

**NWX-FDA OC**

**Coordinator: Irene Aihie**  
**June 28, 2016**  
**1:00 pm ET**

Operator: Welcome and thank you for standing by. At this time, all participants' lines remain on a listen only mode. During the question and answer session, please press Star and 1 on your touch tone telephone. Questions will only be taken via the phone today.

Once again, press Star 1 and make sure and record your name. Today's conference is being recorded. If you have any objections, you may disconnect at this time. I would like to turn the call over to Irene Aihie. You may begin.

Irene Aihie: Hello and welcome to today's FDA webinar. I am Irene Aihie of CDRH's Office of Communication and Education. On Monday, May 16, 2016, U.S. Food and Drug Administration published the final version, the final guidance document post market surveillance under Section 522 of the Federal, Food, Drug, and Cosmetic Act.

Section 522 of the Federal Food, Drug, and Cosmetic Act provides the FDA with the authority to require device manufactures that conduct post market surveillance of certain Class 2 and Class 3 devices.

This guidance document clarifies the 522 post market surveillance process and provides manufactures with information on how to fulfill Section 522 obligations, the recommendation on the floor mat content and review of post market surveillance plan submissions.

The focus on today's webinar is to review and clarify their recommendations in this guidance document for manufacturers and other interested parties. Your presenters will be Nilsa Loyo-Berrios and Nicole Jones both from the Office of Surveillance and Biometrics here in CDRH.

Following the presentation, we will open the lines for your questions relating to the topics in this guidance only. Now, I give you Nilsa.

Nilsa Loyo-Berrios: Good afternoon. I'm Nilsa Loyo-Berrios an Associate Director in the Division of Epidemiology. I'm here today with my colleague Nicole Jones, the Associate Director for Program Operations in the Division of Epidemiology.

We are housed in the Office of Surveillance and Biometrics. In Epidemiology I oversee the programs from mandated studies as well as regulatory research on medical devices and Nicole Jones, she oversees the program operations. Next slide.

This is an outline of the presentation. We are first going to go over background, what are the criteria for this in Section 522 of the act. Then we'll go over the 522 guidance document, what is within the guidance and what are the additions in the new Section in the guidance document and we'll conclude with final remarks for discussion for questions.

I want to begin with definition of surveillance. The regulatory definition per 21CFR822.3(i) post market surveillance is defined as active, systematic, and

scientifically valid collection and that analysis interpretation of data other information about a marketed device.

And prospective surveillance is defined by 21CFR822.3J, the surveillance in which subjects are identified at the beginning of the surveillance and the data or other information is collected from that time going forward. Next one.

The Section 522 of the Food and Drug, Cosmetic Act are given authority to order post market surveillance for Class 2 and Class 3 medical devices that meet any of the statutory criteria, which I'm going to go over in the next couple of slides.

The data that is collected via post market surveillance can reveal unforeseen adverse events, the actual rate of anticipated adverse events or any other information that's required to protect the public health.

So there are several criteria and I'm going to go over each of them in the next slide, next slide. The first criterion is that failure of the device will be reasonably likely to have a serious adverse event or adverse health consequence.

And the adverse health consequence is defined by any significant adverse experience related to a device, including device related events that are life threatening or that involve permanent or long term injuries or illnesses.

The second criterion is that the device is expected to have significant use in pediatric populations. And with the new provisions by FDAAA in 2007, significant pediatric use is defined on case by case bases and there's some leeway written into the study to allow for studying devices that's not specifically labeled for pediatrics.

The third and fourth criteria are that the device is intended to be implanted for more than one year and that it is intended to be a life supporting device used outside of a user facility.

And the definition for a life supporting device per the regulation, is that a device is essential or yields information essential to the restoration or continuation of a bodily function that's important to the continuation of human life, and is used outside a hospital, nursing home, surgical facility, or at a diagnostic or outpatient treatment facility. A physician's office is not a device user facility.

Prospective surveillance under the 522 Section of the Act can be up to 36 months for non-pediatric studies. For pediatric studies the length of follow up is determined by the questions that need to be addressed.

