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FDA's Work Plan ... the 21st Century Cures Act ... and You:
Disruptive? Absolutely. But ... How Much?

Webinar

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Speaker: **Jim O'Reilly**, professor, University of Cincinnati College of Medicine

Rotzler: Hello. I'm Craig Rotzler, senior conference manager with FDAnews, and welcome to today's webinar on "FDA's Work Plan ... the 21st Century Cures Act ... and You."

At this time, all participants are in a listen-only mode. Please feel free to prepare questions for our presenter, as we will conduct a live question-and-answer session following the presentation. To ask a question, use the question-and-answer panel, type your question in the area provided and press Enter. Questions will not be viewable to other attendees.

You may also submit them to questions@fdanews.com. Again, that's questions@fdanews.com. We encourage you to ask questions at any time, and questions will be addressed at the end of the presentation.

It's my pleasure to introduce our speaker for today.

Jim O'Reilly is a professor at the University of Cincinnati College of Medicine. He teaches public health policy at the University of Cincinnati. The author of 53 texts and 215 articles, he was quoted in a 2000 Supreme Court ruling as "the expert" on medical device law. He chairs the FDA Committee of the American Bar Association; serves on the Editorial Advisory Board for FDLI's Food and Drug Law Journal; and is a longtime program chair of FDLI conferences.

Jim, it's great to have you with us today. You can go ahead once you're ready.

O'Reilly: Thank you, Craig. Our theme today is going to be change is in the air. It's in the air in the way that perhaps a fog or a mist is lifting off the river. But we are looking carefully at how the 21st Century Cures Act, that new piece of legislation signed in December, is going to affect companies who are affected by the pharmaceutical and medical device approval panels, which today are within FDA's Centers for Drugs, for Biologics and for Medical Devices. So, change is really in the air.

And to introduce our project we look at it and say what's going to happen next? We're not quite clear. But we have to look at it in terms of how the FDA will learn from us and how we'll participate.

Because I'll be using some designations or abbreviations in this talk, I'll start by saying the FDA's Center for Drug Evaluation and Research is center stage. I'm going to be calling it CDER, or Center for Drug Evaluation and Research. The other agency portion that'll be discussed most significantly is within that CDER group. It's the Office of Translational Sciences, including a variety of the clinical and preclinical roles within the FDA.

Two other FDA centers are important. The Center for Device Evaluation and Research governs medical devices, diagnostic products, and the like. The FDA Center for Biologics Evaluation and Research, or CBER, is also involved. They're the who's who of what we'll be talking about today.

Think of this in a summertime setting. It's summertime. The swimming looks very easy. FDA is like a peaceful, mellow pool or a beach, a very nice venue. And your team, the people that are working on your

O'Reilly (cont.): pharmaceutical, your generic product, your biologic or your medical device, you're swimming easy laps around that big pool. But now there are three separate waterfalls coming down into this quiet lake to disturb your peace and quiet.

And one is the complexity of implementation of a law adopted by Congress in December, the 21st Century Cures Act. The second are the conditions and the language used as appropriations riders in the user fee legislation, which was signed or has been signed or should be signed this week by President Trump. It's called the FDA Reauthorization Act, but it basically continues the process of getting funding from the sponsors of drugs, medical device products and biologics and using that funding to staff up the FDA's ability to respond to applications.

The third process is one that's coming from the international side, from the agreement of International Conference on Harmonisation members, about changes to the clinical study reporting system which we call ICH E6(R2). Now, it sounds like a chemical formula, but the international agencies that regulate pharmaceuticals, medical devices and the like are working toward upgrading the requirements for clinical trials, and especially for the reporting and recording of the results that occur during clinical trials.

So, these three streams are coming into your process as you're thinking, "Oh, it's a summer pleasant day." And all of a sudden they're giving you these waterfalls into your peaceful, mellow venue. So, those are the streams we'll be talking about.

The waterfall that's biggest is going to be the 21st Century Cures Act. It's going to have a big impact on the approval requirements within the FDA for new applicants and updated applicants, updated applicants meaning supplemental new drugs, supplemental premarket approval applications and the like. To do a quickest summary of it, the law changes what had been for many years the requirement for controlled clinical trials. It changed it because Congress was very upset—at least the members who spoke in Congress were upset—that the process had taken too long.

And so they're looser now, they're looser, if you will, more flexible, about what it will take to gather the data and change an existing drug or device after that existing product has come onto the market. The change is a significant one because there's more flexibility in the submission of the supporting data. That submitted data is going to take the form of what's called real-world experience, and the development of this real-world experience is going to be a matter for very significant debate over the next three to five years.

FDA is also empowered to work on drug development tools, tools that are not the conventional controlled clinical trials but they're being cleared by the FDA for use in those particular product approvals. And so, back to my analogy of swimming in a very pleasant pool in the summer, the waterfall that's coming in is saying no, no, no, not stopping at the clinical trial, the controlled trial at a university hospital, but going on to payers, insurers, healthcare providers, hospitals, hospital groups and the like, and digging out from that real-world experience, and also developing biomarkers and other forms of drug development tools.

