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PDUFA without the Politics

When politics trumps the public health bad things happen. The current conversation surrounding the reauthorization of the Prescription Drug User Fee Act (PDUFA) must focus on (among other things) the First Principle of Predictability as well as ensuring that the FDA can fulfill its role as an important ally in advancing healthcare in America.

**Comments and commentary from the Capitol Hill conference held on
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in the Rayburn House Office Building**

Peter J. Pitts (Moderator), Former FDA Associate Commissioner, President of the Center for Medicine in the Public Interest

Tim Franson, Former Vice President, Global Regulatory Affairs, Eli Lilly & Co., President, USP Convention, Senior Vice President, Health and Life Sciences Sector, B&D Consulting.

Paul T. Kim, Former Deputy Staff Director for health policy for Senator Edward M. Kennedy, Partner at Foley Hoag LLP in the Government Strategies practice.

Vincent J. Ventimiglia, Jr, Former Assistant Secretary for Legislation at the US Department of Health and Human Services, Senior Vice President in the Health and Life Sciences Practice at B&D Consulting, a division of Baker & Daniels LLP.

Michele J. Orza, Former Assistant Director of the Health Care Team at the Government Accountability Office, Principal Policy Analyst at the National Health Policy Forum.

The Honorable Michael C. Burgess, M.D., Vice-Chairman, Subcommittee on Health, U.S. House of Representatives

Peter J. Pitts: My name is Peter Pitts. I'm President of the Center for Medicine in the Public Interest and a former FDA Associate Commissioner. Welcome back to session and welcome to the Center for Medicine in the Public Interest's seminar on PDUFA without the Politics.

The PDUFA deal on the table has, at its beginning, a philosophy statement and I'm going to read it to you verbatim. FDA agrees to "promoting innovation through enhanced communications, specifically via timely interactive communications with sponsors during drug development." Something to consider as we listen to today's speakers.

Some people say that FDA is the problem, but what does that mean? Well, let me posit that it means many people believe the FDA is a sea anchor, rather than a facilitator and partner to innovation, in advancing the public health. And part of that problem is the slide from predictability, nascent predictability brought to us courtesy of the PDUFA concept, to regulatory ambiguity. And, as you know, regulators love ambiguity because it gives them ultimate power. The 30,000 foot philosophical bedrock of PDUFA is predictability and my question is whether or not PDUFA V will give us more modern, more up to date predictability or not. Shouldn't PDUFA stand for the Predictability Deposit User Fee Act?

Let me mention a couple of issues and then introduce our panel. FDA days or calendar days? The intellectual dishonesty, at least in my opinion, of non-binding advice. Complete response letters resulting in pseudo on time PDUFA dates. The role of the patient voice in the drug review process. A more defined yet appropriately elastic methodology for understanding benefit/risk. Aggressive leadership in 21st century bioequivalence and narrow therapeutic index standards. New authority for a behind-the-counter (BTC) drug category for products such as statins. A predictable regulatory pathway for molecular diagnostics and perhaps even a separate FDA center for diagnostics. More predictable views on off-label communication and off-label promotion. More effective models for Phase IV safety monitoring and adverse event reporting because, let's face it, early safety signal communications just isn't cutting it. The potential for progressive or conditional drug approvals relative to things such as the pending TREAT legislation. The issue of comparative effectiveness as a third leg in the FDA review process. The evolving role of outcomes data and adaptive clinical trials. FDA's Advancing Regulatory Science Initiative (ARSI). The future of the Reagan-Udall Center and the agency's role in supporting the promise of personalized medicine. And lastly, enhanced congressional oversight.

Nobody said it was going to be easy.

So, with that, let me introduce our panelists and get into the meat of the program. Our first speaker will be Dr. Tim Franson. Tim is the former Vice President of Global Regulatory Affairs at Eli Lilly. He is currently President of the USP Convention, and Senior Vice President Health and Life Science Sector at B&D Consulting. Tim is generally known as one of the fathers of PDUFA. Tim, we will be doing a paternity test after the reauthorization legislation passes.

To my immediate left is Vincent Ventimiglia. Vince is the former assistant secretary for legislation at the US Department of Health and Human Services. He is a Senior VP in the Health and Life Sciences Practice at B&D Consulting.

To my immediate right is Paul Kim. Paul is former Deputy Staff Director for Health Policy for Senator Edward Kennedy and is a partner in Foley Hoag LLP in their Government Strategies Practice.

To my extreme right, no political comment intended, is Dr. Michele Orza. Michele is the former assistant director of healthcare team at GAO, the Government Accountability Office, and is currently the Principal Policy Analyst at the National Health Policy Form.

You might note that nowhere on this panel is there anyone from PhRMA, BIO, or from the FDA. We want to present to you the unbiased, thoughtful and provocative views of people who understand where things began, the principles on which they were founded, where we are now and where we might be going. A little later on Congressman Michael Burgess will join us and we're looking forward to that. So, with that, Tim, why don't you come up and get us started.

Tim Franson: Peter, thanks very much and I have great respect for my fellow panelists. And as you see, they've all had extensive experience in private as well as governmental sectors. I respect their leadership efforts and what they've done and I think they'll have some very interesting comments. I will begin by saying the definition of PDUFA is not as you suggested, but as an acronym for Pharma's Dollars Underwriting Federal Appropriations.

