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Preparing for the LDT Regulation

CLIA Won't Satisfy the FDA

Webinar

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Speaker: Dan O'Leary, President, Ombu Enterprises, LLC.

Operator: Hello and welcome to "Preparing for the LDT Regulation: CLIA Won't Satisfy the FDA." This webinar is being presented by FDAnews.

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I would now like to introduce our speaker.

Dan O'Leary is the President of Ombu Enterprises, LLC, a company offering training and execution in Operational Excellence, focused on analytic skills and a systems approach to operations management. Dan has more than 30 years' experience in quality, operations, and program management in regulated industries including aviation, defense, medical devices and clinical labs. He has a Master's Degree in Mathematics. He is an ASQ certified Biomedical Auditor, Quality Auditor, Quality Engineer, Reliability Engineer, Six Sigma Black Belt and is certified by APICS in Resource Management.

I'll now turn over the floor to Mr. O'Leary.

O'Leary: Thank you very much, and welcome, everybody, to our presentation today on preparing for the LDT regulation. As you know, we'll take questions at the end. If you have a question about a particular slide, note down the slide number which is down at the bottom of each slide, and when we do the questions we'll be able to go back and look at the slide and address the question in context.

Here's an outline of what we're going to talk about in this presentation. We're going to look at the issue. The issue is FDA's decision to regulate laboratory developed tests, and that is going to take us into a discussion about what FDA views as the laboratory developed test and what it is that they would like to cover.

O'Leary (cont.): Then we're going to get into a lot of the issues that are going to start to arise, and there's a number of timelines that we're going to end up talking about. So from the time the process starts for FDA, there's going to be an initial six month period in which a number of things are going to have to happen. Then that's going to take us into a subsequent understanding of how FDA regulates medical devices, and that's going to be risk classes and then all the appropriate controls. Then there's going to be other regulatory requirements that the labs are going to have to implement. And that will take us to a summary and we'll open it up for questions.

So here's the issue. FDA has always asserted that it has the right to regulate laboratory developed tests because they are a particular kind of medical device. And FDA has said that up until now, FDA has chosen not to regulate them, and this is often called enforcement discretion. So FDA might say, well, yes, we can enforce the regulations, but we choose not to because of a particular reason.

FDA has now changed its position. It intends to regulate most if not all laboratory developed tests. And that means that the laboratories who make laboratory developed tests are now going to become device manufacturers, and they're going to fall under a different regulatory system than what they've been used to in the past. They're going to fall under the FDA regulations in addition to continuing their laboratory operations, which fall under the CLIA regulations.

So the difficulty for the labs is that there is going to be two different sets of regulations that they've got to follow at different aspects in developing and using a laboratory developed test. And that's what we're going to explain today.

The approach is that FDA is going to regulate laboratory developed tests through guidance documents. The idea is that the laboratory developed tests are going to come into the device regulatory scheme in a phased-in approach. The position from FDA is that they already have all the regulations in place in order to regulate medical devices. LDTs are just a particular kind of medical device, and so consequently, there are no new regulations required. So the guidance documents are going to not impose any new requirements, but rather explain how the existing requirements are phased in and applied in this particular application.

So there are no new regulations. There's nothing that the laboratories are going to have to follow that FDA has written that's going to be specific to LDTs. So part of this transition means that different parts of the device regulations are going to apply over time. There's going to be a phased-in approach over a number of years.

FDA is going to continue to use enforcement discretion in a couple of cases, so there are certain combinations of LDTs and parts of the regulations in which FDA is going to say, yes, this still is going to be covered by some kind of enforcement discretion, so we're not going to regulate those. So we'll look at some of those as well.

Now, FDA's position has some detractors—I think that's the polite way to say it—including people who assert that FDA does not have any legal authority to regulate LDTs. FDA claims that it does have the legal authority to do this. The legal authority was granted by Congress when FDA got the legal authority to regulate all medical devices. So FDA's position is that this is just another kind of medical device.

What that means is that it's probably going to take an act of Congress to change any approach that FDA has for LDTs. FDA was required to notify Congress when it started this process, and FDA did do that modification. There are a variety of bills going through Congress. It's not clear what the final version is going to look like, if there even is a final version. But it's unlikely that Congress is going to do anything before FDA's plan to start enforcement. So my recommendation is that you should not anticipate a

O'Leary (cont.): change in direction. That if you're involved in the laboratory, then you need to start to plan the implementation of what are going to be, for you, new sets of requirements. Your best approach is to assume that all of this is going to happen and start to prepare for it.

Now in this presentation we're going to look at a couple of hypotheses. The first one is to understand the use of LDTs. These are laboratory tests that are run in a laboratory. In many ways, they're not unlike the existing tests that are done in the laboratory. The difference is that these tests are developed in the laboratory and run in the laboratory, whereas other tests are developed outside the lab but run in the lab.

I'm going to assume that participants in this presentation don't have a working knowledge of the device regulation, and so we're going to explain some of those things. The device regulations can be very complicated, so we're not going to get into all of them in a lot of detail.

The presentation is following the draft guidance documents. There is a comment period. So when FDA issued the draft guidance document it asked for comments. The comment period has ended. Generally sometime thereafter, FDA will publish the final version of the guidance document, and that's when the clocks are going to start.

I have no doubt that FDA is preparing the final versions, and they have also been quite active in some congressional hearings. They recently published the report explaining 20 cases in which there were problems with laboratory developed tests, with the expectation that FDA will be able to manage some of those problems. So there is no doubt that FDA is actively working on this. What we don't know is when the final guidance document is going to be published.

