Webinar - Draft Guidance on "Principles for Codevelopment of an In Vitro Companion Diagnostic Device with a Therapeutic Product"
Moderator: Irene Aihie
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1:00 pm ET

Coordinator: Welcome and thank you for standing by. All participants will be in listen only mode until the question and answer session of today's conference. At that time, you may ask a question by pressing star one. Today's conference is being recorded. If you have any objections, you may disconnect at this time. I would now like the turn the meeting over to Irene Aihie. Thank you. 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 On July 14, 2016, the U.S. Food and Drug Administration issued the draft guidance principals for co-development of an in vitro companion diagnostic device with a therapeutic product. This draft guidance is intended to assist with the co-development of a therapeutic product and in an accompanying IVD companion diagnostic. This guidance is also intended to assist FDA staff with reviewing companion diagnostics or their associated therapeutic products.

The focus of today's webinar is to share information and answer questions about the draft guidance document. Your presenters will be Christopher Leptak from the Office of New Drugs and the Center for Drug Evaluation and

Research, and Pamela Bradley from the Office of In Vitro Diagnostics and Radiological Health in CDRH. Following the presentation, we will open the line for your questions related to topics in this draft guidance only. Additionally, there are other central subject matter experts available to assist with the Q&A portion of this webinar. Now, I give you Chris.

Christopher Leptak: Hello everyone. We welcome you to today's webinar and I wish to extend my sincere apologies for the technical difficulties and certainly appreciate your patience for holding on on the line for the last 20 minutes or so. Unfortunately as with most things with computers, the problems arise when you least expect them. So again we appreciate your patience.

As was said, we're going to start this presentation with a more formal discussion of what is in the guidance and that will be followed by a Q&A. So I'll be kicking us off for the first couple of slides and then Pam will be finishing the presentation. We'd very much appreciate if you could please hold your questions until the Q&A session and that'll be an opportunity to have a more general discussion.

So just to begin, the co-development guidance was a tri-center effort here at the FDA between CDR, the Center for Drugs, CDRH, the Center for Devices, and also for CBER, the Center for Biologics. There was a working group that convened to draft the guidance and ultimately the subject content for the guidance affects all three product centers. As was mentioned, the guidance has been published in draft from last month and the open comment period is through the middle of October.

So the purpose of today's webinar is to orient you to the guidance and also to hopefully facilitate your input onto the guidance as part of the public comment period. The webinar is such that given the time constraints, Pam and I will try

to limit the formal presentation initially as we - 40 minutes we'll try to gain some time there so that we can open up and still retain the full 20 minutes for the Q&A as much as possible. So with that, I'll kick us off.

The co-development guidance is the second in a series of guidances in the space where both a drug and a diagnostic are being developed together as part of a development program. For the purposes of our conversation, we'll likely be referring to drug which means both drugs and biologics and then we may say test or device which would be in the CDRH realm of the in vitro diagnostics. The first in this series was the companion diagnostics guidance, which was published in final form back in August of 2014, which defines ultimately what the definition for companion diagnostic was and when it would be appropriate for that guidance to be invoked. Ultimately, it was more of a definitional guidance rather than a process one in that it defined what a companion diagnostic is, which is ultimately a device that is essential for the safety and effective use of the corresponding therapeutic product.

It described the uses of when companion diagnostics could be invoked, which is ultimately identifying populations most likely to benefit or most at risk for adverse reactions from a therapeutic, to monitor the response to adjust for treatment, and also to identify the population for whom the drug would be most taken effective for its use. Ultimately, the guidance describes the regulatory requirements around labeling as such, but it really was not a how to. And that's where the co-development guidance comes into play and that it's more of a how do you do a co-development program where both a drug and a test are in play. So for next slide.

I'm sorry. Right now we are on slide number six for the folks on the call. So for the draft guidance for co-development ultimately it's a how to guidance and in general the guidance that we'll walk through as part of the webinar

presentation will cover the various components that are addressed as part of the guidance's content. So next slide, slide seven.

So first off, we're going to just focus on some of the general to orient everybody since this may be a new concept or topic area for you. And then we'll go through each of the different guidances topics in greater detail. Next slide, slide eight.