Peter has asked each of us to address three specific items. The first is a 30,000 foot conceptual item. The second is a specific topic already in the technical side letter that has been proposed from FDA and industry. And then third, presuming that PDUFA is a Christmas tree which is going to have a lot of ornaments, what's one important ornament to consider hanging?

My 30,000 foot topic is Newton's Third Law. PDUFA V's core topic is Benefit/Risk, not safety in isolation. And the Christmas tree ornament is a little lifeboat. So, leaving you with that, why Newton's Law, specifically Newton's third law states that for every action, there's an equal and opposite reaction. When it comes to PDUFA, sometimes those opposite reactions are not well foreseen and unintended consequences become a very important issue. So, as one who has suffered some of the missteps in pharma development, I'd like to share some thoughts about what is going on since the first time Sir Isaac's apples dropped and two decades since the first PDUFA.

I would submit to you that our frame of reference for innovation has radically changed in the past 20 years. And whether regulations have kept pace over those two decades is subject to speculation. So, let me compare pre-PDUFA 1992 to today. In 1992 new therapies were primarily for acute disorders and abundant familiar diseases, like oral antibiotics for a variety of infections. Now we are focusing on more chronic diseases with many harder targets to research. Very different. Then, predominately small molecules were in development. Easy to make and easy to study. Now? Complex biologics with different and more complex adverse event. Back then, a very predictable development pathway with fairly high success rates later on. Now, a high failure rate, with many blind alleys in late phase development. Expensive and disappointing to patients. And finally, then, a focus on innovation. Now, because of PDUFA IV, I would submit to you, a high degree of focus on post approval safety more so than an innovation -- inconsistent with the initial goal of PDUFA.

And PDUFA IV, if you will, is a potential poster child for unintended consequences. It fairly significantly shifted the attention from investment in innovation and portfolio advancement to investments in post-approval rather than pre-approval safety. I am by no means arguing against the importance of safety. It is absolutely vital and it needs to be carefully looked at for all drugs post-approval, but that was not how the mission of PDUFA was conceived. It's clearly an important and pivotal part of FDA's mission.

So, let's look at PDUFA IV, follow the money and follow what gets tracked as a result of PDUFA IV productivity. FDA's PDUFA IV implementation site has about 90 items that are listed across drugs, devices, animal health, what have you. Of those, about a dozen are specifically focused on safety matters. There is *one* that's focused on access for new and life threatening illnesses. None are on benefit/risk. It's an interesting display of the Hawthorne Effect, what you track you likely will do. And that indeed is how some of PDUFA IV has been

implemented. What does that mean relative to what happens at FDA and what happens in industry, if you will, the collateral impact?

You may be aware that after the passage of the FDA Amendments Act (FDAAA), FDA essentially put a moratorium on meeting its NDA review timelines in 2009 so they could implement all of the guidances and other activities associated with what they were charged to. That was something clearly not in the best interest of innovation. It was something that FDA was compelled to do as a result of the implementation burden -- and without commensurate resources. That is significant. So, if you will, in the first year of PDUFA IV, innovation was not served well. Now, FDA has a much larger infrastructure for safety. In the Center for Drugs, there's a new super office with super powers and we have no kryptonite, do we? Also all of the review divisions now have a Deputy Director for Safety. Again, very important activities. But let's step back and say there is no Office of Benefit. There is no Office of Benefit/Risk and perhaps that should be part of our concept moving forward.

So, the collateral impact, for industry was where should your resources be deployed? As you're aware, most companies are shrinking. They've had to shift resources to safety areas so that they're compliant with the new requirements for REMS, Risk Evaluation and Mitigation Strategies and similar matters. And that means less attention focused in the laboratories as many trials have been shut down. Those are all unintended consequences of what occurred and I would also submit to you that portfolios in companies have been impacted as a result of FDAAA. As an example of the expanded safety requirement there have been at least four companies that have discontinued programs in diabetes drug development. Not welcome at a point where we're all wrestling with a global diabetes epidemic, as the World Health Organization and others have highlighted for us. We need more, not less development. And yet because of new cardiovascular pre-approval and post-approval studies for diabetes drug candidates, the financial kinetics have not been favorable.

So, to close on the first point, Newton was right. For every action, there is an opposite reaction, but it's not always foreseen in advance or necessarily welcomed.

So, topic two: benefit/risk, not safety in isolation. Why would I be so insistent on that? Well, if you look at what safety means, consulting the font of all knowledge, Wikipedia, safety means freedom from harm. That is not what we mean with drugs. No effective therapy is without its side effects. Said another way, show me a drug without side effects, and I'll show you a drug that doesn't work. So, benefit/risk is a much

more appropriate way to balance our thinking and how one does that in PDUFA V is probably half a loaf at this point.

