



# YourEncore Regulatory R.A.N.T. Relevant Assessments | New Trends

## Topic: Pondering PDUFA & Other Policy Drivers

Expert Panel Discussion with:

Tim Franson, M.D. (Tim.Franson@YourEncore.com)

Joe Lamendola, Ph.D. (Joe.Lamendola@YourEncore.com)

Peter J. Pitts (Peter.Pitts@YourEncore.com)

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EXPERIENCE MATTERS

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## BACKGROUND

With the upcoming PDUFA renewal, 21<sup>st</sup> Century Cures uncertainty, and a leadership transition at FDA, it is a dynamic and uncertain time in the biopharma industry. The outcomes of these key policy debates, along with others, will impact how industry pursues drug development and works with patients and regulators to improve public health.

To advance the conversation and propose practical ways forward, YourEncore assembled a panel of regulatory experts, including former industry and FDA leaders, to share their best thinking on pressing regulatory policy issues in the biopharma industry.

## PANELISTS



**TIM FRANSON, M.D.**

[Tim.Franson@YourEncore.com](mailto:Tim.Franson@YourEncore.com)

Tim Franson, M.D., is the Chief Medical Officer for YourEncore, Board Member for the Critical Path Institute, and current President of the USP Convention. Dr. Franson was also a key contributor to PDUFA V, particularly as it relates to rare disease incentives, and co-authored the first-ever patient advocacy-initiated guidance for a rare disease submitted to the FDA in 2014.



**JOE LAMENDOLA, PH.D.**

[Joe.Lamendola@YourEncore.com](mailto:Joe.Lamendola@YourEncore.com)

Joe Lamendola, Ph.D., is the former VP of U.S. Regulatory Sciences for Bristol-Myers Squibb and is responsible for over 20 global approvals across 10+ therapeutic areas. Over a 25+ year career, Joe also led the Regulatory Policy and Intelligence Organization for Bristol-Myers Squibb, which was responsible for assessing and influencing regulatory policies, including PDUFA V and multiple therapeutic guidances.



**PETER J. PITTS**

[Peter.Pitts@YourEncore.com](mailto:Peter.Pitts@YourEncore.com)

Peter J. Pitts is a former FDA Associate Commissioner and key influencer of PDUFA V and its renewal. Peter is an authority on global regulatory issues, founded drugwonks.com, a blog which receives over 100,000 web hits a month, and was named one of the 300 “most powerful people in American healthcare” by Modern Healthcare magazine.

## PANEL INTRODUCTION

TIM FRANSON:

I'm thrilled to introduce my colleagues who have been longtime friends as well. Peter Pitts is an Executive Partner with YourEncore and Chief Regulatory Officer for Adherent Health Strategies. He is the President and Co-Founder of the Center for Medicine in the Public Interest, and former Associate Commissioner of the Food and Drug Administration under Commissioner Mark McClellan. Joe Lamendola is also an Executive Partner at YourEncore. Joe has a wealth of experience in interacting with the FDA from his roles formerly not only at Bristol-Myers Squibb as Vice President for U.S. Regulatory Affairs, but also previously at Schering-Plough. Joe and I between us have had quite a few battle scars as a result of our exchanges with FDA colleagues.

Let's talk about topics of shared interest.

The objectives of this session are to be both practical and interactive. We want to talk about what we have observed, but we also want to hear about the things that concern you. What is causing you

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*What is causing you to pull out your hair? How do we help anticipate all the things that will impact the pharmaceutical industry both near and long-term?*

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to pull out your hair? How do we help

anticipate all the things that will impact the pharmaceutical industry both near and long-term? What should companies be doing today to both anticipate and defend against threats to their quality, speed and value propositions?

We would like to begin talking about one of our favorite topics, PDUFA, both PDUFA V and the FDA's report card (good, bad, indifferent, what has it meant for your respective enterprises) and then PDUFA VI, what should be next. And then we'll roll into a discussion of something many of you may be acquainted with or are following - 21<sup>st</sup> Century Cures legislation now being considered primarily by the House Energy and Commerce Commission, which some have called PDUFA Jr. I would love to also give attention to the people topics, specifically the changes in leadership at FDA. And some of the other evolving issues; withdrawn guidances, biosimilars, and what's going to happen with new regulatory pathways? Will there be conditional approvals or other similar adaptations? A lot of exciting things to discuss. We're not going to let you get somnolent because I think there are a lot of stimulating topics for us to touch on, and perhaps the three of us are unusual, unique, but we get excited talking about regulatory things. It reminds me of the boundaries around the Indianapolis 500 Speedway. The regulatory rules are the hard barriers, but you can drive awfully fast inside that boundary if

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you have a very good appreciation of how to navigate, and that's what we would like to share in terms of our perspectives. We want to talk about things like PDUFA because policy shapes practice. There is really no way to separate those things, and also the important admonition: if we don't like the rules, let's change them. And the way to change them is through proper

legislation for all drugs, all products, and in the best interest of patients. So let's dive right in. This is a

RANT and I know that a RANT is an impassioned plea or soliloquy. Our RANT is Relevant Assessments and New Trends. Peter let me start with you. So PDUFA V, how do we scorecard it? It was supposed to help us be transparent and predictable. Has it been exactly the opposite or where are we?

## PONDERING PDUFA: GRADING V AND CONSIDERATIONS FOR VI

### PETER PITTS:

That which gets measured gets done. Something that bothered me a lot about PDUFA V was that when you asked people in industry, what does success look like to you (because you want to design a program that delivers things that you want), almost unanimously people in the industry said to me, “success means getting it [the PDUFA negotiation] done early and having it done cleanly.” And, you know, I’m as neat as the next guy and I like getting things done early as well. But it just punted on an amazing opportunity. If success is fast and clean, you miss the rare chance to negotiate hard, to hold the agency’s feet to the fire. And as far as what the report card is going to look like, it’s easy to get high marks when you are taking Physics for Poets. There are a lot of things in PDUFA V that were easy for the agency to succeed in: have a series of meetings, write a couple of guidances, very few date-certain, very few requirements to do hard finished work. And I think as we move towards PDUFA VI, people will look hard at what PDUFA V delivered, which was in many respects a lot of meetings. Today, people are saying, “now that we’ve had the meetings, now that we’ve gathered, we want action, we want movement forward, we want greater predictability in new, more complicated areas.” It’s going to be interesting to see if industry is really willing to step forward and hold the FDA’s feet to the fire, not necessarily hold them hostage but be hard negotiators rather than kind of roll-over puppy dogs.

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*If success is “fast and clean”, we’re missing the rare chance to negotiate hard, to hold the agency’s feet to the fire.*

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TIM FRANSON: Sounds good. So, Joe, walk that dog a little further.