So, that's why this waterfall or series of waterfalls is affecting our quiet summer pleasant moments.

What should we try to explore today? Well, we're going to be building upon what the FDA Science Board had talked about recently. They had a meeting. They discussed new standards leading to faster product development approvals. They're talking about developing the qualified data summary. How would you, then, get this best in class qualified data summary in order to get your product to market faster?

You'll want to be attuned to the faster approval of the biomarker-based applications as well as the faster approval of breakthrough medical device applications. You'll want to better navigate when you have a

O'Reilly (cont.): product that's used in combination, a drug with a device, a device with a biologic. You're going to want to navigate those channels more carefully, because the approval of the combination product can take this channel away from the more traditional Center for Drug Evaluation and Research, or CDER, and perhaps get approval of the finished product as a combination in the Office of Combination Products.

We also recognize that FDA has been under some pressure as a result of the cancer concerns to coordinate the process for oncology drugs, and they've strengthened the office dealing with oncology in ways that will impact product development.

We'll also try to understand how the FDA is going to allocate the so-called $500 million to affect your products directly. We'll look behind that $500 million and we'll see that it's a drip here and drab there, drip here and drab there.

And we'll also look at the new role of the Office of Translational Sciences. That's the office that's going to be engaged in the science of getting clinical approvals that will govern the clinical process.

So, these are all things that are in the works for us, and they're worth exploring today.

First, what happened in December? Congress demanded changes in their review of drugs and medical devices. It demanded changes in the approval processes. And that's something big, because the last time they tried that was 1962. The 1962 legislation had created the controlled clinical trial requirements of Section 505 of the Act. And that was a day when the law was much more simple, easy to read, easy to follow. Changes are in the works because of what Congress is demanding.

I'm from a big family of seven children, so I remember mother saying, "Play together nicely." And so you'll notice as you read the history of the 21st Century Cures Act, that the Congress, particularly the drafters who were most active in the Senate Health Committee and the appropriators of funds in the House, they're pressing for better coordination of approvals within FDA.

You might want to go back and re-read what the Senate sponsors had said that was so critical of the FDA's means of operation. In the December 7, 2016 Congressional Record, for example, and in the earlier stages of the progress of the 21st Century Cures Act, there was a lot of feedback given to the FDA saying, "We don't like"—we, Congress, we, Senate—"don't like a slow process." And so that hostility, that disappointment, sent a message to the new Commissioner Gottlieb and to Gottlieb's team that approvals need to be speeded up mechanistically and not simply rubber-stamped, of course, but the mechanism for approval has to be improved and speeded up.

And so the FDA guidance that's been issued and the FDA's Science Board discussions have focused on transitioning from two adequate and well-controlled clinical studies within a university hospital setting, transitioning from that paradigm to one of much broader product approval. And so the FDA took its best shot at it, as it were, and gave that to the FDA Science Board. It told the Science Board this summer to look at the implementation strategy and give the FDA feedback.

At the same time that they were working on it, other people in the FDA hierarchy were meeting with members of Congress to talk about the user fee provision and what would be required from the FDA in order to get the additional money that the FDA wanted. User fees, in case you haven't experienced them yet, user fees are different than the average congressional appropriation.

Congress says we're going to take from all the taxpayers and give X thousands of dollars to this purpose. That's the general taxation and appropriation process. What occurs here, what's so different, is that the

O'Reilly (cont.): user fees, which have been updated in the FDA Reauthorization Act, those user fees are going directly to hiring the staff, hiring the scientists, hiring the consultants, getting the equipment, getting the space, and using that as a vehicle for review of drug applications. So, pay close attention to what the Congress passed in the user fee reauthorization, and particularly the riders or conditions that they put on it.

The Office of Translational Sciences is more important than you might have recognized in the past. The new role of the Office of Translation Sciences is to govern how the FDA sees the product approval moving from the bench to the clinical process, and that includes promoting the collaboration of regulatory review across the branches that review products and that provide technical depth and technical expertise. It's going to promote the collaboration and innovation of that regulatory review.

Then it's going to try to assure the validity of the trial design and analysis in making regulatory decisions. It's not to say that clinical trials have been bad. It's just that as we speed them up, as we get faster and faster progress of patients, we also should continue to be assured of the validity of the work being done to make sure it's translatable into really safe drugs.

Then they said let's develop this statistical approach and quantitative approaches to decisionmaking in the regulatory review process—X percent, X number, etc. Those need to be developed. That's what the Office of Translational Sciences will be working on.

They also want to help the technology transfer and the agreements between companies, associations, universities and the like. Those technology transfer agreements are going to be vital to how the FDA works with others.

And then FDA will be looking to this new Office of Translational Sciences for knowledge management. Knowledge management becomes extremely important as we are mining into the data to take out the data from which we can draw conclusions about the effectiveness or safety of a product.

So, these are factors that shouldn't be lost in translation.