The benefit-risk provisions in the PDUFA V technical letter suggest that FDA's commitment needs to be interviews with stake holders and the development of a plan about how to move forward on benefit/risk by 2017. That's probably too little, too late. The European Medicines Agency already has a template that's being used by their drug reviewers to look at benefit/risk and those kinds of things need to be advanced rapidly here. There are a number of effective and reasonable tools that have been brought forward by academics, by industry, the so-called multi-criteria decision analysis, the so-called BRAT. All of these are acronyms for programs that could help us accelerate and further develop thinking on benefit risk. Being a physician and a pharmacist, I would not present a bedside discussion about a drug which only covers risk. You want your physician, if you're considering a new therapy, to talk about a fair depiction of both the upsides and downsides of what you're being offered so you can make an informed decision. Talking about safety in isolation to the public as in safety alerts bears the risk of frightening instead of appropriately warning the population.

So, how do we gain a better balance? And, as we invite more patient input into the processes of REMS and benefit risks and so forth, how do we embrace their demands for more attention to both sides of the benefit/risk equation in PDUFA V? How do we think about that final balance of benefit/risk to further enhance and accelerate what it is in the current legislation?

And, finally, as an ornament for the Christmas tree, a little lifeboat. Women and children first, plus those with life threatening unmet needs. First and faster, what can we do for women and children? Well, one thing, as was done as in PDUFA IV, is adding renewal of the Best Pharmaceuticals for Children's Act and PREA. Those companion pieces of legislation have done more for pediatric drug development than anything else in the past. I recall being involved in this when I was doing clinical trials. Very difficult to get companies to do studies on young children. These acts have stimulated that. It's been good for American children and it should be made permanent.

Second, providing additional latitude for unmet needs. Are concepts, such as conditional approval, appropriate for consideration? It is used by the EMEA. These concepts have been tested and they should be considered. And whatever ornaments you choose to hang on the PDUFA tree should all have a tether to PDUFA's core mission.

So, to summarize, carefully consider unintended consequences. Sir Isaac was right. Second, how do we restore better balance to benefit/risk? Third, man the lifeboats. And finally, PDUFA I through IV, despite criticisms, have been incredibly successful at keeping pace and improving the developmental processes. How do we make sure that continues in the best interest of innovation? I have great hopes for what you're going to do to build on that strong foundation to make an even better PDUFA V.

Paul Kim: Well, thanks for having me, Peter, and it's a pleasure to be back in Rayburn. Peter mentioned that I'd worked for Senator Kennedy once upon a time and, in a previous life to that, I'd worked for Congressman Henry Waxman on the Energy and Commerce Committee, and so had the dubious pleasure of having worked on PDUFA, on the Hill while the team was negotiating with the agency on the original package and then, subsequently, on the reauthorizations both on the Senate side or here.

I bring you a little good news and a little bad news. First is a wonderful anecdote that Tim and Peter began in terms of the acronym. I think the most important thing of any reauthorization is, how good is the acronym? The last go-around we didn't do so well with "FDAAA." I love the way Tim and Peter reconstructed PDUFA. During my time on the Hill, I had been aggressively pushing another acronym. We had some half serious conversations about the "Giant Omnibus Drug and Medical Device Amendments Act" or GODDMAA. But at the end of the day, the staffs were unwilling to bring it to their bosses' attention -- which I think to our infinite regret it is not part of federal jurisprudence. An opportunity lost.

My first central truth about the reauthorization is the fact that the money is so indispensable to the agency. That's absolutely one of the core truths.

The other central truth is the Christmas tree Peter and Tim were talking about, all the ancillary provisions. I think that speaks not only to the fact that there's a great deal of legislative interest in what the agency does, but also to the five-year cycle. It's a good opportunity for Congress to reexamine the agency's performance in a classic oversight style, something old school that we're supposed to be doing half the time *in addition* to reauthorizing. And, with hearings being convened on both sides of the Hill, that's an important function that should not be dismissed or denigrated. Because when you shine the spotlight, you're not just bringing regulated industry issues to bear. You're not just hearing from companies that think the agency's too slow or inflexible or unpredictable. You're also hearing from patients and

consumer groups. You're hearing about the usage of post-market safety and product-specific issues. And I think that's very, very healthy and we should not lose sight of the fact that it's a great part of this process. And as painful as it can be, as sort of nail-bitingly close to the wire and to up to the deadline we get with that function, it still serves a very important public purpose.

The only two things I want to point out about this reauthorization are looking backwards and pointing to the dollars. And I wanted to give you the baseline numbers.

I have FY10 numbers here. They're a little bit different for the last go-around, but with the CRs and the way that we've been doing appropriations recently, it's really hard to know exactly where the numbers are. For fiscal year 2010, the PDUFA revenue the agency actually collected was about \$550 million. That's a big number and it is a sizable investment if you will, by regulated companies and sponsors into the agency. And you need to compare that \$550 million against \$465 million in budget authority for the drug function. Those are the appropriated dollars that Congress brought out of the public purse to pay for the agency function. It was substantially less than the user fees collected in fiscal year 2010.

Under PFUDA V, we'll see that same trend line. We will see user fees account for a greater proportion of the human drug review and approval process. That is a huge and important truth about the agency and I think it reflects the broader challenges the agency had in getting the dollars it needs to do its job. And as you know, FDA doesn't stand just for drugs. I don't know how many people I've met who think it stands for the Federal Drug Agency. But it does count for food, for devices, for drugs, for any number of very complex, regulated products that improve human health.