Now there are two guidance documents that we're really going to end up talking about. The first one is the framework, so it's the framework for regulatory oversight. And the second one is FDA notification medical device reporting. You can download them from the FDA website. Go to www.regulations.gov and put in this docket number that I've given you, and you'll be able to read all of the FDA's documents and any comments that anybody has made on the draft guidance documents. They're all there. They're all public information.

So when you go to this website it will ask you for a number of things. One of them is the docket number. Put this docket number in, and you'll be able to get to all of the comments and all of FDA's documentation about what it is that they plan to do. As I said, the guidance documents are still in draft. They're not in the final form yet, but at some point there's no doubt that they're going to get published.

Now let's look at FDA's view of LDTs, and this is really important. The idea here is that initially, FDA believed that it wasn't worth anybody's effort to regulate LDTs simply because they were very limited in use, very limited in scope. They were often built in a hospital laboratory, for example, for one or two or a small number of patients, and it didn't seem to FDA that it was worth getting in the middle of all of that.

That's all changed. Large laboratories now do LDTs on a regular basis. They used to be often called home brew. The concern that FDA has is that there is going to be a development of medical device activities in the lab and a running of tests in the lab. And FDA is going to assume that the lab is going to therefore run with two distinct parts. One part is going to develop the test; the other part is going to perform the test.

So the easy way to think about this is that as these regulations come into effect, the laboratory management needs to make a clear organizational distinction between the two parts. This is often called a bright line. You need to be very careful to make sure that laboratory operations and test development and manufacture stay separate. And what's going to be really important is that the clear regulations are not going to apply to development and manufacture of tests.

O'Leary (cont.): The easy way to think about it is this slide. For some reason the part of the left didn't come through, but the part on the left is inside the laboratory. It's test development. In other words, you're going to develop and manufacture tests. And then there is this red line between that side of laboratory and the other side of laboratory that performs the test. So the group on the left is going to be developing tests and they're going to fall under the FDA's device regulations. The group on the right is going to perform the test and they're going to fall under CLIA regulations.

Then at the bottom is another box, companies that develop and manufacture tests. These are not laboratory developed tests. These are typically the IVD manufacturers, so the laboratory may be buying tests from IVD manufacturers. They are regulated by FDA as device manufacturers, and in essence, that's what's going to happen in the lab on the left hand side of the red line. The left hand side of the red line is going to be a device manufacturer. The right hand side of the red line is going to be a laboratory that performs tests and reports results. On the left hand side it's going to be FDA regulations for devices. On the right hand side it's going to be CLIA regulations for laboratory operations.

So let's look at what an LDT is. Now this is FDA's view, and this is very important because this is going to be the basis for the regulatory system. So a laboratory developed test is an IVD. It's an in vitro diagnostic intended for clinical use, and designed, manufactured and used within a single laboratory.

It's the design and manufacture that FDA is going to regulate. The use part is going to be on the CLIA side. A single laboratory refers to a facility with a single CLIA certificate. An LDT should only be designed, manufactured and used by labs that meet the requirements for high complexity testing.

That's the way things are looked at today. But in essence, what's going to happen is that all of those issues that involve high complexity testing, they're all going to remain, because they're on the CLIA side. But the development and manufacture of the LDTs is going to fall under the in vitro diagnostic regulations, and that's what's going to make them devices. So this is what FDA's view is. That these LDTs are a particular kind of IVD, and IVDs are a particular kind of medical devices.

So what is an IVD? Here's a somewhat complicated definition. We're not going to go through all of them, but IVDs are reagents, instruments and systems used to diagnose diseases, etc., for humans. So veterinary products are excluded from all of this. These products are devices as defined by congress in the Food, Drug and Cosmetics Act. They could also be biologics. But the idea here is that as far as FDA is concerned, these in vitro diagnostics are devices as defined by Congress. And then the LDTs are a particular kind of IVD. So that is going to bring into force all of the device regulations for LDTs. And that's what FDA has been saying, well, we've not bothered to enforce them, but we're changing our position.

So here's the picture. In the inner circle are the LDTs. And as we've said, LDTs are a particular kind of IVD, and IVDs are a particular kind of medical devices. So consequently, FDA is saying, well, they haven't bothered with LDTs before, but now they are. And that's the whole issue that we're going to explore.

Now one of the things that's really important is to understand what FDA considers out of scope for the definition of an LDT. So there are some things that FDA is already saying, doesn't make any difference, these are not LDTs. They are already IVDs and the issues that we're going to talk about do not apply here. There already medical devices and should be regulated as such.

So, a company develops an IVD in one lab and transfers it to other labs the company owns. Now many of these companies have a large number of laboratories in a network. If an IVD is developed in one lab and transfers to another lab, then that means it is not being run inside one facility, and therefore it doesn't

O'Leary (cont.): qualify as an IVD. If a company were to do that, then it automatically is a medical device and none of this is going to apply.

The second case, an academic institution develops a test, licenses it to a CLIA lab that produces the test, and offers it for clinical diagnostic results. So the fact that it was developed outside the lab is what's going to trigger the in vitro diagnostic regulations. So developed outside the lab but manufactured inside the lab. Well, you haven't satisfied all of the parts of the regulations, and so consequently it's not going to be an LDT.

A laboratory contracts with a third party manufacturer to produce a key component of the IVD. Well, this means that the whole thing is not being made inside the lab because there's a key component that's being made outside, so that can't be an LDT in FDA's view.

A laboratory contracts with a specification developer to design a new test that's transferred to the lab. A specification developer is a company that develops—this is a technical term in the FDA regulation—a company that develops a medical device but then contracts with somebody else to manufacture that medical device to the original company's specifications. So that means that those original specifications came from outside the lab, so again, that's not going to be an LDT as far as FDA is concerned.