FDASIA in 2012 added that an order can be issued at any time, at approval or clearance of a device or at any time throughout the total product life cycle; and postmarket surveillance must commence no later than 15 months from the date of the order.

So, what are the consequences of not complying with a 522 order? The not complying is considered a prohibited act under Section 301(q)(1)(C) of the Act. The devices can be considered misbranded under Section 502(t)(3) of the Act and FDA can issue warning letters, seizure of the device, civil money penalties and prosecution.

The 522 study program is housed in the Division of Epidemiology, and we provide the oversight of all the aspects. This includes the pre-522 process, issuing the orders, tracking the requirements after the order is issued, we

maintain the public webpage and we do have internal SOPs and the guidance document, which is the focus of today's seminar.

Our reviewers in the division are the lead of the 522 review team. We lead the discussion on the need for post market surveillance, identifying what are the questions that need to be addressed and making the recommendations on the most appropriate methodologies to fulfill the postmarket surveillance orders.

This is a schematic of what the pre-522 process entails. The first step is identification of the public health issue. This can be done by any reviewer, , issue can be identified using any data source, can be MDRs, literature, or anything other source of data.

We have a pre-522 screening form that is filled out. We establish a cross center team and there is a series of meetings during which the public health issues are discussed and a determination made regarding the need of a 522 order. The pre-522 team makes a recommendation on whether or not a 522 order is needed.

If it is - then the order is processed and signed by the Director of the Office of Surveillance and Biometrics.

These are just examples of device types that have 522 orders, like for example surgical mesh , metal hips, [more examples on the slide].

d This slide presents the progress status of active requirements as of May of 2016. We currently have 44 active requirements and about 40% of them are progressing adequately. The status of the requirements is something that varies, every time we receive a report, we assess the status and update the public webpage.

And now I'm going to hand over the presentation to Nicole Jones who will go over the content of the guidance and what's new.

Nicole Jones: Hello, my name's Nicole Jones and I'm going to go over with you what currently is included in the guidance document. In the beginning of the guidance document, one of the first things that is available, will tell you about the legal background and that's much of what Nilsa's over.

In addition to that, there is the process for ordering the 522 studies and this is covered in the guidance document as well as the post market surveillance plans, what to include in those plans. There is also a Section in the guidance that goes over the interim report.

This includes what types of content and guidance should be included in those interim reports and there's the Section for final reports, which includes the summary of the data and findings of the study.

In addition to that, we also ask the companies to go ahead and include what they believe their post market surveillance study status should be and that's covered in the 522 guidance.

And it also covers -- as Nilsa stated -- what happens if folks manufacture fails to comply with these requirements.

In addition, it goes over what is the process for public disclosure and what will be disclosed as well as now one of the new additions is a checklist for administrative compliance in making sure that all of these items that we have requested be included in the documents are actually there to allow for a proper review.

What I'm going to go over now instead of going over all of the things that are currently in there, in the guidance document is both things are new or have not, were not in the previous versions of the guidance.

So when we finalized this guidance, we wanted to make sure that we included all new additions. And so one of the things that we made sure was reflected in the guidance was the amendment to the Section 522 under FDASIA.

This, these amendments were for the post market surveillance studies and they stated that any post market surveillance study orders that were made must commence no later than 15 months after the date of the order.

And this means that if they are not commenced within the 15 months, if they have not started, they will be considered to be out of compliance. In addition to that, the agency also may issue a post market surveillance order at the time of the device approval or clearance or anytime thereafter.

They also added a new study status. This study status will also be displayed on the web pages now and it's called non-compliant. The definition for this study status is when study surveillance fails to comply with the requirement under the Section 522.

For example, if that study has gone past the 15 month mark date, then the order is then considered to be out of the compliance and therefore we would mark it as such on the webpage of being not compliant.

FDA also clarifies in the new guidance document how manufactures should request for post changes to an improved study surveillance plan and how the FDA will review such changes.

So this falls into effect when you have an already approved protocol and you then want to make some, whether that be small change or a larger change, it needs to be submitted in and approved by FDA.

The guidance document also describes new types of decision letters that we will issue. This includes the first one, a not acceptable letter. This not acceptable letter is for a submission, it comes and is not considered to be administratively complete because it does not include the items requirement under 21CFR822.9 and 822.10.