This is increasingly what my old boss, Senator Kennedy, used to describe as the century of life sciences. So, the challenges before you become even more challenging, more difficult. The science is more sophisticated. The targets are harder. The agency is in the same environment we find the rest of the federal government and the rest of the economy. It's incredibly difficult to find the resources that need to be appropriated for the agency. In that context, you realize the user fee reauthorization is absolutely a must-pass piece of legislation. If we don't enact it in time, the ability of the agency to collect that revenue literally stops in its tracks. So, I think that central truth has become even more important to the agency's realities the past 25 years. That's my first point.

The second point I had was actually about the Christmas tree. Peter had asked for some specifics we think will be coming up this year that will be important to bring to everybody's attention -- that hopefully will be enacted as part of that package. But the truth is that everybody aspires to a clean reauthorization and I think that's an important starting point anytime that we start this cycle. But my colleague (and now my client) Bruce Arden, who used to work for Senator Hatch, made an excellent point, which is even the first bill that we passed, the Prescription Drug User Act of 1992, wasn't in fact truly clean. There was another provision in that enactment that related to dietary supplements given Senator Hatch's very strong interest and championing of that industry. So, you can't really point to any authorization or reauthorization of the user program that's actually been strictly clean. Having said that, when you look at the wheat and the chafe and the many, many proposals that are going to be up for consideration this year, there are some standouts.

There are bills that, even in a very partisan environment, you'll find a lot of bipartisan/bicameral support and interest in. And there were two I just felt I had to call out. They go to the innovation gap. I think an issue and a set of concerns that are so much more resonate now in this economy is the role the agency plays in promoting innovation. There are two proposals. The first is called the Gain Act. It's sponsored by Congressman Gingrey - Dr. Gingrey, here in the house -- and Senator Blumenthal in the Senate. Wonderful bipartisan, bicameral support. It would enhance incentives in terms of exclusivity for sponsors that are trying to generate, create and innovate on microbials. Given the enormous challenge that microbial resistance presents to public health, this is an area where there's been a classic market failure. There aren't enough players in the field. The marketing incentives are not strong enough to draw interest or investment. So, that's a proposal that already has bipartisan support in both chambers and it's the subject of a lot of discussions in the committees of jurisdiction. So, do look at the GAIN act as a possible ornament somewhere in the upper branches of the PDUFA Christmas tree.

The second proposal is one that has also received bipartisan support, sponsorship and interest on both sides, Senate and House. And that's to reform the humanitarian device exemption or HDE process.

Little known, it's kind of the less known sibling to the Orphan Drug Act, which has promoted and really generated tremendous innovation for rare diseases and disorders affecting some 30 million Americans. When it was originally enacted in 1990, there was a profit cap. It said if you develop a device for a very, very small population, you can only charge for cost. It was intended as a safeguard, but instead what's

happened is it's blocked and chilled interest in using that pathway to market. As a consequence, we've had some 54 HDEs or Humanitarian Devices approved since 1990 in contrast, literally hundreds of orphan drugs approved since the enactment of that act. Again, it's an issue that has bipartisan interest and support. It's a very small change to existing law. It's not overturning the apple cart -- but I think you'll see some significant changes in the marketplace among sponsors, investors, investigators, and scientists as a result of any federal change like that.

Vince Ventimiglia: I was going to approach my three topics in a slightly different way by capturing a few myths that live around the UFAs, all the UFAs, and offer a little depth and complexity.

One myth I'll call *Everybody Loves Raymond* or *Everybody Loves PDUFA*. A myth. Not everybody loves PDUFA. PDUFA is a must-pass bill and it's always passed. Not always on time, but it does pass and with broad bipartisan, bicameral support. But not everybody loves the UFAs. And there are several reasons for that. A number of folks, increasingly in this Congress, are concerned about the tax-like nature of user fees. And we were very careful in the early days to structure these as fees, not taxes. And the committees and jurisdictions recognized the distinction. That distinction has been very carefully guarded throughout the history of the UFAs. But they can be perceived as a tax and you'll see some concerns about that.

The general concern is that a tax supplants appropriated dollars while a fee supplements them. PDUFA has always been structured as a fee that rides on top of the appropriated dollars. It's going to be really important in this budget environment to watch that those appropriated dollars and triggers remain in place so that this doesn't actually become a tax and generate some opposition, particularly in the House.

Other people don't like the way the fees are used as a way of increasing the size of government. You're going to hear some concerns about eliminating user fees as a way to tamp down on the role of the FDA and the regulations they put out and eliminate some of the perceived barriers of getting products to market. I think the stronger point is that, today, the agency cannot survive without these fees. 66% of agency revenues are coming from fees. Very difficult to eliminate that funding source outright -- but some folks are concerned about it. And a third component that people don't like is that these fees are paid for by the industry so that the industry can essentially "own" the FDA. The fox is now guarding the henhouse. There are ways to protect against that dynamic. One of our historical approaches has been never to allow those fees to ever support post-market activities. That was a line that we drew very early on, so that we limited the fox

guarding the henhouse phenomenon. But that barrier has now been broken on the prescription drug side and it threatens to encroach on the device side. It's something for people to be watching, because it can generate concern with respect to user fees going forward. So, *Everybody Loves Raymond?* Not everybody, but most people do.