Now, we needed some clarifications. If a lab has been offering an IVD as an LDT even though it doesn't meet the requirements, FDA is going to say, well, we're going to assume it's already an LDT. We're going to bring it into the framework, and they're going to exercise enforcement discretion temporarily. The idea is that if the lab has already thought of this as an LDT and it's been managing that way for some period of time, then FDA is going to say, you've been doing this as an LDT in good faith, so consequently, we'll accept that. What this means is that if you want to make sure that FDA understands your position, you probably want to document what you've been doing with this LDT that doesn't meet the new understanding of what an LDT is.

If a lab offers an IVD or LDT as a direct to consumer test, then FDA is not going to apply enforcement discretion. They are going to insist that these are devices and should be in the regulations. And in the last few weeks there's been letters from FDA to a couple of companies that are offering direct to consumer tests, and FDA is saying, these are not laboratory developed tests. You've got to bring them under the device regulations. And please stop offering these tests until you get all of this sorted out.

There's probably been about six companies that have gotten letters like that. One of them, the well-known one, is 23andMe, but they've gotten all of that issue put behind them. But in the last month there's been two or three other companies that have gotten similar letters.

Now FDA intends to continue enforcement discretion in full for certain LDTs. And enforcement discretion means registration, listing, adverse event reporting, premarket review, quality systems. We'll talk about what those all mean.

Laboratory developed tests that are used exclusively for law enforcement, so forensic tests. Exclusively for forensic tests, so that's going to be a big word. And LDTs used in these labs for histocompatibility tests for transplantation; FDA is going to allow enforcement discretion for those as well. So if you have any of those tests as an LDT, you need to document in full what it is that you're doing so that you can know that they're going to be excluded. And you can bet that FDA is going to ask you about those things.

Now let's look at some of these timelines. There are multiple timelines and they tend to be complex. So we're going to have to look at a couple of these things and we'll explain them.

O'Leary (cont.): One timeline covers the premarket review, and this is the mechanism by which a device manufacturer is going to get—the word I'm going to use here is permission—to put the device on the market. And the reason I'm using this word is that there's a couple of technical terms that we need to understand. So rather than using those technical terms yet, I'm going to just use this generic word, permission. The other timeline covers other regulatory requirements of medical devices.

Here's the legal timeline. There was a change to the Food, Drug and Cosmetic Act called the FDA Safety and Innovation Act. Everybody calls it FDASIA. Congress passed a law that says that FDA must give 60 days' notice to Congress before they go down this path. FDASIA went into effect on July 9, 2012. A little more than two years later, July 31, 2014, FDA sent the formal notification to Congress, then waited out the 60 day period and then published the draft guidance documents that we're going to talk about.

Those also went out for comment and the comment period was set to be 120 days. Now if you want to comment on them you still can. FDA doesn't have to deal with the comments. But they're still on the docket and somebody will look at the comments, even if you submit them after the 120 day period, but before the final guidance documents are issued.

The comment period ended on Feb. 2 of this year, so FDA has been digesting the comments, rewriting the guidance documents and so on. And at some point they're going to publish them, and that will be the final guidance document and that's going to start another timeline. So the clock for the other timelines begins on the day of publication of the framework guidance document. Comment period ended on February 2nd. They can publish the final draft at any time. They might get it out before the end of the year. Whenever that publication day comes, that will star the clock, and we'll have to look at some of these other clocks.

I told you that these are all going to get phased in. So the first thing that's going to happen is the final guidance document is going to be published. I'm telling you what's in the draft guidance documents, and some of this may change in the final, and we don't know. But the idea is that within six months of publication of the final guidance, all the laboratories are going to notify FDA about all the laboratory developed tests that they currently have.

Now this notification is a special case that FDA is developing. It's basically a form that you're going to fill out, a blank form. It's a couple of pages long. It's not really a form, it's answering a bunch of questions, and you're going to have to submit that for every LDT that you currently have in your inventory that you're using in the lab. And this is how FDA is going to find out what all the LDTs are out there, because right now, there is no list. So FDA is saying to the labs, you've got six months to tell us what all the LDTs are that you have in a particular format. They want specific information.

Also in that six month period, the labs have to start to implement medical device reporting as required by manufacturers. Now the labs should already be doing medical device reporting because they are user facilities. So if they're utilizing IVDs, then they should have all the system in place, IVDs meaning the kind that are purchased from another company. They should have all the systems in place to do the reporting. So that's six months from the date of publication.

After six months, the lab is going to notify FDA of any new LDTs or any significant changes in existing LDTs. And FDA is going to use that information as well. Then starting 12 months after the guidance document, premarket review requirements are going to begin. So what this means is that in the first six months you're going to notify FDA of all the LDTs in all of the labs. And then at 12 months, FDA is going to start requiring the labs to provide all of the information to FDA to make it regulated as a medical device.

O'Leary (cont.): From the lab's point of view, which is the point we're taking here, there's really three periods. There's the six month period following publication; there's all of the activities that go in the lab up to the first premarket notification; and then there's all of the activities after the first premarket notification. So the idea here is that you're going to have a six month period in order to notify FDA. Then 12 months, labs are going to start doing their premarket submissions. And then once you do the first premarket submission, you're going to be ready to implement all of the device regulations.

So let's look at this initial six month period. We want to make this distinction between notification, which is a system that FDA has put together particularly for this LDT case, and registration and listing. They are two very different things.

FDA is going to ask the labs to notify FDA about all the LDTs. For labs that notify, FDA is going to exercise enforcement discretion for original registration and listing. Remember, this is the six month period. For labs that don't notify, FDA is going to enforce all of the regulations. So you get a little relief—you actually get a lot of relief—by doing the notifications. If there's a large number of LDTs in your lab—I know of some labs that have thousands of LDTs—you should start gathering all that information together now. The questions that you have to answer are in the back of the draft guidance documents. It's probably going to be a lot of work to pull all of this stuff together.