Now we look at the new tools. What's going to be the tool that you'll be using as you're considering your drug? Well, the roadmap starts here. The Science Board has given its blessing to some of the new standards, given feedback to other standards that will lead to faster drug development approvals. Under Section 507 of the user fee provisions there'll be qualifications of the drug development tools that were added to the Act and will formally establish an updated, multistage process for the qualification of a biomarker or other kind of new drug development tools.

This is not your uncle's Cadillac. This is going to be a very different approach. And there'll be three process milestones for the submissions you'll be making. You'll be talking to the FDA about what the biomarker might be or what the number will be or how you're going to account for it.

You're going to do that first in a letter of intent. Then you're going to have meetings with the FDA and qualify that particular tool through a qualification plan. And then there'll be a full qualification package. So, it's a three-step process to get the FDA buy-in to the approach that you want to take.

Section 507 also includes provisions on disclosure, transparency, the submissions that you make and the FDA's responses to them. Transparency is a big change, because previously the owner of the new drug application would claim total confidentiality, not want any of it disclosed, and there we were. So, we'll be getting more detail, more numbers, more processes, and hopefully more speed.

O'Reilly (cont.): What does the drug development tool process look like? Well, let's say we're working on a relatively novel approach and we want to show that the biomarker will indicate the success of the clinical study, or we want to do an outcome assessment based upon a recap of the patients who have taken this drug at XYZ hospital. The term "qualification" means that the drug development tool and the context of its use can be relied upon to have that specific interpretation and application in drug development and regulatory review. I know we're getting into the weeds here, but the important thing is the drug development tool that you use in place of the classical, long, controlled clinical trial has a statistical basis, and you can show that it's going to be specifically evaluable in getting drug development and review.

You can also establish a process at FDA for that qualification, because you're showing the conceptual framework, the appropriate standards, the scientific approaches, and showing the FDA why that biomarker is likely to be a successful indicator or road sign or roadmap of how to get from here to there. You're also delineating what the qualification process will be. You're gathering the input of the public regarding that qualification process. Where previously it had been secret, where previously it had been negotiated, very confidential and the like, there's going to be a lot more public input regarding the qualification process.

FDA is going to be issuing public reports on the qualification process. That's great news for the competitor. It may be great news for the litigator who is suing in the case of an injury or death from the product.

And, finally, the FDA is going to be posting information about the submissions made about qualification. Again, it means a change in character from the FDA's previous aloofness, shall we say, the FDA's previous isolation. It's going to get much more active.

Why do I want you to watch this critical transition phase? Because there's going to be more out there which you can take immediate advantage, be more aware than your competitors of what's going to be done. So, if the product is going through the FDA pipeline right now and if a submission was made about an alternative biomarker or an alternative means of getting approval, and if that was sent in to the FDA over the last eight months, since December 13, then there's got to be transparency. Transparency means there's going to be more disclosure, more public awareness.

Again, the goal is to get away from controlled clinical trials rigidly managed within a university hospital setting, moving away from those to the new Section 507 qualification process for the drug development tool. You need to watch this if you are going to be involved in the approval of a drug in the next 10 to 15 years. You need to watch this, because the approval of your product may depend upon the qualification of that drug development tool.

Now, CDER, the Center for Drug Evaluation and Research, is developing a transition plan to move the existing classical older-style stuff into the newer-style stuff, the existing projects and templates for the Section 507 submissions. That could mean a big savings to the right company. It definitely will mean a change in thinking inside the company's clinical specialists.

What really matters at the FDA side, what really matters to the drug reviewers is the three endpoints that the law requires. The drug reviewers are going to look at whether the product is actually safe and effective and whether the benefits of the drug outweigh the risk. That we all know. That we can recite in our sleep. We know that Widget XYZ is going to be safe because we've had a controlled clinical trial. We know that Widget XYZ is going to be effective in the proposed use. We can extrapolate from the data in the controlled clinical trials that the benefits of having Widget XYZ will outweigh its risks.

O'Reilly (cont.): Now, the second thing the reviewer wants to know is what are you saying about the drug's use? What are you saying about the safety? How are you telling prescribers to limit or not select certain patients? Is the drug's proposed labeling appropriate? What should that labeling or package insert contain?

And then the third, less relevant to what we're talking about today but still important, is whether the methods that are used in making the drug and the controls used to maintain product quality, whether those are adequate to preserve identity and strength and quality and purity.

So, you see, those are the big factors the reviewer wants. And, like anyone that's trying to sell something to someone else, listen to your customer. This is what the FDA reviewer wants, and you, if you will, sell that drug application to them by being cognizant of what they expect and how they'll be thinking about it.

Now, how's it actually going to work for the reviewer? Well, there's no change to the electronic submission rules. You're still going to be doing the esubmissions, and we assume some form of electronic filing that matches the requirements set out by CDER or CBER or CDRH. The data's going to be presented in those files with tables and charts and summaries.