The second myth resides around what I'll call *Dirty Sexy Money*. Are these bills clean? They've never been clean. They are too sexy a vehicle. There's too much money associated with them to ever go through clean and we have never seen a user fee act go through clean. Some of the riders have been suggested by Peter and my colleagues here. There are lots of other riders, but I will tell you the one clean part of these bills that have always been respected are the sidecar functions. This is essentially a negotiation between the agency and industry. The exchange of industry fees for faster performance by the agency. That's the core, the heart of the User Fee Act. Congress has, in my memory, only once ever rewritten that core side letter agreement between the agency and the industry. That part is always kept clean and the one exception I can think of is the small company exemption for medical devices. When people talk about clean user fee bills, that side letter has always been kept succinct. The rest of the bill, its ability to pull on unrelated policy riders, has actually been viewed by Congress as being an essential part of oversight duties. Congress' ability to rewrite FDA law in conjunction with the User Fee Act has almost been as sacrosanct as the side letter.

A third myth, and I'll call this one *Lie to Me*, addresses the numbers, information and data that the FDA brings up to the Hill. Are they always true? And the answer is no. The building down the street houses the Department of Health and Human Services (HHS) and the Secretary's office. It doesn't house FDA. Down Pennsylvania Avenue at 16th Street is the White House, where resides the Office of Management and Budget (OMB). Those players often are at odds with the agency and the numbers it brings up here and talks about privately. It behooves you to look very carefully at FDA numbers, Department of HHS numbers, and OMB numbers as a package. They're not always in sync with each other. There are important fault lines you can work with when you see these disparate numbers, policy approaches, and policy objectives.

The final myth we probably ought to bust is *Deal or No Deal?* Do deadlines matter? You're going to be talked to a lot in 2012 about the importance of any number of deadlines. September 30, that's the end of the fiscal year, that's when the Act and its authority expire. Boy, you better act by September 30th otherwise, it's all over. Others are going to come to you saying June and July, that's the real deadline.

That's when the agency sends out riff notices to its employees telling them there will not be user fees. Many folks are going to say that you really have to enact this by April or May because Presidential politics are going to complicate this so much we can't handle this later on.

I'm here to tell you these bills always get passed. They don't always get passed by the deadline -- by any of the deadlines. I worked on one that went into day and night negotiations. There are ways to extend fee collection authority so that you have the time you need to pass the bill that is the right bill. Now, I'm not urging you to wait that long. We all know that deadlines are action forcing events. If you're telling yourself Christmas next year is the real deadline then it won't be until January 1st when you pass it. The world will not end if you need another week or two or another month. So, deadlines matter, but don't believe all the deadlines that are being thrown your way.

Finally, let me just touch on the core component of user fees. You've got to keep your eye on the prize here, on the exchange of money for better performance from the FDA. That's the core agreement that has got to happen in this bill. Otherwise, it has no value to anybody.

Key riders and a little bit of self-interest here, we're working with a group of pharmaceutical wholesale distributors and others who are interested in cleaning up the supply chain and keeping drugs safe. Sometimes that involves overseas API raw material coming in, Heparin type products. Sometimes that involves domestic product, but I think at heart, you're all aware that there's strong interest in cleaning up the drug supply chain, so that it is safe for American patients. I believe that's going to be one of the big issues that does ride on this user fee act. Thank you.

Michele Orza: I, too, want to thank Peter for inviting me to participate in old home week. I enjoyed working with Vince and Paul and Tim when I was at the GAO in the 90s, where I had the opportunity to get into the guts of somewhere around 100 INDs and NDAs, including an entire year's worth of applications for new molecular entities.

I also got to interview sponsors who had developed these NDAs and the teams at the FDA that had reviewed it. And my overriding impression, that still stays with me from that experience, is just the tremendous variability on any dimension, any parameter you can think of across applications, across sponsors, across conditions, across FDA reviewing divisions. In terms of the three items that Peter asked us to address, I think this eye of the eagle/view of the mouse is a very apt framing for thinking about FDA and what they do, because they simultaneously are responsible for very broad, highest order public

health decisions, based on an enormous amount of minutia and detail - - incredibly important detail in order to make good public health decisions.

So, first, in terms of the eye of the eagle, I wanted to speak a little bit to Peter's point about predictability, which is very much a two-way street. It's a problem both for sponsors and for the FDA. The FDA has virtually no control over what's submitted to it. And the situation that we find ourselves in when dealing with new drug applications is really fundamentally unpredictable. We're in a world where everything is dynamic. The conditions, drugs, and marketplace are all changing. And I'll just give you three small examples of the kind of change I'm talking about.

First, in terms of a condition, in our lifetime, our understanding of what causes ulcers has changed completely. Imagine that you had in the pipeline or under review at FDA one of the old drugs for treating ulcers -- when we came to the understanding that they're really caused by H. pylori. It would be incumbent on both the sponsor and the FDA to reconsider the whole deal. In terms of drugs, imagine that you had pending at FDA an application for a COX-2 inhibitor at the time that the whole Vioxx thing erupted. Again, both the sponsor and the FDA would be remiss if they didn't take a good hard look again at that COX-2 inhibitor.