Now implementing MDRs for a device manufacturer. Labs are user facilities already, and should have already put in place part of the medical device reporting in Part 803. LDTs are also going to make the lab a manufacturer, so the lab has got to implement the manufacturer's portions of Part 803. And one of the things that's going to be curious is that the lab, if it's dealing with an LDT, may have to report it as a manufacturer and report the same event as a user facility, because the lab is actually going to be both.

Registration and listing. The idea here is that when you register you're going to tell FDA that you are in the medical device business. So you're going to submit a registration to FDA. It's going to cost you some money to file the registration. Then you're going to have to reregister every year, so this is an annual requirement.

You also have to list all of the devices that you're involved with. So if you're a medical device manufacturer, then that means that you're involved in medical devices, so you have to tell FDA which ones they are. That's called listing.

The listing is going to be updated when you make a change. Registration is an annual requirement. Listing updates are required when you make some changes.

During this transition period, labs are going to have an option to notify FDA in lieu of registration and listing. What this means is that you can do the notification form without registering and listing and paying all of the fees. During the transition period, FDA is going to emphasize enforcement discretion for registration and listing. So you notify FDA that you're making all of these medical devices that are LDTs, and because you've done that, FDA is going to say, then we're going to continue enforcement discretion. This is going to be really important in your implementation strategy.

Now as I said, FDA requires registration. That tells them that you're involved in the device business and what you do. And listing informs FDA of the specific devices that are involved, and the requirement is that you must do this electronically. So you go on to a certain portion of the FDA's website, pay the fees, answer all the appropriate information. You've got to do it electronically unless you've asked FDA for a waiver and they've granted it, and those waivers are hardly ever granted. So consequently, you're going to have to set up all of that mechanism for registration and listing at some point for all of these LDTs.

O'Leary (cont.): You're going to name an official correspondent. This is going to be the person who is responsible for managing all of this registration and listing activities. The official correspondent is going to give all the registration and listing. It's the person that is going to receive official correspondence from FDA. If FDA asks, then the official correspondent has to be able to provide the names and other contact information of all officers, directors and partners in the company, and receives communications from FDA by email or postal mail, depending on how their system is set up. So you're going to name a person who has the responsibility to do all of this, and you're going to tell FDA who that person is by name, contact information, telephone number, email address and so on.

You're going to resister. Firms must register annually and pay a registration fee. The first one is due within 30 days after you put the first device out there. Then it's got to be submitted every year between Oct. 1 and Dec. 31 if no changes have occurred.

For fiscal year 2015, the registration fee is going to be $3,646. There's a complicated algorithm by which FDA figures this out. Congress passed a law to tell them how to do that. The fee amounts are updated every fiscal year so it could change. And so what this means is you need to plan on about $4,000 to $4,500 a year for the registration feel.

Listing. This is where you tell FDA what devices you're involved in. So you're going to list the devices and whether or not the output of the establishment enters interstate commerce. So what this means is, you're going to tell FDA all the devices you're involved in, and then you're going to keep this list updated. So if you introduce a new device, if you remove a device that's previously listed, if you bring it back, then you're going to keep the listing updated. And there's a requirement that you do this at least two times a year if there are any changes. FDA will accept changes at any time, but there are at least two times a year when you need to make sure that your listing is correct.

FDA is going to inspect medical device manufacturers. They do inspect medical device manufacturers. The idea is that they're going to inspect them once in every two year period. So this is the law. If a company makes a Class II or Class III device, it's inspected at least once in the two year period starting from the date of registration, and then at least once in every successive two year period thereafter.

Now, this is for FDA. This is not CLIA. CLIA inspections are not going to satisfy this requirement. One of the problems that FDA has had is that there have been more firms than FDA has resources to inspect. So they don't always make the two year period, but they're certainly going to be looking at the labs in all of this initial stuff, so you can expect there's going to be an inspection as soon as you register. There's even another case we're going to have to talk about.

When they come in to inspect, they're going to look at something called a quality system inspection technique. It's the guide by which FDA investigators do their inspections, and it covers a bunch of parts of the regulation: medical device reporting; corrections and removals, think of this as the initial step in a recall; registration and listing; quality system, that's the quality management system you have to implement; medical device tracking. It's unlikely that LDTs and IVDs are going to be involved in medical device tracking.

You can download this book from the FDA website. I've given you the URL at the bottom of the page. It's got a set of flowcharts and a description about what the FDA investigators are looking for. You need to make sure that you have that, that you've gone through it. You're going to have to develop internal quality audit programs. Your internal quality auditors should start off using QSIT to build their audit program.

O'Leary (cont.): Medical devices are subject to an excise tax, and this excise tax is administered by IRS, not the FDA. IRS uses information from FDA listings. All of the FDA listing information is public, so IRS just goes to the FDA website to find out who is making medical devices, and then they expect the medical device manufacturers to pay the 2.3 percent excise tax. It's not clear how this is going to work for the LDT case, because usually what happens is the expectation is that the medical device is being sold to another company.

So it's not clear what's going to happen. And there is some indication this week that Congress may do something with the medical device excise tax in the new bill that's going through to fund the government. So this one is pretty much up in the air, but you need to make sure that you keep on top of it.

You're going to have to make an initial notification. Remember, this is what happens in the first six month period. Labs are going to notify FDA of the current LDTs, and the notification is for each LDT. The details are in the guidance document. There's about 14 data elements that you have to provide, and they're going to be things like what is the target population? All of those things you think about for laboratory tests. So for every LDT that you make, you're going to have to answer these 14 data elements and then send it off to FDA.