### JOE LAMENDOLA:

From the industry side, I will say that I always thought that success would be -- no surprises. I don’t know about any of you guys who have to work with the agency and have to be responsible to your management for drug approvals, but the one thing that really, really, really drove me crazy was surprises or not getting good transparent information, especially leading up to an NDA review and discussions and Advisory Committee prep. PDUFA V was supposed to address a lot of that, right? We were going to have a lot of meetings. And I found, just as with all human beings, it’s very dependent on the Division and on the people that you’re interacting with. With some guys I had the sense that I walked in (and they had auditors in the room because that was part of the deal) and I thought that they were just checking a box because they were required to have the meeting and I really wasn’t getting a lot of information. But then there were other Division Directors and their review colleagues who were just fantastic. So it really is something that still has to evolve. You’re always going to run into the human element because that’s just the nature of the game. So, scorecard. We gave up two months in the review process because it was two months for the

thing to get filed before they would start the review clock, at least for new entities. The question then is: Did we gain anything on the approval side for that? I'm not so sure. But the fact is that I don't know how much it really made a difference. In some Review Divisions, I think the transparency is obvious and in others not so much. I think that's an inconsistency that I would like to try and find a way to address in PDUFA VI.

## PETER PITTS:

Let me pick up on that. I think there are two other things, three other things actually, that the FDA will get high marks for but actually shows no iterative learning. One is Patient-Focused Drug Development; a fabulous idea to really talk to patient groups in more serious and life-threatening disease situations. To let them tell the agency how they view risk and benefit versus Division or sponsor. There were a lot of meetings and they were very good. They were respectfully contentious. There was creative tension. So the FDA gets an "A", they held the meetings. Now, in PDUFA VI, what is going to be the requirement, what is going to happen next? There's been exactly one draft guidance generated out of the Duchenne folks. How is the FDA going to work with all of the groups that it met with to help them help the agency? I think the next step is helping these organizations draft guidances. What's the mandated requirement? How quickly is it going to happen? Because again, if you don't measure concrete results, it's just going to kind of drag on and on. The road to Hell is paved with good intentions. The second thing that was hot for a while, by which I mean 15 minutes, that's been ignored lately is the whole issue of the agency really moving forward with a benefit/risk assessment grid of some kind. Not necessarily a grid but a benefit/risk assessment tool for industry. And again, I think John Jenkins made it clear this doesn't mean the agency can't be creative and change its mind and do what it thinks is right, but a tool to explain to sponsor, industry, and patients why certain decisions were reached and how. That's kind of fallen off of the cliff. Will they get an "A"? Did they technically deliver what was supposed to be delivered? Yes, they're really good at being responsive to what's required. But being responsive is one thing. Actually moving things forward is something else.

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I think the third thing is this is all happening in a context – I know we're going to talk about the Acting Commissioner situation. PDUFA VI negotiations are going to probably take place with an Acting Commissioner. How is that going to impact the negotiations? It's going to empower Janet Woodcock to move forward with her agenda, which I think is great. I think when Janet and John Jenkins and Bob Temple and all the senior folks inside CDER say things, they mean it. But I think to Joe's point, when it trickles down to Division, you're not necessarily seeing what's being said by the big guys at the table.

## TIM FRANSON:

So what I've heard are some very interesting things from both of you. And if you boil it down, in PDUFA V, in order to get the negotiations done fast, the industry conceded, what, about a 9% increase to make it \$4.5 billion over five years that industry pays to FDA. And in return, FDA got to go two months slower on reviews. And while there was some more predictability, perhaps the feedback was not as frank or helpful or as instructive as it could have been. So was that a good deal? And is next time going to be much more rigorous in terms of negotiations on both sides?

## JOE LAMENDOLA:

I couldn't agree more. I don't know if it was a good deal other than it put us on a path toward increased communication. Now, whether it was effective with every Division or whether it's going to be effective with every Division, that's a different issue. But one thing I'd like to say, as I mentioned earlier, there were auditors in the room. There was supposed to be an audit report that was going to be written at the conclusion, which I assume the agency is going to utilize to help develop their stance for PDUFA VI. It would be nice if industry could see that report. I don't know what the likelihood is that that's going to be made public. Maybe it is; maybe it isn't. But I would love to know the nature of that report. I believe that the mandate for both FDA and industry is to provide for public health: new therapies, new treatments and new approvals. So there's a benefit I think from us knowing how that audit report worked, how we could do a better job on the industry side of the table, how they could do a better job on the review side of the table, and maybe partner in getting some of these things through in a better fashion.

## PETER PITTS:

Communication is a key. Obviously, PDUFA V spoke to more and more regular communications both post but also in the early stages of the process, and that happened. So again, another "A" or gold star on the top of the paper. But what hasn't changed is who is doing the communicating. Has there been more communications or more meetings at higher levels when there is scientific dissidence between sponsor and agency? I don't know whether you can write that into PDUFA, but I think philosophically it's a significant industry shift. I don't know how FDA would facilitate that because there are only so many senior folks, but I think it has to move forward.

## TIM FRANSON:

So when you think about that, there are some points of progress across all Review Divisions. You have mid-cycle and late-cycle review sessions, so you have a better sense of understanding where the reviews are. Are you likely to get a complete response letter, what are some of the issues? Is that enough to build on? Or as we move ahead, what other more rigorous or radical changes may be needed?

## PETER PITTS:

Well, I think to Joe's point, what is the FDA's mission? When I was there, the mission was to protect and advance the public health. Today the advance part has become the silent partner. It's an extraordinarily complex, slow, bureaucratic process. How do you empower line-level staff to make tough decisions? We have various new pathways to approval. We're looking at more complicated molecules and clinical trial design. How do you empower line staff to take appropriate risks?

## JOE LAMENDOLA:

Risk aversion is key. I've talked to some ex-FDA people who are, believe it or not, still friends of mine. (I don't know how that happened!) But we've talked about this very thing. And the fact is that nobody wants to get dragged up on the Hill if they make a mistake. So what you see is that some companies have moved to a focused strategy on developing drugs for unmet medical need or orphan drugs, and the reason is not that the agency is willing to take more risk there, but that there's a cooperation I think in the spirit of developing those types of drugs as opposed to a primary care setting where you're going to be the fourth

diabetes drug or the fifth cephalosporin or whatever it is. It's a little bit different. And when you have those conversations with them, I can understand why they're going to be much more conservative. I actually was told one time, "I'm not taking a risk here because what's the public health need for me to do so." And so I get that. I get that. But if I'm developing something in an unmet medical need space, that's a different situation. And so then the partnership, the communication and transparency are at a different level.

#### PETER PITTS:

What's interesting, something that is not, strictly speaking, a PDUFA issue -- is how is the FDA dealing with the regulation of opioids. One of Commissioner Hamburg's big victories was really putting her foot down and saying, "Listen, all therapies have risks, you know, a broader pharmacopeia within any therapeutic categories is important. We have to enhance education." So where in PDUFA is the FDA's mandate to do better physician, pharmacist, patient, and caregiver education in a lot of these areas, especially in areas where the medications are of higher risk?