So ultimately as part of a co-development program what we've seen here at the FDA is that the role of the diagnostic as part of the drug development program can occur at many different points during that drug development paradigm. It could be an intended co-development program from the beginning, everything from the preclinical development, early clinical development, all the way through the program. But many times, depending on the analyte that the test is assessing or the biomarker, the role of that biomarker in terms of the product development cycle may not be appreciated until after some exploratory studies, especially in the early phases of that drug development program.

So as such, co-development is not necessarily intended to be a simultaneous development but rather that, once the co-development paradigm has been identified that at the time of approval of the drug and the therapeutic that there would be a co-approval or a contemporaneous approval such that once the therapeutic product and the drug product are then marketed, that both products are available to the public at the same time since it's important that they be available for healthcare decisions on the part of healthcare providers.

I should mention that the co-development guidance is focused on companion diagnostics. With that said, even if a diagnostic doesn't reach this essential definition to be called a companion diagnostic, the principles of co-

development are - would apply even in scenarios where that essential threshold has not been met. So it's very much important that as part of a therapeutic program that the device is in play that you sort of plan ahead and plan in advance even if you're not sure of what the role that biomarker or diagnostic is going to ultimately be. Next slide, slide nine.

So let's talk a little bit about some of the co-development clinical trials at a very high level. So on slide number ten, when you're doing a co-development program not only are you developing the drug and the device, but many times the data to support both the drug and the device are occurring from data that's gathered as part of a single clinical trial design. Sometimes there's aspects of the therapeutic program or for the device program that necessitates sort of separate studies that are focused on only one of the two products. So many times the data that is collected can be supportive of both the drug and the device sort of in tandem.

The considerations as part of the clinical trial design are fairly complex and then also dependent upon the nature of the disease and the mechanisms of action, etcetera. So there's really no one-size-fits-all, but some of the things that the product developers would like to consider are the mechanistic rationale for selecting the marker that's in play, the nature of the disease and whether or not there are other therapeutics that are available, whether or not you're moving people away from standard of care, the level of characterization and the test negative population and also some prospective retrospective analyses. Slide number 11 please.

So ultimately the guidance talks about the process by which a drug and diagnostic are co-developed, but it's not a prescription of how to design your clinical trial in any great detail. Certainly there are many different trial designs that are feasible. Two are listed here. And honestly, there's another guidance

in this space called the enrichment strategies guidance that I'll talk about in a moment where these different trial designs are discussed in much greater detail.

Ultimately when it comes to which trial design best fits your particular program is in large part depending upon the knowledge of pathogenesis of the disease, the strength of evidence for the biomarker, the biologic plausibility and ultimately what the results of that biomarker are leading to, whether it's identifying the patient population of interest, adjusting dose, trying to move people away from a potential adverse outcome, etcetera. So these are just two examples of what a program may look like that's incorporating both a therapeutic and a device product. Next slide, slide number 12.

So the enrichment strategies guidance is a draft guidance that's in the process of going to final. It was published as draft back in 2012 and we certainly list the reference here for your perusal. The purposes of today's seminar is not to discuss the enrichment trial guidance in detail but certainly there is content there that is very much supportive of what's covered in the co-development guidance. Slide number 13.

In terms of retrospective - sorry prospective-retrospective approaches, as part of a development program, as I mentioned earlier the role of the biomarker may not be fully understood, especially in early phase development. As such, it's beneficial if the drug developers at that time end up storing samples or tissue that ultimately later could be studied as the role of that marker is further elucidated. And as such if you have this - the stored material, you could then prospectively design a study to look at that collective information and then see what information might be gathered from that, both for the drug and the device as that product's co-development continues forward. Next slide 14.

In terms of trying to identify your patient populations, ultimately you want to ensure, to the best extent and that is feasible, that you have an adequate representation of the biomarkers within that patient population as part of that drug development program. Depending on the mechanism action of the drug and the strength of evidence of the biomarker, as we talked about at some of the clinical trial designs, you may end up focusing only on marker positive patients to a large degree or it may be more prudent to actually look at all marker status as part of the trial. And again it's very much context specific. If you are going to differentiate based on marker status, determining what the cutoff values are between the marker positive and marker negative are going to be essential for the interpretation of the clinical trial results, especially from the device perspective. Next slide, slide 15. And at this point, I'm going to turn it over to Pam who is going to be discussing the aspects of the co-development guidance that are more in the device space.