Now one of the things that's probably going to be happening in the guidance document, the final version, is exactly how you transmit this to FDA. It's probably going to require you to go through something called the gateway, and that means setting up additional accounts and managing another submission path into FDA. So we're going to have to wait and see.

New LDTs that are offered more than six months after publication are also subject to notification. Or if you make significant changes, then you're going to require another notification. So you're going to keep this notification list current until you actually make your first premarket submission. And FDA is going to say, as long as you keep us current on the notification and you haven't done the submission, we're going to continue to exercise enforcement discretion.

Now let's talk about this medical device reporting issue. The reporting regulations are in Part 803, and one of the requirements is that device user facilities have to do this reporting. A lab is a device user facility, so if you are bringing IVDs from another company into your lab, then you need to have already set up the device reporting requirements for user facilities.

The problem is that LDT manufacturers are on one side of the organization, designing and manufacturing LDTs, so they are device manufacturers. On the other side of the organization they're actually using them, and so they are going to be user facilities. That means that if you have a problem with an LDT, you're going to end up having to report it two times. Now you can combine the reporting, but you're going to have two different sets of reporting criteria.

These are called medical device reports. There's a lot of details in them. You're going to submit the reports within 30 days of becoming aware of a reportable event. This is the manufacturer's side. If you have to take remedial action, then you've got five days from when you become aware. And if you submit a report and it's not complete because you don't have all the required information, then you've got to submit supplemental reports.

FDA wants the reports on time, even if they're incomplete. It will be a violation if you wait until you get all the information before you make the first reporting. So the important thing is to make the 30 day calendar, not to submit a complete report. You're going to fill in the information later as you learn it.

O'Leary (cont.): You're also going to have to build a set of procedures. And the procedures are going to link into the complaint system that you're going to have to develop in QSR, and then you're also going to have to do a lot of recordkeeping as part of MDR. So this has got to be in addition to what you're doing as a user facility. So you're going to create MDR event files. These are going to be where you keep all of the information about anything that you've done with an MDR. Whether you end up reporting it or not, you still have to keep a file that explains what you did.

Reportability—deaths, serious injuries or malfunctions that could contribute to death or serious injuries. And for manufactures, they must submit using electronic means. So user facilities can send in the form, the 3500A form. Manufacturers cannot. They have to submit all of this stuff electronically. So that means that you need, as an LDT manufacturer, to set up the whole MDR system, the electronic version of the MDR system.

Five day reports. If you're going to initiate remedial action, then the clock changes from 30 days to five days. And then if you have incomplete reports, you're going to fill them in with supplemental information. And from the time you learn new information, you've got one month in order to update the supplements, in order to submit the supplements.

This is a diagram of the reporting types between manufacturers and user facilities, and there's a couple of things that are going to give you some grief. If there was a death or serious injury, then the manufacturer has got 30 days, but the user facility has got 10 days. You're both the user facility and a manufacturer. So in essence, you're going to have to follow the 10 day rule.

Malfunctions, remedial actions and FDA requests, those are not typically reportable for user facilities, but they are going to be reportable for manufacturers. So you're going to have to expand your system and build a set of procedures that cover both roles, manufacturer and user facility.

Electronic submissions for manufacturers started August 14th. The issue is that you're going to have to set up all of these electronic files, go through the electronic gateway and set up a large number of accounts. It's fairly complicated, but not extraordinarily hard. There's just a lot of things going on. You can expect that it will take, from the time you start until the time you're actually ready to submit reports, you should expect between three and four months of calendar time. Now you're not doing things for three or four months, but you're going to have to get some information, submit it, wait until FDA acknowledges they've got it, and then the next step and so on. So three to four months is what most companies have found.

And again, you're going to have this conflict between manufacturer requirements and user facility requirements, so you're going to have to switch to manufacturers' stuff and include the user facility information in the same report. So that's going to be an interesting situation.

If the event evolves on LDT, then both aspects are going to be reportable. So the draft guidance document gives you some information about filling out each section of the form. And presumably ,they're going to update the electronic submissions. User facilities can submit electronically today if they want, so presumably, the final guidance of this document is going to talk about EMDRs.

Now this is a list of the differences in the form. The form is organized in a set of blocks, and so this is going to give you some information. And notice that they don't line up. So the manufacturer and the user facilities have different sets of requirements for reporting.

One of the things that you have to worry about is corrections and removals. So now, as an LDT manufacturer, you're going to have to submit corrections and removals. And this is a case where you've

O'Leary (cont.): shipped a device and you found a problem with it, and you have to make a change. So think about on one side of the lab you manufacture a device, send it over to the lab side. You find a problem. You pull it back to do some work on it. That's going to be either a correction or removal. All of those are going to have to be reported to FDA, and there's a 10 day clock there.

Regulations in Part 806 have got a bunch of other requirements, and they're described in the draft guidance document as well. So you're going to have to set up this part of the regulation. That's going to happen in the first six months.

Let's talk about risk class and controls. FDA classifies medical devices, including IVDs, by risk. There are three risk classes, I, II and III, and the Class I is the lowest risk devices. There are about 14 specialties in this system. All the LDTs are probably going to fall into the same specialty area. Three risk classes, and then every device is going to get a three letter product code, and there are thousands of these three letter product codes. You have to know what the three letter product code is in order to know the details about how to do the submissions and so on. The difficulty is that since FDA doesn't know what all the LDTs are, they're going to depend upon the manufacturers in order to do the notification so they can get this whole system set up.

The specialty determines the panel of experts, and they're going to assign the risk class. Then that risk class, along with the product code, gives you all the information you need to know in order to put together, what are the requirements that you have to satisfy for the submission. And so FDA is going to end up actually augmenting these panels of experts as they get all of the notifications in order to be able to handle the workload.