And finally, one of the examples I saw when I was going through NDAs at the FDA was of a drug that was a perfectly good drug. FDA was about to issue an approval, but the company decided to withdraw it because a competitor had just brought to the market a similar drug which didn't need to be refrigerated, but theirs did. They pulled a drug the FDA would have approved, which they would have been able to sell, but the marketplace changed underneath them.

A certain amount of unpredictability is the nature of the beast. It's what we're dealing with all the time when we're dealing with drugs. And I think an interesting way of looking at it is the way that people who work in the field of public health preparedness do. They're always dealing with a certain degree of unpredictability whether it's bio-terrorism or an earthquake or a flu pandemic. They have what they call the 80/20 rule, where they expect that about 80% of what's going to happen in a bio-terrorism attack or a flu pandemic or an earthquake will be predictable or standard. And so they prepare and drill and try to have things they can pull off the shelf to deal with that 80%. The other 20% is anybody's guess, so what they try to develop is the ability to be innovative and responsive and creative and agile and flexible. I'm not sure what the right breakdown is for industry or the FDA. I don't know

if it's 80/20. It might be 50/50. PDUFA seems to suggest that it's 90/10, which I think is ambitious to say the least. But I would be a little provocative and say I think that complete predictability, while it might be desirable, is maybe not that possible in this field.

Moving forward, there's a lot of emphasis on goals and timeliness and whether or not FDA is meeting their goals and whether they should be changed. And I'm not sure, because of fundamental unpredictability and uncertainty, how much room there really is to go faster. We might already be going as fast as is humanly possible and I think that's important to consider.

On both sides, there are human beings engaged in trying to understand very complex science. It's not just a manufacturing process you can control where everything comes down to measurements that can't be seen with the human eye. And I wonder, too, whether there's a little too much focus on time and, after so many years of PDUFA, maybe this isn't the right question or the right focus. The amount of time that an application spends under FDA review is a very small part of its very long lifespan. There might be more opportunities to gain efficiency and time if we look at both the front end and the back end and seek opportunities for both speed and public health benefit.

In terms of the view of the mouse, the PDUFA V detail that caught my eye is tucked away in section 9B, enhancing regulatory science and expediting drug development by advancing the science of Meta analysis methodologies.

Meta analysis is what actually brought me to Washington, DC. There was a little, very negative piece in the Pink Sheet about some kind of hocus pocus that was going on at FDA with meta analysis and the GAO was looking for somebody who understood the issue. That's what I was doing my doctoral thesis on. GAO recruited me and I came down and took a look at what FDA was doing and found that it was reasonable for them to be exploring this methodology. And so to see this, so many years later, actually being codified in the PDUFA agreement, really fascinates me.

Meta analysis is a fancy word really for a set of tools that tackle the entirety of a database, the entirety of the evidence about a particular drug. It's a set of tools for finding and collecting and sorting usually by quality, and then analyzing that evidence. And it could be an extremely useful tool, not only for drugs but for most of the things FDA deals with. So, I will be very interested to see what happens to meta analysis, which is near and dear to my heart.

And then, in terms of the last thing where we might be headed in the future or where we maybe should be looking, I'm interested in a lot of the proposals that are coming out around improving transparency. I think two kinds of transparency are needed. One is on administrative data. There's a whole range of things that happen and it would be nice to know about them, because approval times only tell us so much. It would be nice to know what's being submitted to FDA and how many applications, for example, are refused, how many of them are going through multiple cycles, and how many of them are having major amendments and all that kind of detail.

And the other kind of transparency that's needed is with respect to scientific and clinical data. Previous PDUFAs have really opened up a lot of the scientific data. I think *clinicaltrials.gov* has gotten better and better, but there's a lot more clinical data that needs to come out so that academia, consumers and others outside of FDA and industry can provide both more oversight and additional analyses. There's a wealth of data that FDA sits on -- one of the most powerful databases in the world. And there are analyses that only they can do, but that could also be done by outside people if more of the data were made available.

Peter J. Pitts: Vince mentioned something I think is very important to remember, and that's the rhetoric that so often goes along with discussions around PDUFA "paying for approvals." PDUFA does not pay for approvals. PDUFA pays for reviews and I think that, in terms of properly communicating the value of reauthorization, both to Congress and the public, that's a very important distinction.

Tim brought up the Hawthorne Effect -- that which gets measured gets done. Mitch Daniels, formerly of Lilly, formerly of OMB, currently the Governor of Indiana, is famous for saying that if you can't measure it, it doesn't count. Within the technical letter, FDA promises many things and many meetings. When it comes to things like benefit/risk or a benefit/risk action team or a grid as the EMA has in place, why isn't there a date certain to reach closure on a procedure?