Keep in mind four items, though. The quality of the data is going to matter very significantly because of this rapid transition from the old way to the new way. So, what's the quality of our data? Secondly, what's the quality of our summaries? As we summarize it, are we presenting them accurately, are we presenting them clearly? Third, how do we deal with the patient who happens to die or happens to have a significant stroke or other problem? How are we going to deal with that adverse experience that occurs during the trial? And then, of course, because we'll be meeting with the FDA either at the White Oak Campus or by Skype or some other means, we'll be meeting with the FDA, there'll be questions from the FDA. Our responses will matter. So, this, if you will, as you're selling your new product, your expanded indication alike, think about how the reviewers are going to view that NDA.

Now we turn to qualified data summaries, a new buzzword, but one you'll be hearing for many years to come—qualified data summaries. The procedures of assembling the qualified data summary will be essential if we're looking to substitute for the controlled clinical trial. The outcome assessment, particularly the cases of looking at the healthcare insurer or Medicaid, define the outcome of the use of this drug on patients. Qualification means that the drug development tool and the context of the use of that tool, such as a biomarker, need to be relied upon to have the specific interpretation, and they need to have an application of a certain type that can be used regularly in drug development and regulatory review.

Oh, you might say, that's easy. In my case, in my drug, it's going to be obvious that biomarker X is going to show outcome Y, and that's the core of success for my product. But watch carefully as the FDA in the first couple of years establishes its processes for the qualification of the drug development tools. Again, the big picture is we're transitioning from the university, tightly controlled, IRB-blessed principal investigator standard. From that standard we're moving on, and drug development tools are where we're moving to.

The FDA is told to develop guidance that provides a conceptual framework describing appropriate standards and scientific approaches to support the development of biomarkers. It's heavy words. What do they mean? Watch what the FDA does in the qualification process. Watch how the FDA comes up with the qualified data summaries. As they do that, think about how this is going to impact on your brand, your new product, your new therapeutic benefit. How is that going to change things?

O'Reilly (cont.): Now, with biomarkers it's likely to be faster. It's likely to be faster because there'll be FDA approval of the application that contains a relation to that qualified biomarker. Or in the case of medical devices it's going to be relevant to have a breakthrough device application, a breakthrough based upon what's been observed in biomarkers. But look carefully. FDA's acceptance of certain things as biomarkers might be less than you would want. So, there may be a pushback from the Center for Drugs about the biomarkers that you're proposing.

And, of course, it's important that the controlled clinical trial had as its purpose catching bad stuff. The role of the controlled clinical trial was to catch the adverse effect or the death before it occurred in regular prescribing practices. So, it's important to show the FDA that the biomarker or the alternative drug development tool is going to catch the bad outcomes that previously would have required millions more dollars and months more effort in the controlled clinical setting of the universities' clinical trials field.

I know it's heavy stuff, but please hang with me. It's where we're going.

Now to the cell and tissue drug developments. These are called regenerative medicine advanced therapies. The regenerative medicine therapies would include the product that's taken from cells or the products that are various forms of human tissue, human cell, human tissue products. They're being taken and adapted at the cell level. The biologists are having a field day experimenting with this stuff, and it's going to be an advanced therapy.

It's going to be used for serious or life-threatening disease conditions in those cases where the preliminary clinical evidence indicates this drug has a potential to address an unmet medical need in that disease or condition. It's going to fight blindness, or it's going to fight a particular kind of cancer. It's very significant.

A designation program is underway as the FDA starts to expedite the development and the review of these advanced therapies. But you have to watch the new program carefully, because rushing in might not be quite the right thing for your product. There may be other issues that come up if you rush through, and you may find that the advanced therapy approach isn't quite fit for what you want.

FDA is pushing the envelope. It wants to get more cell-based drugs faster. And so it says the FDA will facilitate the development of standards to help foster the development, evaluation and review of regenerative medicine advanced therapies. OK. Wow. Pull on your thinking cap. What will it take for those standards, and what will regenerative medicine look like when they're through?

And it says FDA will coordinate and prioritize the development of standards and consent to the definitions of terms in consultation with the National Institute on Standards and Technology and other stakeholders. FDA will identify opportunities for the development of laboratory regulatory science research and documentary standards.

Well, the good news is it means the FDA is going to focus more on the quality of what's being done in the laboratory before it gets to humans, and the FDA is going to look more carefully at the standards that you're trying to set that would be met by your product or be met by the people using your product in the clinical setting. But it's not a simple process. And for a cell product, cell technology and the like, it's going to be very complex. We hope the FDA has staffed up to do it. We hope the FDA is capable of doing it, but we'll see.

So, think of this as the FDA pushing out there with regenerative therapies for those who want to be there.

O'Reilly (cont.): If we trace the effect of the 21st Century Cures Act on these cell-derived drug and biological products, you'll recognize several sections have helped you at the FDA. One says there should be accelerated approval for these regenerative advanced therapies. So, that's Congress saying to the FDA speed it up.

Section 3034, the FDA has to send their guidance, and the guidance will help those who are gathering the cells, using devices for the recovery, isolation and delivery of those therapies. Section 3035, FDA has got to report to Congress about what it's doing about cell and tissue and the like. And 3036, the FDA will adopt standards for this regenerative medicine and regenerative advanced therapies.