There are three classes, I, II and III, and Class I devices are the lowest risk and have the least controls. Class II devices have more risk. They've got all the Class I controls plus extra stuff. Class III devices are the highest risk. They've got the Class II controls plus extra stuff. So this is built as a cumulative approach. FDA is going to tell you the risk class of your device, and then you're going to have to satisfy all of the controls.

Here are some things that are usually in the controls: registration; listing; adverse event reporting, those are MDRs; quality management system, that's going to be the quality system regulation; labeling, you're going to have to put specific information on the device; and then premarket review. This is the "permission" that I talked about.

The form it takes depends upon the risk class. Usually it's not required for Class I devices, the lowest risk. For Class II and III, different sets of requirements. So premarket notification and premarket approval, they're different. And premarket approval is much more extensive than premarket notification, and usually goes only with Class III devices, but not in every case. So there's some exceptions.

Now, in general, premarket approval is going to demonstrate the device is safe and effective. This is usually called a PMA. Then when FDA comes back and says, yes, then that's terms approval. So this is one of the technical terms where I've used the word permission before. So this is called approval.

Premarket notification, you're going to demonstrate that the device is at least as safe and effective as a device that's already legally marketed. This usually applies to Class II devices. The process is usually called the 510(k) because that's the section of the law that describes how to do it.

Unless FDA changes this for the LDT case, you're going to find a legally marketed device and you're going to show that your device is substantially equivalent to that legally marketed device, which usually called a predicate device. And then when FDA comes back and says, OK, you've satisfied all the

O'Leary (cont.): requirements. That's called clearance. So clearance and approval are the two technical terms that I was putting together in the word permission.

You're going to have to pay FDA in order to examine your application. So there's a fee, and these are regular fees and small business fees. Small business is $100 million or less in gross sales, and here is the cost. So if you file a PMA and it's a standard fee, it's going to cost you a quarter of a million dollars to have FDA read your application. It's probably going to cost you at least a million dollars in order to do all the work to put the application together. If it's a 510(k) for a standard company, $5,000. Small businesses get a break.

There is a plan to waive the fees initially for LDTs. The law, FDASIA, says that the Secretary of Health and Human Resources may grant a waiver or reduction in the fees. FDA took the position that if FDA gets the statutory authority to do this, they're going to waive the fees in selective instances for LDTs up until MDUFA. This is the Medical Device User Fee Act.

Now the fee structure is going to end in 2017, and a new one is going to be put in place beginning in 2018. That's under negotiation right now. It's not clear what FDA is going to do about waivers or reduction of fees for FDA starting in 2018. They've just not made any decisions yet, so we're going to have to wait and see. So it may very well be that there's going to be reduction or waivers of fees for some period of time, and then they might come back in. We just don't know yet because the negotiations aren't complete, and then Congress has to pass the appropriate law.

An IVD kit contains a lot of different kinds of products—reagents, diluents, controls, calibrators, calibration verifiers. There's no guarantee that they're going to have the same risk class, and there's no guarantee the premarket review will follow the risk class. So one of the things that FDA does is think about, particularly for controls and calibrators, whether they're assayed or not, and whether the values are quantitative or qualitative. The end result is that that can change the device class. So you might end up with controls and calibrators that are a different device class than the reagents, so this can cause a lot of confusion. So you just need to wait until FDA comes back and tells you want the device class is. They're going to start by looking up the information you include in the notification.

The other thing that happens here is that a lab that modifies a device that's already cleared by FDA or approved by FDA is going to be a device. That means that I'm giving you some examples here of modifications. Right now, FDA has been exercising enforcement discretion on that as well. It's covered in the CLIA regulations. Now what's going to happen is that if you get a device from an IVD manufacturer and you modify it, then it's going to be a new device as far as FDA is concerned, and you're going to have to report the modifications to FDA and go through the premarket notification processes. So you need to realize that that's going to change as well, in conjunction with the LDT changes.

FDA is going to assume that it's not assigned risk classes to LDTs. So you're going to take the notification information and start to assign risk classes and product codes. The panels are going to evaluate this stuff, and FDA is going to make the decisions. Then they're going to use that information to prioritize the order. I told you that this is going to extend over a number of years, so FDA is going to put together a priority order in which they want all of these things submitted.

So beginning 12 months after publication of the final guidance document, FDA is going to enforce review for three kinds of LDTs. LDTs with the same intended use as cleared or approved companion diagnostic; so this is a lot of reasons why LDTs are out there. If they're the diagnostic that's a companion to the LDT, then that's going to be at the top of the list. The same intended use as an already cleared Class III device, or any LDT that's used for safety or effectiveness of blood or blood products. So right now, in the plan,

O'Leary (cont.): those are the ones that are going to go first. So they're going to start 12 months after publication of the guidance document.

Within 24 months, two years after publishing the framework, FDA is going to publish the priority list for the remaining Class III devices. Then they're going to start enforcing for the highest priority group within 12 months after publishing the priority list. So they're going to start phasing this in. They're going to do a subset of these high risk devices, and then they're going to publish a list for the rest of the devices and then they're going to start enforcing discretion, start enforcing the regulation. And that's going to take a couple of years.

For Class III devices, here's the diagram. Publication of the framework guidance document is going to start the clock, and 12 months after that publication date, enforcement discretion is going to end for these three types of LDTs that we talked about. Twenty-four months later, FDA is going to publish the priority list. And then 60 months later, enforcement discretion is going to end for all Class IIIs. So all Class IIIs have got to get into the system. You've got 60 months from the date to finish off all of your Class IIIs, but you won't know what the priority order is until FDA publishes the list at the end of 24 months.