#### TIM FRANSON:

Let's talk about some of the potential incentives that have redefined the benefit/risk elements, and then we can go to some of the more fundamental benefit/risk considerations because clearly the US has not progressed as far as Europe has, and we can debate on whether that's the case. But in the last PDUFA renewal in 2012 with the FDA Safety and Innovation Act, and this was just alluded to by you, Joe, we talked about rare diseases and, Peter, you mentioned Duchenne. Incentives were built in to offer companies the opportunity to have that Priority Review wildcard. In addition to getting a Priority Review for an orphan disease, you would get something to use on your latest what would be otherwise Nonpriority Review; very valuable.

PETER PITTS: Tradable.

#### TIM FRANSON:

Tradable. And in the last two years a third of the new approvals have been for rare disorders. So you get what you incent. Are we headed in the right direction there? Is there the right balance in terms of unmet needs?

#### JOE LAMENDOLA:

You do get what you incent. And I know there was a big debate, and we'll get into this in a second on 21st Century Cures, as to whether exclusivities should be built in for certain things. And so finally the orphan drug stuff came back in. And there's still a lot of debate around it. I think it's clear, and we saw this a decade ago with pediatrics, that when you provide those types of exclusivity incentives to industry, given the amount of money that's being spent on developing these therapies, it has a lot of meaning. So I do believe it's something that should be in PDUFA VI negotiations.

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## PETER PITTS:

And there's another player. You get what you incent, and clearly the incentives, on purpose, were to move forward on orphan and serious and life-threatening diseases, but you also get incented by what's driven by the marketplace -- by what's getting reimbursed. And innovative treatments for serious and life-threatening diseases are more likely to be reimbursed at a better price. I think what's more interesting is not just from a risk/benefit perspective, because all drug development is hard, but what happens on the postmarketing surveillance side, with pharmacovigilance? How is the FDA going to be empowered via PDUFA VI to bring drugs to market quicker with a more serious and structured postmarket surveillance plan in place? The Europeans are again ahead of us on this. The PRAC system is superior to anything we have in place. It's not just getting a drug through the review cycle; it's what happens once the medicine is on the market.

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*How is the FDA going to be empowered via PDUFA VI to bring drugs to market quicker with a more serious and structured postmarket surveillance plan in place?*

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## TIM FRANSON:

And we may want to come back to that because one of the interesting things about benefit/risk, which was an important part at least in concept of FDASIA, was to get back that balance; not to be talking about safety in isolation, but post approval the only information that most sponsors collect is safety. And there's no new benefit information so the benefit/risk balance is going to obviously tip to the negative for any given product because that's all the information you're looking for. Benefit relatively erodes. How do we get beyond that?

## JOE LAMENDOLA:

Yes and no. There's an opportunity for efficacy. There's life cycle management of a program, where, with appropriate design, sponsor and agency can keep the benefit/risk profile in balance. So I think that yes, you're right, if you're just looking at the adverse event profiles and you're doing nothing but the safety evaluation over the life of the product you could then start to see things -- and get surprised. Look what just happened with the SGLT2s and diabetes. All of the sudden now, we're seeing ketoacidosis in these products, not a lot of cases but enough to get the attention across the class that something is going on. So I hear you.

## PETER PITTS:

Rhetoric is important because words count and when we're talking about postmarketing surveillance, we're not talking about efficacy; we're talking about effectiveness. What's happening to a product outside of the rarified world of a clinical trial? What's actually going on? When you look at this conversation on the payer side, you're looking at a value-based insurance design model. You're looking at outcomes. Companies are used to reporting safety issues, safety meaning risk, adverse events, and substandard pharmaceutical events. The question I have in my mind is, will the FDA start being interested in outcomes data, real world data? And what

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are they going to do with it? Is it going to be used towards label changes? Because clearly from the generic side, the FDA wants to look at outcomes and be able to change labels for small molecule generics. What is the agency going to do with effectiveness data from the real world? Is it going to inch the FDA into regulating the practice of medicine? These are tough questions and how do you address it in PDUFA?

## TIM FRANSON:

Vis-a-vis PDUFA, there have been some good developments and there have been some other areas where perhaps too many concessions were made by both sides. What about PDUFA VI? Peter, I'm going to steal something that you wrote which essentially said: For PDUFA negotiations, if you're not at the table you're on the menu. How do all companies assure that they have the kind of representation necessary so that their interests in patients and in productivity are protected?

## PETER PITTS:

That's a tough question because you can't hold PDUFA negotiations at Fenway Park. You can only deal with a relatively small circle of people; otherwise it's not workable. PDUFA V was the first time where patients actually had a seat at the table. So rather than having it be PhRMA, BIO, and FDA, you now have a new guest at the PDUFA party – patients. But what

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*How do you empower companies who aren't major players by volume to be a valuable part of the regulatory policy conversation? That's a tough question.*

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about the smaller biotech companies that aren't dealing in tens of billions of dollars of issues, who have one product or no products? How do you empower companies who aren't major players by volume to be a valuable part of the regulatory policy conversation? That's a tough question.

## TIM FRANSON:

Interesting. So let's think a little bit more about what's on the table as well as who is at the table. We've talked a little bit about 21st Century Cures. Is that going to be PDUFA junior? What kind of funding is likely

to occur? And I'm struck by the reminiscence of what happened on unfunded mandates at the start of PDUFA IV, when the FDA essentially said, "You know, we've got to do all these guidances, we didn't get staff to do it so we're suspending the PDUFA review time clocks. So industry, you can go ahead and pay your X millions of dollars for your NDA reviews but you're not guaranteed it will be done on time." Is it going to happen again?

### JOE LAMENDOLA:

When 21<sup>st</sup> Century was being talked about, well, it's still being talked about, FDA already signaled that there would be a resource problem if they had to take this on and implement everything that was going to be implemented. Now, you can take a look and say, well, 21st Century may or may not get passed, but I will tell you that if it doesn't, it's a foreshadowing of some of the things that are going to be looked at to go into the PDUFA VI negotiation; and if so, the resource issues and constraints at the agency will still be the same. Then the question is: How do you fund that? So it'll be PDUFA fees and all that again, and whether that's enough I don't know. I do think that's going to start the ball rolling in the PDUFA negotiations. And of course there are a lot of things where industry could take a position. For example, and we can get into this, too, some people call it off-label promotion; I like to call it off-label communication because it is different, and it puts a burden on both the FDA and industry.

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### PETER PITTS:

The issue of what data can you use in approvals, which is within the current draft of 21st Century Cures, is fascinating and a potential game-changer -- but should that also be a PDUFA VI conversation? And the issue of off-label communications, off-label education, whatever you want to call it, it's time that we talk about it because I would rather have that dealt with in PDUFA than in the courts. A potential legal decision is a sledgehammer solution that will do nothing other than empower people with ill intentions. The issue of communications isn't only about who's presenting it and in what context, it's also about the intent. And when you begin to try to litigate intent, it's a blunt instrument.