I want to put a small footnote here. This is not just the cell that's going to break brain cancer. This is not just the tissue product that's going to undo Alzheimer's. It will also impact on in vitro fertilization, which doesn't address a disease but certainly is a part of our modern biology. And so we're going to be seeing more activity from the FDA talking to tissue and cell sponsors who have mechanisms and methods and systems and the like.

Now I'm going to switch from that to patient-focused drug development. How will this patient-focused drug development affect you as a sponsor or drug? Well, let's look at this very recent user fee law, which is or has been signed by President Trump. It applies to the biomarkers. It applies to those clinical outcome assessments. And it means that FDA can rely on that tool. The tool will be good enough to rely on for an interpretation or application, and that's pretty good. That's pretty important.

And here are the PFDDs, as they're called. They're going to have to have a process for qualification. And what will the guidance look like? Well, the first guidance is going to be the conceptual framework. What standards will FDA have? What scientific approaches will FDA use to allow a biomarker to substitute for the full classical human trials?

Secondly, how do we delineate the steps in the qualification process? It's not going to be one size fits all. How are we going to delineate that process?

Third, how are we going to gather public input—hear the transparency, hear the public disclosure, hear the scientific meetings, hear the patient advocacy groups, etc.? How are we going to get that public input regarding the qualification process. You can picture, for example, the Alzheimer's Association sending a really high-level delegation to talk to the FDA on behalf of their patients and say, "We are very concerned that the qualification process should not rush through and allow us to have a less than effective product, or on the contrary sit quietly and not change, because that causes sufferings for the Alzheimer patients and their families."

Here again, Congress wants to push, push, push the FDA. So, they require FDA to issue a public report on its process of qualification. FDA will be required to publicly post information on the status of the submissions. So, you'll be able to track what your competitor is doing to qualify their way of getting to the market or getting to that new indication. That could have very significant business advantages to you if you're savvy enough to watch what's going on, and in some cases if the company you're competing with isn't very savvy about its effects. How is this going to affect me? How will this be used? These are all aspects that are, at the moment, very highly confidential and very highly competitive.

Now, beyond the 21st Century legislation that was signed in December, the user fee law, which is or has been signed by President Trump this week, is going to require careful attention. What is this patient-focused drug development going to be? It's going to bridge from the meeting with the FDA to the development of tools that are fit for a particular purpose. The tools might be a survey. They might be an interview process. They might be a phone. They might be a review of patient records. It's going to be a

O'Reilly (cont.): tool to collect meaningful patient input that says this widget is actually going to work, or it's going to say 500 people taking this benefited from it.

The FDA will be doing this, of course, in public workshops and this further series of guidance documents, and FDA will host a repository of the reference documents and the tools and everything.

Well, what does this mean, looking behind the curtain, as it were? FDA staff, who have been brought up in the tradition of the controlled clinical trials, are going to be the doorkeeper for the new changes. It's going to be a significant change of direction. And you'll watch carefully, because you'll be looking at those workshops and you'll be reading those guidance documents.

Another boring part—methodological approaches for collection of patient experience data to ensure the data are relevant, objective, accurate and representative of the intended population, including, and here's the buzzword, "methods to collect meaningful patient input" through drug development and methodological considerations for data collection, reporting, management and analysis. What's that saying? It's saying that there's going to be more attention to the meaningful response from patients to the dosing, the side effects and other aspects.

Second, methodological approaches to develop and identify what is most important to patients with respect to the burden of disease, burden of treatment, and the benefits and risks in the management of the patient's disease. You may have heard a person say, "Oh, God, if I had to do that I'd rather not be treated. I'd rather just die from it." Well, that's rather extreme, of course. But FDA wants now to identify what's important to the patient with respect to his burdens, and what are the risks in the management of the disease.

Next, approaches to identifying and developing the methods to measure the impacts to patients. How will this allow us to collect patient experience data in clinical trials? Again, we're tying back this clinical experience data in place of the tightly controlled clinical trial.

So, the methodologies, standards and technologies used to collect and analyze clinical outcome assessments will all be in there. Again, this is a big change in the way the FDA approval process has operated.

3022 says the drug sponsor can draft a guidance and ask the FDA's approval of the guidance. They can give format information for the submissions. FDA is rather vague, though, about the responses to the submissions of information. "Well, you've submitted it. I'm not sure we want it." How does the FDA anticipate using the relevant patient experience data and the related information to inform the decision that the FDA is going to be making?

Well, FDA will develop a plan, and the plan will issue draft or final versions of the guidance documents. They're going to cover these eight areas. The FDA's plan is to integrate the planned work and to align the timetables to address the overlap between the December 2016 21st Century Cures Act and the August 2017 Prescription Drug User Fee Act Model VI. So, for the patient-focused drug development we see changes, and we see the changes are quite ripe and quite active.