For Class IIs, very similar timeline, but on different dates. So 48 months out is going to be the priority list; 60 months out enforcement discretion ends for Class IIs in priority order; and then 108 months out all Class IIs enforcement discretion ends.

For Class I devices, FDA plans to continue to exercise enforcement discretion. So one of the things that's interesting here is that in some Class I devices they require premarket notification. So it's not crystal clear what's going to happen here with the Class I devices, but generally, they are low risk devices. And because they're low risk devices, FDA is going to continue enforcement discretion.

There's also enforcement discretion for another set of things, humanitarian use devices. This is a special class of devices where there's a small target population, and the law defines how big the target population can be, the numbers that are used and so on. FDA is not going to get into that.

Traditional LDTs; so this is the LDT that was the old view of what an LDT looked like. It was done primarily in a hospital lab for one or two or small numbers of patients. FDA is going to say, well, we're not going to get into that. We never wanted to.

Then there is a class of things called devices that are satisfying unmet needs. If you're making an LDT that falls into that class, then FDA is going to exercise enforcement discretion. But if some other company brings that to market and gets it cleared and approved, then enforcement discretion is going to end. So if you've got any LDTs for unmet needs, you need to watch what's going on in the rest of the market, because somebody else could get it cleared or approved, and that's going to affect your status.

There are some other requirements that we need. The LDT manufacturers have to implement the device regulations found in Part 820. This is the quality system regulation. So this is the quality management system that you have to have in place in order to make a device for the United States. It's very different than CLIA, and CLIA is not going to satisfy these requirements.

In fact, there's a well-known example. There's a company called Theranos, and they've got some proprietary stuff. They were inspected by FDA because they're going through the submission process. They got some citations from FDA and they put out a public statement that said, yep, these are legitimate findings from the FDA. We made a mistake. We applied the CLIA regulations, not the FDA regulations in some of these conditions, and as a result, didn't do all the things that they were required to do. They

O'Leary (cont.): fixed it all, presumably, but this is a living example of where CLIA is not going to satisfy FDA. The requirements are significantly different.

There's a couple of significant ones here. You're going to have to put this whole quality system in place, including design controls, production controls, acceptance activities and records. This is why I'm suggesting you draw a bright line between design and manufacture of these devices and the use of them in the laboratory. Pretend that you're an IVD company. You just happen to be inside the same building.

QSR has got a bunch of special requirements. So when you make a device, you've got to go through a process of demonstrating that you have done all of the things that you said you were going to do. Those are documented in something called the Device Master Record. It comes out of design. Very often people think of this as the recipe for manufacturing the device.

Then you're going to keep records that show how you manufactured the device and demonstrate that you followed the device master record. That's called the Device History Record. You're going to designate somebody who is going to read all of this stuff, make sure it's complete. They're going to sign off on it and then that devices is allowed to ship. So that means that you're going to have to have this DMR/DHR process before you can take a manufactured device on one side of your lab and move it over into the testing side of the lab. This is one of the places where this bright line is going to have to exist.

Now for an LDT requiring a PMA—remember, this is the highest risk device—the quality system has got to be in place before submitting the PMA. So this is a little interesting twist here. As part of the approval process, FDA is going to send an investigator in to do an inspection. So before FDA will approve a PMA—these are the Class III high risk devices, so these are the ones that are going to go first—you already have to have the quality system in place and up and running. FDA is going to check it by sending in an investigator. And the investigator is going to be there for a couple of days, maybe three to five. Plan on five days. Sometimes they go faster, sometimes they take longer.

Then for the lower risk devices, for 510(k) devices, this is usually the Class II, the quality system has got to be in place before you're allowed to launch the device; in other words, ship it. For low risk devices, these are typically going to be the Class I, FDA is going to exercise enforcement discretion on the quality system.

So if you're making a device that's going to require a 510(k) or a PMA, then that's usually, but not always, Class II and Class III. You've got to put a whole quality management system in place, and it's not CLIA. CLIA is not going to satisfy all of the requirements.

This is going to be a source of confusion for a number of people. There are some common systems out there. ISO 9001 is a quality management system. ISO 13485 is a quality management system for the medical device manufacturers that are outside the United States. ISO 15189 is an ISO document that tells you how to build a quality management system for a lab. 42 CFR Part 493 is the CLIA regulations. None of those will work. You have to have a quality system that satisfies Part 820. That's called the Quality System Regulation. That's the only think that FDA will accept. If you offer any of these other systems, then they won't satisfy all the QSR requirements and you're going to get into trouble with FDA.

There are some issues about labeling. Now the guidance documents don't talk about labeling, they're just there in the regulations. So there's four places where labeling requirements show up. Part 80 is just general labeling requirements. Part 809 is specific labeling requirements for in vitro diagnostic devices. If you're making an LDT, LDT is going to be a kind of IVD, so presumably, Part 809 labeling requirements are going to apply. That's, for example, when you get a package insert from an IVD manufacturer that you bought. It has a whole wealth of information. You're going to have to develop all that information.

O'Leary (cont.): Part 820 has specific requirements for designing and handling labels, and the regulations are phasing in something called Unique Device Identification. You have to assign device identifiers that identify the version or model of the device and report all of that to FDA. Presumably, that's going to happen with LDTs because it's required for IVDs. The labeling requirements aren't going to come into play until you're ready to release it for distribution, although for the PMA inspection, you probably need to be ready to demonstrate that you've got the capability in all the systems in place.

So let's do a summary. FDA has exercised enforcement discretion for LDTs. This is going to end. We talked a little bit about the timeline, but FDA is going to phase in the device regulations so that laboratories that design and manufacture LDTs are going to become device manufacturers, and that's going to cover design and production of devices. And FDA is going to regulate them, and it's going to be a different set of regulations than the CLIA regulations, than what you're used to now.