The appendix one of the guidance which is the last page includes the checklist for determining whether a submission is administratively complete.

If we find within the first 30 days that the submission is not complete, you'll receive notice from FDA that will tell you that it was not completed and therefore not counted as a submission that you will have to resubmit the complete content.

The next one we've used is called an approvable letter and this is used when the submission that has been sent is approved in FDA and agreed upon by the manufactures to conduct the study.

In addition, we have a new letter that we call a minor deficiency letter. So a minor deficiency letter sites specific minor deficiencies that must be addressed in order of the plan to be approved.

When I say minor, one of the examples that I would use is if maybe there's a timeline that has not been submitted in the study or perhaps there's a small



Section that is missing or maybe some clarification is needed on an issue that's a part of the study protocol or plan.

The second option is a major deficiency letter and this sites serious deficiencies related to whether the plan will result in the collection of useful data that will answer the surveillance questions.

Manufactures must adjust these deficiencies in order for the plan to be approved. In this case, the deficiency is a major issue, like maybe there's a concern that the statistical analysis Section of the study plan does not addressed or is not able to accurately define what is needed in this study.

The next type that we'll use is a disapproval letter. This is a new type for us to be using for 522 study plans. And this is when FDA approves the proposed plan, I'm sorry, disapproves the proposed plan because it will be not result in the selection of data that will address the post market surveillance questions in the 522 order.

So in this case, I would leave the example of a sponsor submitting a study plan that the design is not accurately answer the question or will never answer the question therefore it is not an approvable version.

In this case, the letter will direct the manufacture to revise their submission by submitting an entirely new submission that proposes a new plan design to address that 522 so that the questions can be answered in the order.

In addition to that, the guidance specifies the FDA may post on our website or otherwise may public intern data, summary data and/or FDA analysis when appropriate to protect the public health as well as final report results.

One example of this is currently in the FDA website, we post final study results and these will continue to be posted when the study is complete. In addition, there may be some interim study results to be posted for surveillance plans approved after July 1 of 2016 forward.

This guidance document also adds an additional surveillance type to the study design table and that type is called “comprehensive linked registry based surveillance”.

This is a registry based surveillance with shares the responsibilities that leverages the national registry infrastructure linked with other data resources for longitudinal assessment of device performance. It means that the actual registry work is shared between both FDA and the third party registry.

The final guidance document was released on May 16 of 2016 and this is the link that it can be accessed at.

Irene Aihie: And this concludes our presentations. We'd now like to open the lines for questions.

Operator: Thank you. At this time, if you would like to ask a question, please press Star and 1 on your touch tone telephone. Please record your name in order to be introduced.

Once again, press Star 1, record your name so that you may be introduced.

Our first question will come from (Adam Lynch). Your line is open. (Adam Lynch), your line is open.

Woman: Hello?

Operator: Again, if you would like to ask a question, please press Star and 1 on your touch tone telephone. One moment for any questions. One moment.

We have a question from (Christine Siri). Your line is open.

(Christine Siri): Hi, I just had a question. If your device has an adverse event and a 522 is ordered, does the 522 go to all manufactures who have that device type or is it just to that manufacture who had the adverse even that caused the order?

Nilsa Loyo-Berrios: Hi this is Nilsa. It depends on what the question is. If there is a specific, a question that it's specific to the one device, then there would just be one order but in some instances, we have questions that apply to the entire device class in which case then the manufactures with the same type of device will get the order.

(Christine Siri): Okay thank you.

Operator: Our next question will come from (Carrie). Your line is open.

(Carrie): Thank you for presenting this. We will appreciate the information. We were wondering with within that 15 mark timeline on initiating the study, does FDA recommend that we use a pre-submission process to align the agency on the study design or is there another process for aligning on that design?

Nicole Jones: So currently, this is (Nicki Jones). Currently right now we do have a process where we will work with the companies interactively to come up with a protocol plan. Basically, once you're ready to submit that plan, then you can submit it to us and electronically to the review, right?