Tim Franson: Benefit/risk is a fantastically challenging area because of the way scientists and policy makers look at these things differently. They can be quite divergent. From a scientific perspective, finding things that you can quantify or at least put in a common frame of reference is key. It's kind of like do you want 20 Swiss francs or 20 French francs and the response is "I don't know, tell me what the exchange rate is." What there needs to be is an exchange rate for benefit/risk so folks understand for similar life threatening situations how to compare these things. FDA and industry and academia are all far apart in how one does this. Somehow the European Union has been able to at least craft

a kind of baseline tool where reviewers will at least look at various defined segments. It doesn't mean that it presupposes a conclusion. I don't believe FDA has been able to get at that point for a variety of reasons and I don't disparage them for it. I'm just not sure I see the path forward here unless there are imperatives placed before them to say we can't wait five years for a normal review template and perhaps that needs to be considered.

Peter Pitts: At present, at least in my opinion, the FDA's transparency initiative means that industry is transparent, but not the FDA metrics that would be so valuable for all of us to know in order to move things forward in many different ways. But it seems to me that both industry and FDA are complicit in their translucency, shall we say, of what's available to the public. Paul, let me ask you from a commercial confidentiality perspective, what do you feel is the necessary legislative authority for the FDA to have flexibility within its own authority to change what it's sharing?

Paul Kim: That's a fantastic question, an absolutely a critical question to present to the agency and to Congress, which is when you look down at a telescope, which end are you looking through? And this case, I think there is present authority for the agency to do much more.

I think Michele's points about accountability and risk benefit are perfectly dovetailed questions. As Tim said, to push forward into the agency, to manufacture changes in culture, to really bring about analytical, very thoughtful leadership within the agency, to be more aggressive, to change the culture of review teams or divisions, is incredibly challenging. But on the back side, to hold the agency accountable through more specific numbers, I think Michele's examples of how many first cycle approvals, how many multiple approvals and how many cycles in each multiple cycle, the refusal to file -- all that data is already collected and is available at the agency's fingertips. It doesn't require changes in legislative or statutory authority. It's really a question of whether Congress could actually ask the agency to do something different in its PDUFA annual report, which is a feature of the user fee agreement already and simply break out some of those numbers in greater detail.

Peter Pitts: That's a good point. When you look at the report that just came out, showing what a magnificent job FDA did this year relative to approvals, it didn't really discuss cycles or accelerated approvals versus regular approvals. And that would be useful information to know. Michelle, do you want to take another crack at that?

Michele Orza: I was under the impression that it was industry pushing back on a lot of this coming out. For industry, it's not necessarily a nice thing for it to be known that their applications receive "refused to file" decisions or that they've been asked for serious amendments or that they have had to go through multiple cycles. I mean, all of these measures are of both the FDA's and industry's performance. It's not that every NDA, which arrives on FDA's doorstep, is pristine and reviewable and can just sail through. There's quite a range from wonderful, immaculate NDAs that can sail through to those that never should have been submitted in the first place. In that cohort that I looked at, I had a company say, quite honestly, that they knew their NDA was a pile of garbage, but they needed to have it submitted by a certain time in order to report that to shareholders. There are forces acting on industry that cause them to submit applications maybe before their time. So, all of those things are measures of both industry performance and FDA performance. As more information comes out, the more clear our picture will be.

Peter Pitts: Vince, Best Pharmaceuticals for Children? Why renew versus making it permanent? Logically, you'd think permanency would reward and encourage a lot of investment. Why just renewal?

Vince Ventimiglia: The argument I heard when we first set the five-year term, and that I heard again when we tried to make it permanent in subsequent years, was that we want to hold these guys accountable. It's more to use it as a tool against industry -- and hold out the prospect that it could be removed.

Tim Franson: If I'm looking for a return on an investment, I need certainty well in advance of five years on types of studies I should be conducting and I need to know the benefit I'm getting at the end. I think five years is far too short a period of time. There's an accumulated body of evidence, of companies fulfilling their commitments. Maybe its time we make it permanent. I think this point of holding up renewal like the Sword Damocles isn't very persuasive even to sponsors.

Peter Pitts: Tim mentioned before the panel that approvals seem to tick up in the final year of PDUFA. Is five years the right number? Is it too short? Is it too long?

Tim Franson: I think all of the panel and probably many of you in the audience can recall a couple of the reauthorizations that felt more like near death experiences than actual legislative ones. Five years seems right. There's always the opportunity to go at the agency with a stick or with a soft caress.

Peter Pitts: I'm sure that a soft caress is preferred. As the bipartisan, bicameral discussion of PDUFA V moves forward, what role is there -- or should there be a role -- for mandatory enhanced congressional oversight of targets?

Michele Orza: I think the language of deadlines is dead wrong. But you know, that's very much a double-edged sword. The issue is not where the money comes from, it's deadlines or pressure that potentially undermine or compromise the public health decisions that FDA has to make. So, I think we have to be careful about pushing on targets too hard. I think maybe a safer thing is to focus on the process and the resources and the capacity building that PDUFA has contributed to so significantly.

Peter Pitts: The reason I tee that up is because you hear things like, "Congress wants to talk about drug shortages. Congress will want to talk about drug importation. Congress will want to talk about the heparin issue." But it seems these are knee jerk reactions to issues in the headlines, rather than a continuous ongoing conversation about sophisticated, complicated data driven topics that need not rise to the level of "gotcha" conversations. Does there need to be a more formalized and thoughtful roll for the elected branch of government to play?