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JOE LAMENDOLA: I couldn't agree more.

### TIM FRANSON:

If we take a historical look at PDUFA and it's less than 30 years that PDUFA has been around, 1992.

PETER PITTS: It's like 30 dog years, isn't it?

## TIM FRANSON:

30 dog years. Well, you've got a leg up on us, Peter. I'm absolutely convinced if we look at the historical aspects, the first PDUFA was, I believe, \$100,000 per NDA submission and it was a fairly nominal \$100 million for industry overall as a pay. And if you look pre versus post PDUFA I, average review cycle times went from about three years for an NDA to about 18 months. Then PDUFA II had further advances. You got down close to 12 to 14 months depending on priority versus standard, which got subsequently added in. That's pretty good news. And industry and FDA all agreed this was the right thing; that safety and efficacy considerations were not being compromised, things were moving faster. But now the last couple of PDUFAs, more end loading on safety issues, more post approval, and review times for new drug applications have not correspondingly improved. So what's in store this next go around, and does industry have any hope of gaining any additional productivity?

## PETER PITTS:

You make a good point. If you think about PDUFA, you almost want to go back to First Principles. Why user fees? Why was the industry willing to pay for something that it previously got for free? And the answer is that industry wanted predictability, whether it's six months, a year, 18 months, two years, getting a PDUFA date is crucial for industry for a variety of reasons. If you take the concept of predictability one step further and say: We want predictability, not just an action date but predictability on a whole variety of issues -- off-label communications, expedited pathways, postmarketing surveillance, predictability over a broad spectrum of regulatory activities. That will be a more creative and fruitful conversation.

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## TIM FRANSON:

This has fundamentally changed the activities of every company that submits an NDA or BLA pre versus post PDUFA. I mean we weren't even talking about electronic common technical documents. Even in this last PDUFA, any company's infrastructure for how you prepare for mid cycle and late cycle meetings, nobody was fully prepared for that. So how can we all look forward to helping companies prepare for that next PDUFA surprise, where's it going to be and how do companies best position themselves to skate ahead of the puck.

## PETER PITTS:

You have to bring more senior minds to the table, more senior minds from companies currently at the table as well as companies who are on the periphery. If industry, broadly speaking, is willing to say, "We're going to rely on PhRMA and BIO to represent us," and I understand that there's a fluidity of need to do that, how do you expand the conversation? It'll be curious to see who attends and participates at the July kickoff meeting for PDUFA VI. I'd like to see more patient groups there. I'd like to see more representation of

smaller biotech companies there to learn about what's going on. You know, it's a secret club in many respects.

**JOE LAMENDOLA:**

I think that's right. You mentioned patient groups, and the FDA has gone to great lengths at the Advisory Committee meetings to have representation of consumer health and public advocacy groups. Oftentimes in a public hearing, there are specific patient groups that come to the microphone, and rightly so, and I would encourage them to come to the PDUFA meetings.

**PETER PITTS:**

Although it's important to be aware and wary of Genervon-like discussions. You don't want the patient voice to be gamed because that just belittles the people who are there for real.

**JOE LAMENDOLA:** Right.

**TIM FRANSON:**

That raises some interesting points as we go into PDUFA, and there are going to be a lot of patient voices. That's very important, and we ought to be able to much better capture patients' benefit expectations and risk tolerance than just by looking at very simple measures such as survival; obviously very important, but there are 7,000 rare disease organizations according to the National Organization for Rare Disorders. If all of them are speaking and all need guidances, which may be appropriate from any given perspective, then that leads to development of therapies across \$300,000 per patient. There's the old saying: When you pick up one end of a stick, by nature you pick up the other. Is this going to be unsustainable a decade from now?

**PETER PITTS:**

You can't talk about price without talking about value, just like you can't talk about risk minus benefit. So let's talk about Hepatitis C. The initial panic over "oh my gosh, these new Hep C drugs are going to bankrupt our healthcare system," consider the source. Payers, both private and government, deal in financial quarters and annual budget cycles. But when you start looking at the math over the course of a patient's lifetime, it saves money, it saves a lot of money. Certain products are right for some people, a sub-population. The practice of medicine can't be a blockbuster model with orphan products. We have to think hard about value.

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*You can't talk about price without talking about value, just like you can't talk about risk minus benefit. So let's talk about Hepatitis C.*

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**JOE LAMENDOLA:**

It forces industry to rethink the course of development programs. We used to shotgun everything. You shotgun the dose development of a program and you shotgun the efficacy, and it worked in maybe 70% of the people, in 30% we weren't sure why. But now the concept of personalized medicine, especially in the

areas such as Hepatitis and most orphan diseases where you really have to either assess biomarkers or try to find patients where this is going to be an effective therapy, I think becomes even more important given the pricing and reimbursement structures.

### PETER PITTS:

Right. And what is the role of companion diagnostics. Can they be required? Where is the science? How do you pay for them?

### TIM FRANSON:

Interestingly, when you follow up on some of that, you imply a lot of the changes that have gone on in industry. So 20 years ago we were talking about small molecules, acute care disorders and a fairly simple manufacturing infrastructure. Now we talk about a number of the new approvals being biologics. So you have all sorts of distribution issues, cold chain, etc. You have usually more complex chronic disease. And interchangeability. The complexities are totally different and yet we're using the same kind of systems for reviews and approvals.

### JOE LAMENDOLA:

We used to have therapy teams at both Schering and at Bristol-Myers Squibb. Inevitably some clinical guy who was a high-riser in the organization led them, but he was still somewhat green. They would come to me to chitchat. I would tell every one of them, "50% of the NDA is a CMC section and don't forget it," because they were clinical guys and they didn't think that way. And it will kill you if you don't pay attention to it. I think that's even true when they start talking about advances in PDUFA about what kinds of things can you do in the manufacturing setting that will help. Because now what's happening is that the manufacturing guys can't keep up. We're going to advance things in the area of unmet medical need, in oncology especially, where a drug will be approved in three months and the manufacturing guys are going to gasp, "Oh my gosh!"

### PETER PITTS:

Should there be a discussion within PDUFA VI of the FDA actually putting on paper new, more segmented rules for bioequivalence? It's been almost three years since Wellbutrin, and the FDA is still dealing with bioequivalence on an ad hoc basis for seizure meds, antipsychotics, long-acting release medicines and ADHD products. Industry has said, "enough!" Mallinckrodt is suing the FDA for telling them to take their product off the market because of bioequivalence issues. Now, I don't know whether that's right or wrong, but I do know there are no new rules on paper. If I were a judge looking at this case and I said, "You know what, FDA? I generally want to give you Chevron deference on the science issues, but where's the guidance?" So if I were the FDA, I'd rather drive the process than litigate the process, and maybe PDUFA is a way to move the conversation ahead in a collegial rather than in a confrontational manner.