Nilsa Loyo-Berrios: Yes that's right. We don't have the official tracking system set up for the 522 to receive pre-submissions, but we do have that interactive review , between the reviewer and the company before the formal submission is done, we encourage to do that so in order to have a good submission when it comes it.

(Carrie): Okay thank you.

Operator: Our next question will come from (Jan Zorn). Your line is open.

(Jan Zorn): Good afternoon and thank you. I have actually two questions and the first is if you're, if the request for a post market study is part of your approval or your clearance, then isn't your protocol submitted to the original reviewing group of your premarket submission?

Nilsa Loyo-Berrios: So if it's a Class 3 device, you will likely get a condition of approval. I mean, there are very rare instances in which, if it's a PMA device, there's very rare instances in which we will issue a 522 along with the approval order but there have been cases but very rare.

Now if it's a Class 2 device and they're issuing an order at the time of clearance, there's usually some discussion that takes place before the clearance is issued but a full protocol may not be in place by the time the clearance is issued.

Nicole Jones: This is Nicole. If you're at the time of a clearance. You've already come to an agreement with the premarket side so what that particular study plan should be, then when you do submit it will be to us as well.

(Jan Zorn): Okay to both. My next question is what percentage of Class 2 and Class 3 devices require post market studies at this time?

Nilsa Loyo-Berrios: I can't give you an exact figure on that , just because a Class 2 device meets any of the statutory criteria, it doesn't mean an order will be issued. There has to be a public health problem (issue) for the order.

The majority of the 522's we have are on Class 2 devices, but I can't give you a figure in terms of the percentage of Class 2 devices with orders.

(Jan Zorn): Okay thank you.

Operator: Our next question will come from (Maro Ecolony). Your line is open.

(Maro Ecolony): Hey, I would like a clarification about the difference between a post market surveillance order issued upon PMA approval and the post approval study request that again, issued upon PMA approval without the criteria that agency used to go one way or the other?

Nilsa Loyo-Berrios: So for a PMA device we do have what we call the Post Approval Study Program and those are requirements that are imposed at the time of the PMA approval. So those are conditions of approval and it's a different program that we use .

The 522 order, the 522's are a different program and those can be imposed at time of clearance/approval or any time while the device iis on the market. If it's a Class 2, it could at clearance or after the device has been on the market, and as I said, for Class 3 it's very, very rare that a 522 order will be issue at a time of approval.

There may be, unique circumstances for which we will go that way. We rather use the condition of approval route as opposed a 522.

(Marco Ecology): Thanks.

Operator: At this time, I'm showing no further questions. Once again, if you would like to ask a question via the phone line, please press Star and 1 on your touch tone telephone. You will be prompted to record your name clearly in order to be introduced.

Once again, please press Star and 1 on your touch tone telephone and record your name. One moment for the next question. Our next question will come from (Phoebe). Your line is open.

(Phoebe): Hi. I'd like to follow up on some of your great slides in the presentation and I was wondering when they're going to be available on your website and how to access them?

Irene Aihie: Hi, they will be available on July 7 and they will be available at the web address at the, on the screen, [www.fda.gov/training/cdrhlearn](http://www.fda.gov/training/cdrhlearn).

(Phoebe): Great. So I can go there on July 7 to access those?

Irene Aihie: Yes ma'am.

(Phoebe): Thank you so much.

Irene Aihie: You're very welcome.

Operator: Our next question will come from (Marty). Your line is open.

(Marty): Thank you. During a 522 order for patient registry, at that time is the sale of that device under this order for the study and the registry automatically suspended or no?

Nicole Jones: I'm sorry - I need a little more clarification of what you're trying to ask.

(Marty): If there is a 522 order and that requires a patient registry and a follow up study for that, during that duration, is that device suspended from sale in the U.S?

Nicole Jones: No.

(Marty): Thank you.

Operator: Our next question will come from (Susan Winter). Your line is open.

(Susan Winter): Hi, I'm just wanting to get a confirmation that re-packagers and re-labelers that have to license as a device manufacture are not subject to this post market surveillance?

Nicole Jones: Give us just a second.

Irene Aihie: Hello, caller?

(Susan Winter): Hello?

Irene Aihie: Yes, that's a very technical question. If you could send that question to (dice@fda.hhs.gov).