Pamela Bradley: Great. Thank you Chris. I hope everyone can hear me. I'm assuming someone will let me know if you can't. Okay so thanks everyone for tuning in today and now we'll move on to requirements for investigational products. Okay so in co-development programs it's often the case that you have both a therapeutic product and IVD that are investigational. And both of these products have their distinct requirements so that investigational new drug regulation, at 21CFR312 and the investigational device regulation at 21CFR812. These are separate regulations. They're intended to address separate products and compliance with one regulation doesn't mean that the other regulation is fulfilled. So each regulation needs to be considered in the context of each separate product.

And as we've sort of continued down this path towards precision medicine, we're seeing more and more of these therapeutic product trials that use investigational tests. And so we're hoping that this guidance will help to

answer the questions that we're getting frequently. And since these questions tend to be about the IVD side of the equation, much of the section of the draft guidance is focused on the IVD issues.

So first, what do we mean by investigational IVDs? Well in this context of co-development where a therapeutic product or a drug clinical trial uses a test, the test would be considered investigational if it was used for a purpose and has not already received FDA marketing authorizations for that specific intended use. And just so we're all on the same page, I'll point out that the term marketing authorization is just an inclusive way of saying that it's been approved, clear, or granted a de novo request by FDA.

Okay so you have this investigational test. Now what? Well then the IDE requirements would apply. That the regulatory requirements depend on the level of risk that investigational IVD presents to study subject. So an investigational test can be exempt from IDA regulation or if they're not exempt then they fall into one of two categories, either significant risk or non-significant risk. And this slide provides an overview of - a very broad overview of risk determination. And the first question is: is the test exempt?

And the full criteria for exemption is spelled out in 812.2 but, in short and in this context for co-development programs, an investigational IVD would be exempt in situations where the testing is not used as a diagnostic procedure without confirmation of diagnosis by another medically established diagnostic product or procedure. And also to be in this category of exempt, it would have to be a non-invasive sampling procedure. So for example, if the test is used for exploratory purposes or retrospective analyses using tissue from a routine biopsy, that could fall into this exempt category.

So if the test is not exempt. The next question is, is - does the use of the test in the trial pose significant risk to the trial subjects? So again it's spelled out fully in 812.3 and the most relevant provision of 812.3 is for co-development programs is the quote "is it for use of substantial importance in diagnosing, curing, mitigating, or treating disease or otherwise preventing impairment of human health and present the potential for serious risks to the health, safety, or welfare of a subject." Since you can't see my air quotes.

So the risk comes from using the investigational test for critical medical decisions in these trials, decisions like enrolling subject, assigning subjects in a trial to a different treatment arm or selecting a particular therapeutic dose for a subject. These uses are the ones that could provide - may pose serious risk to the health, safety, or welfare of subjects if the test result is incorrect. On the other hand, something like balancing the marker across treatment arms based on the test result would not be expected to pose significant risk to the study subjects. And this is what we call non-significant risk.

I'll just note that risk determination takes into account many other factors beyond this simple what is it used for in the trial and may look at disease or other aspects, other treatments that are available. And so it's not always a straightforward process. And FDA, in attempt to provide more clarity on this, is intending to put out a draft guidance to explain further this risk determination process. But it's not elaborated to very much extent in the co-development guidance.

Okay so if an investigational test is significant risk, the sponsor has to comply with the IDE requirements again spelled out in 812 and in the guidance. But this includes having to submit to the agency an IDE submission. And FDA approval is required before the trial can proceed. On the other hand, if it's not significant risk, sponsors still have to apply with abbreviated requirements,

which includes providing the IRB with an explanation for why it's not significant risk. But it doesn't - there's no IDE submission in this case.

Okay so co-development trials, they raise unique issues because often you have an IVD that's important for meeting the objectives of the trial as it relates to the therapeutic product but it's also an investigational IVD. So sometimes the information about the IVD is also needed by the therapeutic product center. And we've gotten a lot of questions over the years about where should the information go and we've tried to clarify that in this draft guidance. So as I mentioned, if the investigational IVD is significant risk you need to send FDA and IDE submission and that's where the information about the IVD will go.