There's a whole bunch of things that are going to go on. Registration and listing. So you're going to tell FDA that you're involved in the device business. You're going to make premarket submissions to FDA, either premarket approval or premarket notification, depending upon the risk class of the device. FDA is going to assign the risk class of the device.

So remember, the process is, you're going to notify FDA of all the LDTs that you make. You're going to have six months from publication of the guidance document. FDA is going to use that information to classify your LDT. They'll come back and they'll tell you, and then you're going to have to use that to go figure out whether you were doing premarket approval or premarket notification.

You're going to have to implement adverse event reporting, medical device reporting, MDRs for manufacturers, as well as corrections and removals. And you have six months from the publication of the guidance document to get all of that in place.

Quality system regulation, you're going to have to build the whole QSR system, and it's going to have to be in place and ready to go and pass inspection before FDA will approve your first PMA. So that means you need to start working on that now.

And then we talked about some of the labeling requirements. There's general labeling requirements. There's IVD specific requirements. There's unique device identification requirements. And then all the labels are managed and handled according to the rules in QSR.

So that's the presentation. I'm going to turn it back to our host, who will tell you how to ask any questions.

Operator: 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, and please limit yourself to one question at a time. To ask a question, please press *1 on your telephone keypad. I will announce you by the city from which you are calling. Your name and company will remain anonymous. You may hear a few seconds of silence as we bring you onto the line. You will then be live, and will be able to ask your question. Again, please press *1 on your telephone keypad to ask a question. You may also submit questions by email to questions@fdanews.com or use the Q&A panel within Webex.

Our first question will come from Kyle Asay from FDAnews. You may go ahead, Kyle.

Asay: Thank you. What exactly is included in the quality system requirements that is missing from CLIA, such that CLIA won't satisfy what you need to do?

O'Leary: That's a really tough question because it's extensive. They don't line up well at all. It would probably take a couple of days to go through all of the details, but the idea with CLIA is that it's oriented toward running a laboratory, not toward making devices, although it does have some provisions in there about making LDTs. But the design control, for example, that's in QSR is significantly different. The manufacturing and production controls that are in QSR, they don't exist in CLIA, because the assumption of CLIA is that it's not covering device manufacturing, it's covering laboratory tests. All of the requirements for complaints, supplier management, a variety of things are just not included in CLIA. Or if they are, they're very, very weak compared to the requirements in QSR.

So the differences are extensive, and they're going to cause companies a large amount of work to add QSR. CLIA is not going to go away, it's just going to apply to a certain part of the lab. QSR is going to have to be added to it, and you're not going to be able to transfer all of the CLIA processes into QSR. Supplier control is a big one.

Asay: Thank you. One other question, since I'm not seeing anything in the queue. It seems like there are some significant differences in adverse event reporting between the manufacturer requirements and the user facility requirements. Could you highlight the significant ones there?

O'Leary: Sure. I started to lay them out on a slide, so I'm going to try to go backwards here and find that one slide. I think this is probably it. If you're a lab and you're buying in vitro diagnostics from some other company, then the FDA considered you to be a user a facility. So that means you should be implementing the user facility portions of that part of the regulation.

Now, let me back up to a slightly different slide. If the adverse event is a death, you know the patient died. Then if you're the manufacturer, you've got to inform FDA within 30 calendar days. If you're a user facility, you've got to notify FDA within 10 working days, so the timing is different. If you learn of a serious injury, 30 days on the manufacturer side, 10 working days on the user facility side. If your device malfunctions and it were to occur again and potentially harm a patient, even though no patient was ever harmed, that's reportable as a manufacturer, but not at all as a user facility.

Remedial actions change the clock, and FDA can request that you switch from 30 calendar days to five working days in some cases. So those last three don't apply to user facilities, but they do to manufacturers.

There's a form that you fill out, the 3500A form, and it has a little bit of the difference. If I'm a manufacturer, then I'm going to fill out a whole bunch of information for manufacturers, and other specific information for device manufacturers, because I know all of this stuff. I know lot numbers, serial numbers, product codes, all of that sort of stuff, because I'm the manufacturer. So all of that, that's always been on the manufacturer side, but the user facility doesn't know all of that.

On the other hand, there's another block for user facilities. So there's information that you, as a user facility, are going to provide that the manufacturer may not know. So the end result is that now, in this dual role, you're going to actually end up having to fill out everything in the form except block C, which is suspect products, which primarily deals with pharmaceuticals.

So the difficulty is that manufacturers only filled out some blocks. User facilities only filled out some blocks. When you're now both kinds of companies, you're going to have to fill out the whole form, and the timing is going to change. And because you're a manufacturer, you must submit electronically. A user facility has the option, but probably very few of them actually do report electronically.

Operator: [Operator gives instructions to ask a question.]

Operator (cont.): I'm showing no further questions in the queue. Do you have any closing comments before we wrap up?

O'Leary: Yes. This process is going on inside FDA, and it's going to be very important that you keep an eye on what's happening. Now it's going to get a lot of press when the guidance documents actually get published, but what's really important is to start to prepare now. Because when it gets published, you've only got six months to implement some significant amount of work; do all the notifications and do all the adverse event reporting. We didn't get into the details of the notifications, but if you've got a large number of LDTs, you've got a lot of information to determine. I would recommend starting now, because there's going to be severe penalties if you don't make the six month deadline. Thank you.

Operator: Thank you very much. On behalf of FDAnews I would like to thank our speaker and you.

Just as a reminder, if you'd like a recording of this session, you can order the CD and transcript package from FDAnews by visiting our website or contacting customer service.

This now concludes today's webinar. To end this call, simply hang up your phone and close your browser. Thank you.