The side effect, of course, is disclosure, and with more disclosure of this than any time after June 12. That's, what, six weeks ago, seven weeks ago? Once that has been approved the FDA is going to make public a brief statement regarding the patient experience data and the related information. What does that mean? It means instead of giving the public the summary of product approval, which was formerly on controlled clinical trials, there's going to be a new kind of statement describing where did the FDA find this support, where did it find the patient experience data that was submitted.

O'Reilly (cont.): Now, those of you that have defended products liability lawsuits against companies know that there's a litigation vulnerability. When you discuss the deaths or adverse experience reports that are going to occur with this drug you're going to be deemed in a future liability lawsuit as having known in advance that people would die. Now, we can get into the nuances of that some other time. But keep that in mind, that your lawyer who will be representing you will be aware of and concerned about how this disclosure occurs.

You'll also want to know how will my competitors react. How about the patient advocates, the Alzheimer's Association, the Heart Association and the like? How are they going to react? How will the health insurers, the payers of health insurance, the employers, the pharmacy benefit managers, how will they react? But there's a lot more to be done.

Now, a key term in this law is the real-world evidence. Real-world evidence is data regarding the usage or the potential benefits or risks of a drug that's derived from sources other than randomized clinical trials. Real-world evidence comes from billing data, claims data, product registries, electronic health records and the like. How is this product actually being used by clinicians? If we have that evidence it has the potential to allow the researcher to answer questions about the treatment effects and the outcomes, but it would save time and money, because you wouldn't have to cycle back, go through the IRB again and file more and more of these controlled clinical trial results.

You hope you'll get answers. You hope the answers will be relevant to broader populations other than those who are in the narrow capacity of being selected for this clinical trial. Here we are getting our real-world evidence together.

Who's going to tell the people outside the FDA what counts? Well, the fox guards the chicken coop. If the people in CDER don't want to change, and they get to pick what means of proof they will trust, maybe it's going to be difficult to get these additional trials through. The FDA said its expert staff, who have expertise on statistics, data science, meta-analysis, clinical outcomes research and other areas, will be involved.

And they will, of course, develop the framework and methodologies for evaluating the use of the real-word evidence. What does that mean? It means we've got to watch carefully as the FDA works on further data guidance, because the FDA is going to be having workshops and doing drafts and counter-drafts, etc. There's going to be real money at stake, your money, as that real-world evidence is being developed. This is a significant change.

When we combine the user fee law that's just been signed or is being signed by President Trump with the 21st Century Cures Act signed in December, it's going to have a significant change, because it's going to give us an awareness of the conditions that Congress wanted as riders, limitations. We're going to look particularly at the Reauthorization Act riders such as Section 605. Congress is going to have the ability to compel the FDA to take certain actions using its conditions and money.

Read this phrase: "Innovation Account funds are authorized, but only available to FDA if appropriated every year by Congress." What that means in plain language is yes, $500 million is in the books, but no, it's not actually going to be spent unless the FDA actually appropriates it. So, yes, there will be money. No, there won't be money as much or as rapidly as people in the FDA would want.

Let's pay attention to some of the riders in the user fee bill. Section 605, for example, talks about attention to how the disease affects more than the body organ, looks also at the psychosocial impacts such as depression that's associated with a diagnosis of a high-risk disease. It's going to expand the wording of the

O'Reilly (cont.): law to include physical and psychological—including physical and psychosocial impacts of the disease or condition or related therapy or clinical investigation. So, here we see the impact has to take into account the feelings of the patients in ways that it didn't have to before, because in a controlled clinical trial you didn't have to spend time worrying about the worries of the patients. Now you do.

It also affects three aspects. The user fee law is going to talk about how real-world evidence will be channeled through pilot projects. If you're interested in joining up as a pilot project case, go do that. Section 708 is your guide.

Study of the adverse effects related to drug labeling—this has big potential in the products liability defense world. So, talk to your lawyer who regularly defends you in products liability cases about 606 and what it means.

And then who gets to be part of my clinical trial is going to change, because there's going to be an inclusion policy under Section 610 that means I want to have more classes and genders of persons in my clinical trials than had been there before. And that's a shift.

How is FDA going to use the experience data? Well, Congress uses reports as a way to force the FDA to act. It says, "FDA, we'll tell you to do this. Then we'll tell you to come back and tell us how you've done it." Congress did not want to give up on its quest to change FDA. Congress didn't want the controlled clinical trial process to remain dominant. So, it wrote in Section 3004 it wants the FDA to report on how the FDA is reviewing patient experience data and information on the patient-focused drug development, that's PFDD, as part of accrued applications. In other words, show me, your senator, show me, your representative, show me, FDA, that you're actually doing what I've told you to do to make these changes.

The irony is not everybody in the FDA wants to give up controlled clinical trials. FDA might not fully agree with the need to have this real-world variability. They might want to stick with the nonvariable or significantly less variable human clinical trial experience. It's safe, it's familiar, etc.

What's the impact of going on to define "real world"? Well, you won't be using it for the brand-new drug, because you'll be evaluating the potential use of real-world evidence for a new indication of that approved drug, or to support a postapproval study requirement.