Tim Franson: Well, I would just comment that I think Michele made an excellent point earlier about the need to focus more on quality than time metrics. That said, I think the whole notion of predictability is very important but so too is the FDA not having its feet held to the fire to approve something. It's meeting a timeline for some kind of definitive response. That response may be the need more studies and, in terms of fairness, it would seem it's only appropriate to maintain those limits, not FDA's not being forced to say thumbs up or thumbs down. This is a reasonable time period for a review and I could certainly see Pandora's box being opened if one were to remove those expectations. So, it's a mixed challenge.

**Remarks by Representative Michael C. Burgess, M.D.
Vice-Chairman, Subcommittee on Health
U.S. House of Representatives**

Michael Burgess: The good news about the Prescription Drug User Fee Act reauthorization - at least compared with where the device folks are - is that the user free reauthorization for the prescription drug side is going fairly well.

I think back to the days in the 1980s when I was practicing medicine and you'd read about therapies that were available in Europe that we didn't have in this country. It was irritating to think that the FDA was

taking so long to review applications and approve products. Yes, you wanted the products you prescribed to your patients to be safe, but at the same time, it didn't seem correct that America, the vanguard in the world for medical innovation, was now trailing behind Europe in some relatively simple areas. And then that all changed. And to tell you the truth, as a clinician back in the early 90s, I'm not sure I understood why it changed. I just knew that it changed and that it was a positive effect for my patients.

And what changed was the first passage of the first version of the Prescription Drug User Fee Act in 1992, leading to cooperation between the FDA and the community that develops and produces drugs. An understanding that if there was perhaps some money put forward, that the FDA would do its job in a more timely fashion. And in fact, it's worked. And the difference in the materials available for practice in the 1980s and 1990s was startlingly different.

When the last reauthorization occurred I was on the committee. I was in the minority and was concerned, because of some of the activity surrounding conflicts of interest on advisory committees. You want to be sure that you insulate advisory panels from conflicts of interest, but you don't do that by excluding everyone who might have any working knowledge of what the substance was under consideration. And that seemed to be the direction we were going on the committee. I worked against that both at the subcommittee and full committee level. I got voted down on a party line vote. Chairman Engle said, "Don't worry. I'll help you" and then he never did. So, that's one of the things that I'm looking to change in this round in the reauthorization. I've introduce some standalone legislation and it's going to be incorporated into the reauthorization itself.

My staff and I took a trip out to the FDA just a couple of weeks ago to see how the progress of things was going. There were some high points and some low points but, nevertheless, it is so important just to have communication back and forth. The health subcommittee's oversight and investigations have been active and involved. So, I guess the good news -- even though we're coming up to a very political year where it may be difficult to get anything done -- is that I have high hopes that the reauthorization on the prescription drug user fee will make it across the finish line.

Peter Pitts:

When I was at FDA, I was the final signature on COI waivers. Occasionally, I would see an expert who seemed overwhelmingly conflicted and I wouldn't sign the waiver. When that happened, I would inevitably get a call from a senior career official at the agency insisting this person must be on the panel. I think there's a

misunderstanding that the conflict of interest issue is somehow political as opposed to technical therapeutic in nature. When you're sitting down with your colleagues to discuss conflicts of interest, is there a high level of knowledge and sophistication as to why people are on these panels in the first place?

Michael Burgess: The short answer would be no. And of course it becomes a political issue when you're considering it in a congressional subcommittee. By definition, that's what we are. That's what we do. And it was my hope to remove as much of that as possible, to remove the barriers. And you're right. There does have to be balance. But there also needs to be discretionary authority on the part of the FDA. My understanding is that it can be difficult to actually fill advisory panels. And in that case, if you're excluding more people than you're allowing in, then it's just going to make that task even all that much more difficult.

Paul Kim: It was striking that a letter came from some dozens of patient groups on your legislation, calling for it's enactment as part of the reauthorization and I'm wondering if the reason that you took on this issue in this reauthorization is not only your past experience of 2007, but the fact that you're now hearing for the first time from patient groups who are concerned about how those original provisions would be implemented?

Michael Burgess: Well, I'm over having my feelings hurt. Mr. Dingell said he was going to help me, but then he didn't. This is a problem for us in the real world and patient groups recognize that and want our help in fixing it. So, that's how I think that began. I'm certainly grateful for the support that people have provided on that.

Peter Pitts: Do you feel that – obviously it's a very political environment – that there's somewhat more of a bipartisan view towards this issue now than there has been in the past years?

Michael Burgess: There may be. I mean, it's a multi-factorial problem and there's not just one solution, but I think that's what's going to pull the two disparate political camps together and say we've got to get something done on this. So, I would say that would be more of a driver than anything individually on the conflicts issue, as much as I'd like to take credit for bringing peace to the land.

Peter Pitts: Any bridge that you can find is a good bridge.

Michael Burgess: Probably so.

Peter Pitts: Thank you Congressman.

To view the “PDUFA without the Politics” video, please visit:

<http://www.cmpi.org/about-us/events/pdufa-without-the-politics/>