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*Should there be a discussion within PDUFA VI of the FDA actually putting on paper new, more segmented rules for bioequivalence?*

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**TIM FRANSON:**

Absolutely. So there are a lot of interesting evolving issues. And to that point, quite apart from PDUFA, we saw I believe it was two weeks ago there were multiple draft guidances withdrawn. Have we ever seen that from FDA before? Was that just a strategic move to get them off the table? Or was that a trial balloon for something more?

**PETER PITTS:**

Well, I think it was a very tactical response to Senator Alexander's dictum to finalize old draft guidances. So rather than finalize, FDA just pulled them.

**JOE LAMENDOLA:** And start the clock again if you have to.

**PETER PITTS:** It's a cheap shot.

**TIM FRANSON:**

It's a cheap shot, but a lot of companies depend on draft guidances as at least a navigational tool in interacting with FDA. So you undercut that and what are we left with?

**JOE LAMENDOLA:**

Well, you're left with the statutory meetings and insist on having the discussion with the FDA early. I used to deal with guys who didn't see the need for a pre-IND meeting. Now, the FDA doesn't always see a need for pre-IND meeting. If I'm developing another Type II diabetes drug, I suppose that's the case. But I used to tell my guys, "We should take advantage of every single communication opportunity, even if we don't have a lot of questions to ask, because there's something to be gained just by the interaction."

**TIM FRANSON:** And to be able to understand what FDA may be thinking on particular issues.

**JOE LAMENDOLA:** Correct.

**TIM FRANSON:** Asking the right questions at any meeting, whether it's pre-IND or pre-NDA is key.

**JOE LAMENDOLA:**

And listening to what they really are saying because your job is going to be to interpret for your organization what they're really saying.

**PETER PITTS:**

And have a designated critical listener. It's so easy, as you know, to walk out of those meetings and report back what your people want to hear.

**JOE LAMENDOLA:** That happens all the time. That's absolutely right.

TIM FRANSON:

Because you didn't hear anything bad, but if you didn't ask the right questions you won't hear anything. So that's always a challenge. And you hate to be the bearer of bad news or as some of us were called in our regulatory news and industry, the sales prevention program.

## REMS: ITS UPS AND DOWNS

JOE LAMENDOLA:

And you know what else used to drive me crazy? I know you haven't asked yet, but I'll bring it up anyway.

TIM FRANSON: Go for it.

JOE LAMENDOLA:

REMS. What used to drive me crazy was not the FDA, it was industry. My guys, especially commercial, were so averse, where I always thought that could be an actual differentiator tool. And not only that, I thought it would facilitate approval and certainly facilitate your discussions at an Advisory Committee. I would much rather be in the position where I was developing it and proposing it than have it imposed upon me.

PETER PITTS: Late in the game.

JOE LAMENDOLA: I could never convince a lot of people of that.

PETER PITTS:

Obviously, our world is a world of acronyms. My favorite REMS acronym is ETASU, elements to assure safe use. Now, the concept of safe use oftentimes gets overlooked. The theory is that the way that you make a drug safer isn't necessarily to design a safer molecule, but to have it used as directed, safe use. So I totally agree, Joe, you're going the right way. A company makes a step forward and says, "All drugs have risks; our drug may have a higher risk profile, therefore we, of our own volition, want to develop safe use tools to allow the FDA to allow an Advisory Committee to help doctors and patients understand that there are things at play here other than popping it in your mouth or getting an infusion and walking way, that education is required." And it's hard. It takes up time. And all patients and many doctors have this magic pill concept, where you take the pill and you're magically all better. It's just not that simple. And REMS is time consuming and doctors don't like them, but if you want these products on the market and you want them on the market faster, it's just the cost of doing business. And it's the right thing to do.

TIM FRANSON:

Interestingly, so with REMS, there are upsides and downsides. The argument on the upside is that without REMS a number of drugs may not have been approved because they didn't have an acceptable benefit/risk balance. You had to absolutely assure the safe use. On the flipside, when you have a drug with a REMS

and competing products without, I believe the American Pharmacists Association had a publication several years ago indicating physicians have a REMS flinch, if you will. If I have a choice, even though I think the REMS drug is better, maybe the hassle of going through an ETASU program certifying your ability to prescribe and so forth isn't worth the hassle. And is that good for patients?

**JOE LAMENDOLA:**

Typically though you would think, and at least in most of the instances where I was involved with these things, these were drugs that were true advances; not just a little bit, but true advances but had baggage, as a lot of compounds do. So this was a way for industry and FDA, and for the benefit of the patients, to get these drugs and get them on the market, and hopefully physicians would prescribe appropriately and not because there was an administrative burden but recognize the incremental benefit to their patients.

**PETER PITTS:**

I think you have to give physicians the benefit of the doubt, where they're not going to walk away from appropriate therapy because it's going to cause more paperwork for their office. They may complain about it, but I don't think that they're going to actually walk away from it.

**JOE LAMENDOLA:** Would you?

**TIM FRANSON:**

No, I wouldn't. And I don't think most physicians would. But there is a sense that there would be a flinch, a hesitation because of the hassle. Do I have time for it because I have to see 20 patients an hour?

**PETER PITTS:**

I think it may be more significant as you move beyond current best therapy to a new level of therapy that is different, equally or more effective minus a REMS. Then it may be a question of either/or let's go with the newer drug, and then it becomes a cost issue. So there are all these tradeoffs, as these new products with REMS all of the sudden don't become so new anymore.

**JOE LAMENDOLA:**

But those discussions are had in the conference rooms of industry because we knew whether a drug had a real true incremental benefit or if it was close. And if it's close, with all the extra safety stuff, it may never see the light of day anyway.

**PETER PITTS:**

Right, which makes the whole issue of off-label communication all the more important. If you have a monograph or a poster presentation or a peer reviewed article that speaks highly of your product it's important both commercially and therapeutically for a doctor to know this stuff.

TIM FRANSON:

It's a challenging situation. We don't know if REMS really works. Do we have the tools that say: We did all these very complicated things? And some of the critics would call REMS an acronym for really esoteric messy systems. What do they do? Do they actually impact the patients? And we don't have the right measures yet. FDA doesn't, industry doesn't. How do we begin to develop that kind of monitoring processes to say: Wow, it really did have an impact, it was right for patients, it was worth the investment.

PETER PITTS:

And from a PDUFA perspective, where are the validated methodologies for these programs?

JOE LAMENDOLA:

That would get you to the Sentinel discussion. It's been a couple of years now. One of the things I would talk to the FDA about in PDUFA VI is that the transparency of the Sentinel program to industry was nil. Now, I don't know if it's improved a lot over the last several months, but it used to be: We're picking it, we're designing the program, we're running it, and we'll get a look at the results and we'll let you know if there's a change coming to your label.

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TIM FRANSON:

It's a little scary, isn't it? And do companies have defensive processes where they can look at corresponding safety information from other sources to at least counterbalance what might be unusual trends in some health systems? Remember, if you're gathering data from health systems, a lot of them have restricted formularies, so are you sure you have representative information?