We'll have one of our colleagues definitely get back to you. Please try to be as specific as possible with your question as well...

((Crosstalk))

(Susan Winter): Okay.

Irene Aihie: ...appropriate answer.

(Susan Winter): Okay thanks.

Irene Aihie: You're welcome.

Operator: Once again, if you would like to ask a question via the phone line, please press Star and 1 on your touch tone telephone. Please record your name in order to be introduced. Please press Star 1 on your touch tone telephone.

Once again, if you would like to ask a question, please press Star and 1 on your touch tone telephone. One moment.

Our next question will come from (Don). You're line is open.

(Don): Yes we have two 510K Class 2 devices. My question is under the legal background Section of the 522 statutory criteria, nothing is being added that I can see that, well what I'm saying is our device is not underneath any of the four sub-sections that are listed or four bullet points. Does that mean that we are not subject to post market observation?

Nilsa Loyo-Berrios: For FDA to be able to issue 522 order, the device in question has to meet one or any of the statutory criteria. If there is an issue for a device that does



not meet that criteria then we have to look for other ways for the data collection.

(Don): Okay thank you. I think then that we are exempt because we are not in any of those four. Thank you.

Operator: Our next question will come from (Oscar). Your line is open.

(Eric): Yes, this is (Eric) actually. I – for our 522 Class 3 device, we are in the process of getting a final report approved and I was wondering if the final report will be published on the website or made available to the public in its entirety or if it's just going to be a summary and if so what will be made available?

Nilsa Loyo-Berrios: So we actually during the - this is Nilsa-- during the review of the final report, we always verify with the company if we have questions on the data and the final results, we have a discussion on what are the limitations of study which can have an impact on the interpretation of the final results.

Then a summary of the main endpoints is prepared, it is cleared by the Office of Freedom of Information Act (FOIA) and then it's posted on our webpage.

Nicole Jones: But that's not the report in its entirety, it's just pieces of it.

(Eric): Okay.

Nilsa Loyo-Berrios: It's a summary of the main endpoints yes.

(Eric): Thank you.

Operator: Our next question will come from (Natara). Your line is open.

(Natara): Can you please tell me how many in term diagnostics devices are currently on this surveillance plan?

Irene Aihie: Give us a second. This is...

(Natara): Hello?

Irene Aihie: One second, we're conferring to get you an answer, just one second please.

(Natara): Thank you.

Nilsa Loyo-Berrios: Hi, this is Nilsa. We don't have the data in front of us but you can send the question to the [dice@fda.hhs.gov](mailto:dice@fda.hhs.gov) and we'll provide an answer.

(Natara): Thank you.

Operator: Our next question will come from (Nichole Ralone). Your line is open.

(Nichole Ralone): Hello? Can you hear me?

Operator: Yes your line is open.

(Nichole Ralone): Thank you for the presentation again. I want to ask some, you mentioned as if S9 study is up to 36 months after the device approval. Does this mean the length of the study should be up to 36 months or it should start prior to that?

Nilsa Loyo-Berrios: This is Nilsa. With 522 surveillance orders - we are limited to a three year follow-up. For example, a question on the rate of certain adverse event, it will have to through 36 months after the patient gets the device.

That's for devices that are not for pediatrics. In the case of pediatric population, depending on the question, FDA may require longer than the 36 month.

(Nichole Ralone): Okay but if it's not pediatric, and then the surveillance is only for 36 months after approval, right?

Nilsa Loyo-Berrios: It's not approval. It will be...

((Crosstalk))

Woman: ...study.

Nilsa Loyo-Berrios: ...follow up with the patient with the device.

(Nichole Ralone): Okay thank you so much.

Operator: Once again, if you'd like to ask a question via the phone line, please press Star and 1. Questions are only being taken via the phone. Once again please press Star 1 if you would like to ask a question.

Irene Aihie: Seeing no questions, thank you. This is Irene Aihie and we appreciate your participation and thoughtful questions. It looks like we have questions.

Operator: One moment. Our next question will come from (Bonnie). Your line is open.

(Bonnie): Hi. I'm sorry but could you give me the website address again where I can see the slides and all?

