming the resources that it has at those facilities that have the greatest number of questions and that's smart. At the end of the day, another big problem that no one really talks about is when it comes to the FDA inspecting facilities that reside on foreign soil is they can't match in and do surprise inspections. They have to have these inspections scheduled. To my mind, telling people you're coming and giving them the chance to hide things isn't the optimal.

On the one hand, those types of rules need to change, the FDA needs to negotiate a little bit harder with foreign governments if they want to be in the game of manufacturing products or making API for use in the United States. I think it's in their interest to do so, even though the companies that reside within those countries will lobby ferociously against that. Then of course the issue is resources. The FDA needs more people on the ground in places like India and China, and that is problematic for a variety of reasons, not the least of which is the FDA doesn't have the budget to do it. Hopefully, FDA and the COVID cue, so to speak, will allow for a more forward-looking conversation to address some of these problems.

**Michael:** Looking beyond the US because, obviously, the FDA is functioning, as you just noted, in this really global context where they're working with other governments or working with other regulators. One of the things that I've been curious about is Brexit and where the UK really stands right now with that. On COVID, the UK's MHRA seemed really aggressive and becoming the first regular to grant a conditional approval for Merck and Ridgeback's Molnupiravir. Looking ahead, how do you think the regulatory environment over there is evolving and changing as they deal with a review of EU laws, overhaul of clinical trial frameworks, and stuff? How do you think things are settling down post-Brexit?

**Peter:** I think in a post-Brexit regulatory environment, the UK actually comes out ahead because it frees up the MHRA to do its job for Britain. The MHRA is a spectacular agency. The MHRA also carried a lot of the weight for EMA on some of the tougher review issues. EMA is in a hard spot without the brainpower and the human resources power of MHRA. I think that certainly helps Britain in the sense that MHRA is now focusing exclusively on issues in the British Isles.

I think that their decisions have been very smart. Obviously, the biggest divergence between the US FDA and MHRA over COVID has been over the AstraZeneca vaccine. Even though there are national pride issues there, I think that that shows that different agencies that basically conform to the same standards can reach different decisions.

**Michael:** I guess that's another sign of the various nuances of regulatory science that people can review and come to different conclusions.

**Peter:** I think it goes back to something you said earlier, which is intelligent people can look at a problem and reach different decisions. It doesn't mean that one is right and the others are idiots. These are issues that can sway either way based on a whole variety of issues. I think that, hopefully, what the COVID-19 experience has taught us is that better harmonization on issues that we can agree on, for example, clinical trial design and data derived from those trials should be more widely shared and used in regulatory decisions, both to expedite review and to make the cost of R&D less expensive. That's a nice double play.

**Michael:** That harmonization element is really interesting. I see that popping up more and more in our stories as we cover the regulatory environments across the world. Especially in China, there seems to be a lot of push to accelerate new drug development and also thin out overcrowded spaces. Tell me, is harmonization bringing a lot more focus to the more 21st-century elements of regulatory science to the regulatory of environments elsewhere outside the US?

**Peter:** There are a lot of issues when it comes to global harmonization on pharmaceutical regulatory issues, not the least of which is you need to have somebody who's politically responsible in a country for a decision. People say why don't we just have a global FDA where there's one agency looking at everything, which is interesting after a couple of beers, I suspect, but at the end of the day, when things go wrong, who's responsible? In the US, it's the FDA that is led by appointee appointed by the president so there's political responsibility.

EMA is a little bit more complicated. You have various types of decision-making processes that are continental and there are others that are simultaneously national. Now, of course, you have the UK out of EMA looking after itself. I think maybe a step forward there is broader and more regular communications between regulatory agencies. You have ICH which is a global agency, you've got WHO which is a global agency, and within that, you've got things like the Uppsala Monitoring Center on pharmacovigilance which collects data globally which is important.

How do you have regulators who are doing their jobs on a regular basis talking to each other more regularly, rather than having it siloed between leadership meetings on the one hand or extraordinarily esoteric harmonization documents that take years and decades to move forward? I think that harmonization is good, but how can we make it more of a real-time proposition?

**Michael:** You don't think free beer is the answer?

**Peter:** I think free beer is the start.

**Michael:** [chuckles].

**Peter:** I'm a big believer in incentives of all kind, not just for COVID-19 vaccinations.

**Michael:** It's the inevitable time of a year-end podcast where we have to take off the crystal ball. My crystal ball is terrible. [laughs] I don't predict. Every prediction I've ever made in the industry seems to fall dead on arrival. Tell me a little bit about any read-throughs from things that we've been talking about, things that have happened this year that you think might illuminate the year ahead.

**Peter:** I don't have a crystal ball, but I do have a magic eight-ball. Occasionally, I fall back to that. Again, to a certain degree, and certainly when it comes to regulatory science, the past does inform the future. I think what we've learned from COVID-19 that people get is that when everybody within the broader healthcare ecosystem works together, we can accomplish amazing things more quickly. I guess the question then becomes what lessons from COVID-19 can we apply going forward in areas beyond COVID-19? I think some of those lessons are the regulatory agency, FDA, MHRA, EMA, pick your agency, has to be both regulator of and colleague with industry. That is very politically explosive.

I think that what we've learned from the past is properly controlled, it can pay tremendous dividends. I think what we've also learned from COVID-19 is that innovations in healthcare don't generally come from government-funded programs. They come from a combination of government-funded science, early academic science, and hard-core developmental science that's driven by privately-owned or public pharmaceutical companies. I think that if we can all play nicely in the sandbox together, we can accomplish tremendous things. That's the lesson from COVID-19. Hopefully, we don't fall back to good guys and bad guys in this proposition.

Again, a good example of that is people are beginning to realize what things like user fees mean. In the past people said to me, the FDA can't be trusted because they're in industry's pocket, they get paid to approve drugs, while the truth is that they get paid to review drugs and that you don't get your PDUFA fee refunded if your drug doesn't get approved. I think people are beginning to understand the actual dynamics of how drug regulation works, how biologics regulation works. That's a positive step forward. Hopefully, politicians will be smart enough to stop trying to paint the FDA as a demon to accomplish whatever political goals that might solve for them.

**Michael:** That's the kind of chair I can get behind, Peter. Thank you very much for a very interesting conversation. It's been really great talking to you.

**Peter:** My pleasure. Back at you. Stay safe and let's make the next year the year for smart regulation.

**Lynn:** Peter, we really appreciate your excellent perspective on what are very complex and often politically charged regulatory processes that both challenge and guard the development of human therapeutics and vaccines. Thank you, Peter and Michael. As always, *BioWorld* will continue to keep you informed of all the most important scientific, clinical, and business updates in the field. That's our show for today. If you need to track the development of drugs, turn to bioworld.com, follow us on Twitter, or email us at newsdesk@bioworld.com. Also, if you're enjoying the podcast, don't forget to subscribe. Thanks for joining us.

**Speaker 1:** *Bioworld* published by Clarivate is a subscription-based news service, but all of our COVID-19 content, more than 5,000 articles and data entries since the start of the pandemic, are freely accessible.

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