PETER PITTS:

Another thing relative to PDUFA is recognizing what was done and didn't work. Let me specifically call out early safety signal communications, where the theory was the agency was going to, on a quarterly basis, publish a list of products for which it had enough information to require further investigation. And all that resulted in were sensational media stories and patients who stopped taking their medicines. I don't think there was one label change or one product taken off the market from those reports. So it's clearly something that was mandated that actually had a completely contrary result as opposed to what it was supposed to do.

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**JOE LAMENDOLA:**

And to that point, because I think it does a disservice to patients, so going back to the SGLT2 story because it's fresh, I have yet to read anywhere in any press release where they've really dug in and said: Here's what we think is happening. They're saying: Here's what we see, there are probably going to be warnings coming out. So if you're a patient and you read that and you're on it...

**PETER PITTS:** Panic. Panic now.

**TIM FRANSON:**

So you're walking through the airport and the threat level is orange, what do I do? You sweat.

**JOE LAMENDOLA:** But if you put context around some of this, though ...

**PETER PITTS:**

There's a new Office of Pharmaceutical Quality at FDA. A Super Office. It speaks to the recognition that more attention has to be paid to quality/pharmacovigilance issues. Not sexy. Not cool. It's not a really Bully Pulpit thing like increasing anti-aging funding. Congress wants to give anti-aging \$4 billion dollars. Why don't you give the FDA a billion dollars for pharmacovigilance and see how things change. The FDA needs to step up and ask for things that will make a difference as opposed to more staff for swifter pathways to approval. That's important, too, but it has to be about more than just facilitating new medicines to market faster. It has to be what happens on the backend as well.

**TIM FRANSON:**

Yeah, these are fascinating times because patients have more input into things like labeling now, at least suggestions. They testify at Advisory Committees. Practitioners have similar concerns, not just about REMS but also about limitations for on-label versus off-label use, although off-label does not mean off the wall. And frequently off-label uses are accepted medical practice, which then leads one to say, "So if I follow the label, I'm committing malpractice." A little bit bi-polar but we don't have a balance there.

**JOE LAMENDOLA:**

First of all, off-label use is practicing medicine. Oncologists have been doing it for decades. But you'll hear that if you're going to start the practice of off-label communication, companies will not file supplements, they will not do the work necessary to gain the approvals. They will just go out with their sales force and start talking about this stuff with no controls whatsoever from the FDA. I don't know the answer, but it has to be discussed. It shouldn't be a hurdle that blocks it, but it's certainly something that has to be discussed.

## RIGHT TO TRY LEGISLATION

PETER PITTS:

Can I raise another contentious topic? Expanded access to experimental medicines and Right To Try legislation. For those of you who are following this absurd story, there is legislation out there pushed by the Goldwater Institute in Arizona, and more than a few states have adopted such legislation. People want to blame the FDA for keeping these therapies from patients. Meanwhile, FDA's approval for single patient INDs is something like 99%. If you want the FDA to work faster, that's PDUFA funding. It's a staffing issue. Crucially though, you can't give people experimental drugs and not collect data. And the NORD people, to their credit, are extremely focused on this point. They're for expanded access, but they recognize the absolute urgency of collecting data. And that's scary. It's scary for companies. Because when you're out there in a non-controlled situation, collecting data when you're close to final action, you know, it's spooky. But it's a conversation that needs to happen.

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TIM FRANSON:

Yeah, and what happens if you have somebody on multiple concurrent medicines who is granted Right to Try and they have a very serious adverse event? It is attributable to the drug, to the concurrent medicines? How do you manage that?

JOE LAMENDOLA:

Here's an example of where the FDA needs to get in front of this somehow and do it relatively quickly. There are how many states already with Right to Try?

PETER PITTS: One is too many.

JOE LAMENDOLA: One is too many because it wrestles control away from the agency completely.

PETER PITTS:

A couple of things. I don't believe any FDA person testified at any of the state hearings, one. Two, talk about false hope; none of these pieces of legislation require a company to do it. So it's just bull, quite frankly. It's grandstanding. Joe, your point is exactly right. The FDA either drives it or it drives them. But it is an opportunity to ask for money in PDUFA.

TIM FRANSON:

I'm conscious that we promised folks who are in attendance here and on the webinar to be able to ask questions. We're already an hour in and there's a lot to talk about. We didn't get to biosimilars yet.

PETER PITTS: That's all right, neither has the agency.

## FDA LEADERSHIP: DOES IT MATTER?

TIM FRANSON:

And the exciting question I'm sure everybody wants to know: What do Peter and Joe think about who the next FDA commissioner is going to be and when?

JOE LAMENDOLA: So you want me to answer that now?

TIM FRANSON: Yeah. Is it Bill Clinton? He could be in the White House with nothing else to do.

JOE LAMENDOLA:

I'm going to say this because I want Peter to get upset. I don't think it matters who the FDA commissioner is. Unless it's an extraordinarily strong personality with an extraordinarily strong agenda, I think it's a politically appointed position and the fact is that the work is done from Janet Woodcock on down and John Jenkins and that whatever the message is ...

PETER PITTS: For drugs.

JOE LAMENDOLA:

For drugs. And so the Commissioner is a face to the American public, but I don't know how much it really impacts the operation of the agency.

PETER PITTS:

So maybe PDUFA or maybe 21st Century Cures can change the FDA commissionerhip from a political appointment to a six-year term, like the FBI director. Take it out of the political cycle. I've been advocating for that for a while. I think maybe it's an opportunity to have that conversation. The FDA commissioner does count if the commissioner has an agenda. If the commissioner chooses to just be the public face of the agency, I think it's a wasted opportunity. So what's the difference between having a confirmed commissioner and having an acting commissioner? How does it impact the way the agency operates on a day-to-day

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level? The answer is: It doesn't really impact it at all; the agency continues to run. Interesting fact, the FDA has 16,000 employees. Within that whole 16,000, there are about ten Schedule Cs, political appointments. That means that the director and every employee, every single one, top to bottom of every center without exception is a career public servant. The value of having a confirmed commissioner is having a confirmed commissioner who is engaged, who does not have a strong learning curve, a guy like Rob Califf, for example, who can actually say, "This is my mission." And a successful commissioner sells his mission to the senior staff and then it becomes organic. You can't dictate the way an agency runs because you get, "Hey, you know what? I was here before you came; I'm going to be here after you leave." You can't come in and be confrontational. You have to have a mission developed in collaboration with senior staff that advances whatever your agenda is.

TIM FRANSON:

Pretty interesting. I realize there may be folks who have questions either about PDUFA or would like to pitch something out.

## BREAKTHROUGH THERAPY: I SEE THE CARROT, BUT NO STICK

AUDIENCE QUESTION:

Coming back to PDUFA V and the implementation of Breakthrough Therapy designation, that's gotten a lot of negative press lately. The FDA seems to be tightening the noose.