Woman: Are you following the slide we are on currently?

Irene Aihie: Hello?

(Bonnie): Hello.

Irene Aihie: Yes, the web, the web address at the end of the slide presentation, [www.fda.gov/training/cdrhlearn](http://www.fda.gov/training/cdrhlearn). Thank you.

Operator: Our next question will come from (Bill Task). Your line is open.

(Bill Task): Yes ma'am. If you are not a manufacturer but solely a distributor of a finished project of a Class 2 device, are you still required for a post market surveillance study program?

Nilsa Loyo-Berrios: That is the same question that was posted earlier and we recommended that the question be sent to [Dice@fda.hhs.gov](mailto:Dice@fda.hhs.gov). We'll get an answer to you on that.

(Bill Task): HHS.gov?'

Nilsa Loyo-Berrios: Yes.

(Bill Task): Thank you.

Nilsa Loyo-Berrios: Sure.

Operator: Once again, if you'd like to ask a question, please press Star on your touch tone telephone. Once again, that is Star and 1.

Please standby for any further questions. Once again, to ask a question via the phone, please press Star 1. One moment.

Our next question comes from (Recanan Sanchez). Your line is open.

(Recanan Sanchez): Hi, my question is related to the when a 522 plan would be ordered? You mentioned during clearance or PMA approval but you did also mention MDRs so does that mean for market devices that are not currently going on the A510K submission, would they you know, potential require 522 order based maybe on like, MDRs trending or MDR results if we sold.

Nilsa Loyo-Berrios: This is Nilsa. When we get the, what we call the pre-522 screener, it will include the data source which the reviewer is basing the concern on, and that may include MDR but it may include any other source, any other data sources. It could be any other ongoing study where the problem is identify.

The source could be MDRs, but is not limited to MDRs. It could be any source of data that raises the concern and yes, 522 orders can be ordered on Class 2 or Class 3 devices that are on the market that meet any of the statutory criteria or at the time of approval or clearance..

(Recanan Sanchez): Thank you.

Operator: Our next question will come from (Anne Maria). Your line is open.

(Anne Marie): Hello I was just wondering for Class 2 devices that we're see (unintelligible) clinical data, is there any (unintelligible) for extending the supporting (unintelligible) study to address the 522 order?

Nilsa Loyo-Berrios: This is Nilsa again. So it depends what the question is that needs to be addressed.

If there is a question on the long term performance of the device, that is being cleared, it's a Class 2 device and there is a premarket study with sufficient number of subjects that could provide enough data to answer the question in the long term, then yes. That could be an option.

(Anne Marie); Okay and I suppose to plan for that, what would be the best way of getting feedback through the pre-submission project prior to...?

Nilsa Loyo-Berrios: Give us a second. Sorry about that, we're back. So it's just, your question, if I understood correctly your question, you're asking about those that are issued at the time of clearance of a Class 2 device.

Usually we get involved towards the end of the premarket review cycle, and there's supposed to be some discussion internally about the questions are on what needs to be done to answer those questions and those will be communicated to the company at the time the device is cleared.

Then once we get the order, our reviewers will work interactively with you to ensure that the major aspects of the study plan are covered when you do submit your formal submission.

(Anne Marie): Okay that's great. Thank you very much.

Operator: Our next question or, before we go onto our next questions, please press Star 1 on your touch tone telephone. Please record your name clearly in order to be introduced.

Once again, please press Star and 1 on your touch tone telephone. Please hold a moment while our next questions queue up. Once again, if you would like to ask a question via the phone, please press Star and 1. I am currently showing no further questions.

Irene Aihie: Thank you. This is Irene, I'm here. We appreciate your participation and thoughtful questions. Today's presentation and transcript will be made available on the CDRH motor webpage at [www.fda.gov/training/cdrhlearn](http://www.fda.gov/training/cdrhlearn) by Thursday, July 7.

If you have additional questions about the guidance document, please use the contact information provided at the end of the slide presentation. As always, we appreciate your feedback. Thank you for participating and this concludes today's webinar.

Operator: Thank you. That does conclude today's conference. You may disconnect at this time and thank you for participating.

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