And real-world evidence, as we've talked before, is the data about the usage, the potential benefits and the risks, that's derived from sources other than randomized clinical trials such as health records, disease registries, claims data, billing data, and the like. That's what's changing.

Now I'm going to try to read the FDA guidance. "Use of such evidence has the potential to allow researchers to answer questions about treatment effects and outcomes efficiently, saving time and money while yielding answers relevant to broader populations of patients than would be possible in a specialized research environment." What it means is the controlled clinical trials are taking too long. They'll be streamlining clinical development. They'll be helping to inform the safe and effective use of products.

Who's going to do it? The people who are scientists and data at the FDA of these variations, and they'll hold workshops. So, please, consider going to those workshops. Please take your statistician along, your epidemiologist, whoever you've got. Take them along. Expose them to what FDA is doing.

Now, could the FDA actually do all the things we've been talking about? Yes, it could, if it had a very dedicated, loyal staff; if it could recruit heavily; if it could offer packages of employment and benefits and the like; if it had years. We're going to have to wait and see, because we don't have a clear guidance right

O'Reilly (cont.): now that FDA can actually accomplish the drug development trials and the qualifications and this and that. And I hate to end with uncertainty, but I don't know whether FDA will be able to get as much of this done as you would like them to.

Circling back briefly, the international process of drug approval also is changing. The International Conference on Harmonisation has existed for years. Now the ICH is updating the norms for clinical trials. What's rolling out now in early 2017 is a process of impacting on data development and data recordkeeping. We've done a project—we've done a webinar, actually. We've done a webinar for FDAnews on the ICH E6 project. I'd encourage you to take a look at that if you have a person involved in clinical trial design so they're aware of what other nations will accept or not accept in the structure and design of clinical trials.

ICH, this international part, is the third of streams of change, the first, of course, being the user fee law, more recently; then the second being the big one, the 21st Century Act; and ICH, as well. Three streams of change will be impacting the people in your company who are involved in drug development. They need to know this.

Well, the $500 million was a great press release story, but FDA isn't going to actually get the $500 million tomorrow. FDA is going to get $20 million this year, $60 million next year, $70 million the year after that. FDA balances out the various funding streams that are available, the new money from Congress and the user fees and the like, but it's up to Congress to decide what's the appropriate amount.

These are the so-called Innovation Account funds. Congress might provide them but isn't tying itself to do that. And the funds will, of course, start and end with the user fee money. That is a package you have to submit. You have to transmit not only your NDA but also your check, your electronic check, is going to be a significant amount.

To conclude, then, tell your clients, tell your cohorts, tell your colleagues, the new drug process is changing. It isn't going to be the way it was. Your company should participate in the workshops. Don't be one that just watches. Your company should make informed comments when the guidance documents are disclosed, listed in the Federal Register and the like. Make your comments then. Work with associations and with coalitions, including the patient advocacy groups like the Alzheimer's Association, be heard more effectively in combination.

And for those guys that are wearing those green eyeshades back there in the accounting department, tell the company's financial team and the investment managers that change is going to impact inevitably on the timing of your drug to approval. It's not going to speed everything right through the tunnel. It is going to still take time, but the financial team and the investors need to understand that the changes to drug development tools, the changes to qualification, the use of real-world evidence and the like, is going to have a timing effect. And to the extent that your financial team wants to get that product on the market yesterday, wants to get the income flowing immediately, it is what it is, and you get what you get.

But that's how these three streams come together, and that's the challenge you're going to face. Even though it is the quiet midsummer, think of those three waterfalls coming into the pool and making it more difficult to do what you thought would be a lazy summer afternoon.

I'll turn you over now to Craig, and Craig will host the questions, if any of you have questions. Craig, back to you.

Rotzler: Thank you. Ladies and gentlemen, now is your opportunity to have your questions answered by our presenter. Please remember this portion of the conference is also being recorded.

Rotzler (cont.): [Instructions given for calling in or submitting questions.]

Jim, thank you. I did have a question. You were talking about drug development tools. Is there a similar tool for devices or device development tool or guidance?

O'Reilly: There will be for things that are implanted and particularly for things that are diagnostic or adjuncts to diagnostics. Those drug development tools will have as their parallel the diagnostic tool being not squarely that particular entity that you're aiming for but something so close to it that if you have (a) you probably have (b); if you have (b) then you're got the disease. We'll be looking at ways in which the analog, if you will, is going to be close enough that people will construe it, will assume that if you have (a) then you'll have (b).

Rotzler: Thank you.

[Instructions given for calling in or submitting questions.]

Jim, I was wondering if you could provide any examples for biomarkers.

O'Reilly: Yes, the biomarker would be one that's tailored to the particular—the determination you're trying to make of the existence of a disease. So, if we measure, let's say, cholesterol, and we say there's probably a vascular problem if a person has cholesterol over a certain level or is a certain age, then you're going to get into it. But there's no assurance that a particular biomarker is right. You're going to have to convince the FDA that the biomarker is properly qualified.