PETER PITTS: Some negative press, but mostly positive press.

AUDIENCE QUESTION:

I think there's a lot of pressure that – in the first year, too many got breakthrough, the second year it got tightened down, it seems to be tightened down now. There's talk about withdrawing Breakthrough Therapy designation from products and things. Where do you think Breakthrough Therapy is going to go with PDUFA VI?

PETER PITTS:

The issue with Breakthrough Therapy or any expedited pathway designation is making sure it's given to products that actually deserve it. I've heard from inside the agency that one of the areas of great angst – angst is the wrong word – frustration, is that sponsors are coming in and requesting it because there's no penalty for asking. And all it does is burn

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*I've heard from inside the agency that one of the areas of frustration, is that sponsors are coming in and requesting Breakthrough Therapy designation, because there's no penalty for asking.*

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clock. So maybe a better question from a PDUFA perspective is: There's the carrot, where's the stick? You know, if you're going to ask for a designation and then not get it, should something happen?

#### JOE LAMENDOLA:

I've thought about this because I agree, it's easy for industry, and there's pressure within the management wings of industry to go in and try to get Breakthrough Therapy, especially maybe even more for a midsized to smaller company than for the big guys, because now it becomes an investment tool. So I think what you do is that maybe if I'm FDA, maybe I try to arrange some mechanism by which there's an early discussion with the sponsor with appropriate data that allows them in a room to say, "Don't waste your time," or "This really has a shot." Because otherwise you're just tossing things over the fence to see what sticks, and you're right, there's no consequence to that other than you either get it or you don't, but it does burn a lot of FDA review resources to make a determination.

#### TIM FRANSON:

So just one other thought in that regard for Breakthrough Therapy, the designation obviously has a time fuse. And one of the reasons that at least one of those Breakthroughs was withdrawn is because another drug was approved prior to it, so it no longer was a Breakthrough. Therefore, you're not a me-too, but you're just a me-too late. And the second element is that as a result of Breakthrough, what do you get really beyond Fast Track? You get attention of FDA senior management in the process. So just remembering what incremental gain there is for the company is key. But I've been involved in I think four of these filings in the last two or two and a half years. Very interesting to see the FDA aggregate feedback.

#### JOE LAMENDOLA:

And you do get the FDA senior management engagement; however, I will tell you, and I have some colleagues who I think would concur, from the industry perspective I don't know that I saw a whole lot of difference if I had Fast Track or Breakthrough. And I mean Janet will tell you what the differences are on paper, I understand the definitional differences, but I don't know how much really means.

#### PETER PITTS:

The key point is it cuts through red tape and it gets attention of higher-level people at the agency to discuss tougher scientific issues. And I think that is oftentimes underplayed. Some people are saying we're allowing too many partially tested products on the market. And I think that's a dangerous pathway to go down because if you look at all the drugs the FDA has approved in its entire hundred years plus of history, all of them have risks.

#### AUDIENCE QUESTION:

And I wonder with a stick, if we're talking about a user fee. Put a little bit of extra thinking into: Do we file for Breakthrough Therapy designation? You know, \$100,000 or something like that, not insurmountable but enough that a company is going to think twice about it.

**JOE LAMENDOLA:**

I like your idea about maybe a user fee attached to it, that's interesting. But all I'm suggesting is that oftentimes you can go in early on with a Review Division and give them the landscape and they'll know enough to be able to offer some non-binding advice. I'm not saying that they're going to make the decision then, maybe it just cuts down on the flow, I don't know. I'm sure there'll be other ideas as well, but you're right, something should be done.

**TIM FRANSON:**

When you look at how this has played out in terms of Breakthrough, I think the Hep C examples are absolutely fascinating because if something is truly a Breakthrough, it will displace what was already there. The new drugs essentially lead to cure and, as a result, I believe both Telaprevir and Boceprevir have been withdrawn from the market. That's Breakthrough.

**PETER PITTS:** Twice the level of cure, higher adherence, fewer side effects.

**TIM FRANSON:** That's a Breakthrough.

**PETER PITTS:** The thing is you rarely get these discontinuous types of innovation.

**JOE LAMENDOLA:**

A thousand years ago, I was involved in the approvals of Intron and Ribavirin, and that combination was standard of care forever. Then when these things came, it was just amazing how much of a difference it made in patients' lives. So that is really a true Breakthrough?

## **PATIENT VOICE: DOES IT IMPACT FDA DECISIONS?**

**AUDIENCE QUESTION:**

I'd like to actually hear your perspective on the process that occurred this week by an FDA Advisory Panel for an important company here in Boston for the treatment of cystic fibrosis. How does the patient advocacy piece play into that kind of decision-making?

**TIM FRANSON:**

This has a lot of fascinating elements. I'm glad you asked that because Peter actually used to be responsible when he was at FDA for Advisory Committee oversight so he can speak to the process. I know Joe has very strong feelings about this as well.

**PETER PITTS:**

Let me specifically address your question about what impact does patient testimony or open public comment have on a vote, or should have on a vote. The first question is: Do you feel the right people are

on the panel? The second question is: Why does the FDA call an Advisory Committee meeting, because not every product has an Advisory Committee? The FDA calls an Advisory Committee if there are outstanding scientific questions. You call an Advisory Committee if it's political and the agency wants some third-party cover. You call an advisory committee if there is some really interesting scientific question hanging out there. I don't think that open public comment, whether it's from legislators or patients, especially parents of patients, changes any votes. I think the votes are pretty much, or at least in theory should be and in my experience are, driven by what the data say. Now, you have to understand that when the FDA presents the briefing material, it kind of telegraphs how they want the committee to vote. And the FDA generally gets the vote it wants.

Let me just mention something else – when I was at the FDA, we began to ask speakers during the open public comment period to volunteer if they were paid to attend the meeting. And people have been kind of squishy there. So I think there's a difference between people who are there by dint of a relationship with a sponsor versus people who are there to speak their hearts, and the two are not necessarily mutually exclusive. I think the value is to have it read into the record, so when the FDA looks at the minutes of the minute, which they do, they can glean important parts from that. Now the important thing that open public comment as it progresses, just like with Patient-Focused Drug Development, is anecdotes don't help. Anecdotes aren't science. How can we use patient organizations, patient testimony to drive data? That's an interesting 21<sup>st</sup> century twist.

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*When it comes to Patient-Focused Drug Development, anecdotes don't help. Anecdotes aren't science. How can we use patient organizations, patient testimony to drive data? That's an interesting 21st century twist.*

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**JOE LAMENDOLA:**

I think that it has to do a lot with the indication. Last year I was involved in an AdComm for a drug to treat a disease called lipodystrophy. I talked to the chairman afterward about the very question, and he said whenever they have those types of hearings it's heartbreaking, but he said that it didn't necessarily influence the vote, but he believed in conversations with the FDA that it might have an influence on how they label because they take it into account.

**PETER PITTS:** Good point.

## JOE LAMENDOLA:

Advisory Committee meetings are high stakes propositions for sponsors. The preparation that goes into them is just amazing. I hate the fact that we vote. I almost think that if it's an Advisory Committee meeting and the purpose is to gain advice that that should be adequate and then the agency can do with it as they will, as opposed to them saying, "Well, we went against the Advisory," or "We went for the Advisory." Sometimes I think the vote is for the benefit of financial analysts, *The New York Times* and *The Wall Street Journal*.

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## TIM FRANSON:

So I think there is one example we could pick up on, and it's something we have done recently with Duchenne muscular dystrophy and really what the Duchenne community has done, because as we noted before, 7,000 rare diseases, everybody is going before FDA to say please help my children, and we get that, and FDA gets that, and I believe our counterparts at FDA are truly sincere about their mission there. But they can't develop the drugs; that's the companies. And they can't create 7,000 new guidances because they don't have those capacities. But what if the patient community begins to work with the investigative community and says: Let's redefine what benefit expectations are. It's not just survival. Perhaps it's preservation of ambulation. And what are the risk tolerances and what are you willing to trade off there? That then changes the reference points FDA has for benefit/risk. And that's what the Duchenne community did. They gathered patient preference information and presented that to FDA as part of this guidance process, so independently bringing that forward. I think that's where companies and patient communities can actually collaborate and FDA has been very good about receptivity and advice. So that's where all boats can rise.

## PETER PITTS:

What should a patient say at an Advisory Committee? Consider IPF -- Idiopulmonary Fibrosis, where the accepted metric is a six-minute walk test. Patient groups say that is completely irrelevant to their life. They want to be able to go down stairs and make coffee. They want to be able to make the bed in the morning. They want to be able to go outside and to the school bus with their kids. That's the type of testimony that I think is relevant because it speaks to both the Advisory Committee and the reviewers per endpoints. Not just, "Oh, please don't let my son die." And I don't mean to trivialize this, but that's kind of the traditional role that the patients play - and that has to change. The patient just can't be the weepy mom. That is unfair and it's not taking full advantage of who these people are and what they have to offer.

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*The patient just can't be the weepy mom. That is unfair and it's not taking full advantage of who these people are and what they have to offer.*

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**JOE LAMENDOLA:** There's also more merit to patients who spontaneously show up rather than those who are sponsored.

**TIM FRANSON:**

And if we boil it all down, what persuades FDA in terms of changes in their thinking? The answer is data. If patients bring data, preference surveys, other elements that are highly motivational. And if it is just an anecdotal appeal, I wouldn't cast that aside; it's just how do you factor that in? So you give FDA data, they have something firm in their frame of reference that they can use for labeling or other considerations, and that's powerful.

**PETER PITTS:**

Good science. Tim and I both work with a couple of Johns Hopkins researchers who are fielding solid social science surveys on these topics, and that will carry weight because the FDA is obviously very strong in science, not so strong in social science, but good solid real studies drive decisions.

**TIM FRANSON:**

Right. And this is consistent with the patient reported outcome and similar measures to try and capture things that really are meaningful in patient lives. What other topics have we missed?

## BIOSIMILARS

**PETER PITTS:**

Biosimilars. Don't think that the FDA's decision on the Sandoz Filgrastim product is going to be representative for every biosimilar that comes in front of the agency. It's a well-understood molecule. Sandoz is a well-respected company. It's more important to focus on the current new draft guidance on interchangeability. Crucial. Because remember, Sandoz' Filgrastim was not approved as interchangeable. That's the next hurdle to see how the agency approaches this question.

**TIM FRANSON:**

And the U.S. is different from Europe because there are two levels. There is interchangeability and then there is just the lesser biosimilar, if you will. Will reimbursement be different? And in Europe, of course, there's a single track. Also in Europe, there have been at least four or five withdrawals of compounds. So after being on the market were shown – there were several insulins, which had different time action profiles, so people had very unpredictable responses compared to what the originator product was. The other thing that's fascinating to follow in biosimilars, if you try to put all the folks who have concerns about naming programs, the USP, the WHO, the FDA, you find incredible discordance in terms of what they believe to be the right pathway. So until those things get resolved and until we try to focus on what's right for patients in this regard, I think we'll be struggling.

**PETER PITTS:** And another reason, to focus on pharmacovigilance.

TIM FRANSON:

Indeed. And if you don't have a distinct name, how do you track the differences? Unfortunately, we didn't have enough time to touch on new pathways, and that really wraps back to PDUFA VI. In Europe, there are conditional approvals, and you can get that kind of designation and it does represent a different pathway, and I believe it was proposed in the last PDUFA and FDA was not excited about that. Essentially it's a one-year renewable license. For companies, be careful what you ask for because a renewable license means you essentially do another NDA every year, or BLA. Is that what you really want to do? And with conditional approvals, people have also talked about class approvals. So if drug A is approved and there are similar genetic elements, the whole class ought to be just approved. The other end of that stick is there can also be class withdrawals if there's a problem. And that becomes very disruptive.

JOE LAMENDOLA:

Well, and a mistake. Because I mean Vioxx is gone and Celebrex is still on. And then patients lose options. So I don't think that anything should be done in on blanket case basis. I think all of these, even drugs within the same class, have different profiles, whether it's safety profiles or whatever. And I think you really need to pay attention to that kind of thing.

PETER PITTS: I think there's no appetite whatsoever inside of FDA for conditional approvals.

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*I think there's no appetite whatsoever inside of FDA for conditional approvals.*

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## PARTING THOUGHTS: SUCCESSFUL RELATIONSHIPS WITH FDA

TIM FRANSON:

Do you gentlemen have any parting words of wisdom to share regarding how to have a successful relationship with the FDA?

JOE LAMENDOLA:

I have a ton of respect for the people that work at the agency. You must as well. As leaders of your company's regulatory functions, you are the bridge and you must insist on scientific credibility and respect when you go into those meetings because if you don't, it's a non-starter.

TIM FRANSON:

And I have to say, my experience with FDA counterparts has been exceptional. They're almost all healthcare professionals, physicians, and pharmacists. They care about what they're doing. They're very data oriented.

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**PETER PITTS:**

They're overworked, they're underpaid. They are on personal public health missions. And even if you don't agree with their position, respect the fact that they're reaching it for the right reason.

**TIM FRANSON:**

So this is one of those times when if we could leave folks with any advice, for me, going into FDA meetings, it's all about being an ambassador for your company. Think about it as being a kind of diplomatic relations. And what is the currency of diplomatic relations? It's data and respect. What are we talking about, how do we get to common ground? And those things I think are very helpful in creating win/win situations. So let me take the opportunity to thank my friends and colleagues, Peter Pitts and Joe Lamendola, for providing us with a respectful RANT -- Relevant Assessments and New Trends. It's always hard to predict the future, as Yogi Berra said, but we'll try to continue these kinds of things. So Peter, many thanks. Joe, always a pleasure. Thank you all for being here.

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