Rotzler: Thank you. We have a question coming in. If one is filing a new IND, will Phase II studies be impacted?

O'Reilly: Yes. If one is filing a new investigational new drug application, one probably knows already from scoping studies, Phase I, the laboratory, the bench, the animal-type studies, you probably know that you're going to get into a variety of ways of proving that this actually works in humans. So, yes, if you're filing a new IND you'll look ahead to what the FDA's going to want in the pre-Phase II meetings, and you'll be convincing the FDA that since they had approved the drug development tool for Pfizer or for GSK or someone, that that's a precedent and that the FDA ought to use the same measurements, if you will, in the Phase II studies for that product.

When you're filing the new IND you're very concerned about the cost, and the cost that you've put together is typically what you're paying to the clinical investigator, her or his institution, the paperwork people, the team, the documents, etc. Maybe you can cut some of that money out and instead use a particular marker that says if we have A1c then we're likely to have this form of problem.

Again, we're predicting. We're predicting based upon the quality of the science that's been done up to this date. But we don't know from a particular day to day what the FDA team is going to accept. Will the FDA want more? Will the FDA insist on more? We just don't know, because these will be highly—I can't say individualized—these will be tailored, these are going to be much more tailored than have been the case in the past.

In the past you'd show up. Here's your IND. And the FDA would say, well, show me the investigator brochure. Show me the number of patients. Show me the enrollment. Show me where you're going to be doing it, etc., and then we'll go on from there. And you might be able to say instead of doing that, here is the study of what Humana has paid out, here's a study of what Illinois Medicaid has paid out, etc., etc. So,

O'Reilly (cont.): doctors are actually prescribing this type of material for this type of use. We should get full consideration from the FDA for that real-world evidence.

Rotzler: Thank you. We had another question. We're moving away from controls, controlled studies, or getting less controlled studies. What kind of impact is that going to have on IRBs?

O'Reilly: There's a particular provision in the 21st Century Cures Act that allows the consolidation of a nationwide study or a large multicenter study into one IRB. As a result, there will no longer be the delay of six different IRBs blessing the test. And unless there's something very peculiar, like a surgery or something like that, it's very unlikely that the local IRB will be involved at all. They may be given notice, but they will not be the parent IRB, which will be giving the blessing to the research. So, it'll reduce the number of IRBs that'll be involved in many of these clinical trials.

Rotzler: I don't know if you know the answer, but how many IRBs would be equipped to kind of handle this?

O'Reilly: Oh, I would guess 25 to 30. There are hundreds of IRBs, but I assume that the more sophisticated, the larger the institution, the wider the scope of its participation, it's likely that these are larger entities, the Mayo Clinic's IRB or Massachusetts General's IRBs or UCLA's IRBs. They're not likely to be the smallest IRBs and they're not likely to be the ones out in the more distant areas.

Rotzler: Well, thank you. You gave us a lot of good information. If we wanted to keep abreast of this, any tips where we can go to get more information—logs, websites, conferences or periodicals that you like?

O'Reilly: I recommend reading FDAnews. It's got a very good group of people. I'm sorry. I know that's the sponsor. But they're a very good group of people and they're staying up on it.

The Food and Drug Law Institute's conferences are also very timely. My group, the American Bar Association FDA Committee, has meetings for lawyers in the food and drug law field that might be relevant. The associations that are into that particular area, the Alzheimer's Association, the Heart Association and the like, they've got groups.

So, put your—cast your net out widely and you're very likely to find a lot of people interested in this, particularly when two entities within this sphere of cardiovascular products, when two entities fight, it's going to be very interesting. They might fight over whether something is an appropriate biomarker. They might fight over whether something should have been done through controlled clinical trials. They're going to be, in some cases, in dispute, and you want to watch them.

The hidden factor, of course, as I mentioned two or three times, is the products liability lawyers who are later going to say you did not do enough to test this product. If they say that loudly enough and vigorously enough and if courts start to agree that they didn't do enough, there could be millions of dollars at risk. And so the companies and their lawyers should look carefully at the implications of giving up on controlled clinicals or accepting a weaker form of biomarker.

Rotzler: Thank you, Jim. That looks like that's all the questions that we have for you for today. Any additional remarks before we wrap things up?

O'Reilly: No, just recognize we're at the start. We're at the start of new pieces of legislation. And I'm sure that if we'd been doing this in 1962 we'd be saying, "Oh, my God, I don't know what's going to occur as a result of the adoption of this new 1962 requirement for controlled clinical trials." We're going to be in

O'Reilly (cont.): a new world, and you, the people listening to me today and the people listening to the tape, you're ahead of the game. You're going to remain ahead of the game as long as you remain informed. And that's our point. Watch what's happening. Don't wonder what happened.

Rotzler: Thank you very much. On behalf of FDAnews, I would like to thank our participants for joining us today.

Be sure to fill out the survey at the conclusion of this webinar. Your feedback is very important to us. This now concludes today's webinar. Have a great day, and I hope you join us again in the future.