Putting significant risk IVD information in an IND will not suffice for the IDE requirement. So it has to be done in its own IDE. But if the information is also necessary - if the IVD information is necessary to determine - for the therapeutic product center to determine whether the trial can meet its objectives, it may be sufficient for the IND to cross reference the IDE.

And then in the case of non-significant risk, an IDE isn't submitted. So if the therapeutic product center needs the IVD information then it may - it will go into the IND and there will be a discussion about this with the therapeutic product center.

Okay so what information actually goes into this IDE? And here's some of the things that we think are generally useful for assessing investigational IVDs in co-development programs. You know, obviously these would only be included in the IDE if they're relevant for the use of the IVD in the particular trial. So we're looking for a description of the IVD cutoff value, a description of the pre-analytical and analytical studies that demonstrate the reliability of

the assay particularly around the cutoff value. And we're looking for the results of these studies as well.

A description and the results from other analytical studies that support the conclusion that the use of the IVD doesn't expose the subjects to unreasonable risk of harm. These other studies could be precision or limits of detection or specificity, things like that.

And the clinical trial protocol should be included, and this can be done either through direct submission or by referencing the appropriate IND. If you're referencing an IND, a letter of authorization to cross reference should be provided by the therapeutic product sponsor. And examples of letter - of these letters are in the appendix.

Okay so moving onto IVD considerations in co-development programs. There are two sections, two pretty meaty sections, about this in the draft guidance. One, the first one is essentially about what to do when you're getting started and the major theme here is plan ahead. And the second is about things that happen in later stages of co-development programs and how to deal with some of the issues that emerge. Okay.

So I'll start by saying what I hope is really obvious and that is, the test is important. So if the test isn't reliable or accurate it could compromise the ability of the trial to demonstrate an effect on the treatment. It could also compromise the ability to determine whether the test can appropriately identify the subjects for whom the therapeutic product is intended to provide benefit. And we've seen cases of this where the testing was inconsistent and the drug was not able to be approved. These are situations we'd like to avoid. So we provided recommendations in this draft guidance for how to approach

co-development programs from an IVD perspective to help avoid some of the common problems that we have seen.

Okay so what are these common problems that we've seen? And we've been looking at multiple many, many co-development programs over the past 15 plus years. And here are some of the problems. So the tests are not adequately validated prior to use in the trial such that, you know, the test performance is not robust enough for the needs of the therapeutic product sponsor. It's also a problem when multiple tests with different performance are used in the trials. This makes it really hard to know how the tests are comparable and whether they would identify the same population.

It's also usually a problem when changes are made to the test during trials. And again here it's hard to know if the changed test would identify the same population as the test before it was changed. And then there's a possibility of introducing bias from prescreening. So prescreening is what we refer to as the practice of using local tests to funnel patients into marker based clinical trials. One problem is that there's no assurance that local tests are interchangeable or standardized. And another problem is that prescreening could result in a biased clinical trial population that doesn't actually represent the population that would be selected in real world testing. Okay so lots of problems and here are some solutions.

Coordinator: This is the operator. Please stand by for today's conference. Pam will be rejoining us momentarily. Please continue standing by.

Pamela Bradley: Hello operator?

Coordinator: And once again this is the operator. We appreciate your patience. We're just experiencing some technical difficulties. Please hold on the line. Pam will be joining us momentarily. Thank you. You may begin.

Pamela Bradley: Great. Thanks everyone. Sorry. I'm not sure what happened. I hope you can hear me now. I think we were just getting to some solutions. So that's the important part, not the problem. Okay so an overarching theme here is that the test - let's see. Okay everyone can hear me. Great. Overarching theme - the test should be analytically validated and it should be locked down before using in a clinical trial. It shouldn't be changed during the course of the trial. It should be sufficiently analytically robust, particularly around that clinical decision point or the cutoff.

And when you're using a test in a trial that's intended to provide the clinical validation, it's really important to have completed the analytical validation studies that are evaluating those critical performance parameters. And in pivotal trials, you should really be using a test with market ready performance. And in the guidance, we define market ready as a test that's completely specified with complete analytical validation and one that meets the therapeutic product sponsor's expectations for performance.

So on the next slide, we're listing some additional general recommendations for helping to reduce variability and test performance. So all clinical trial assays, or CTAs, should be fully specified including all the components, all the protocols, all the instrumentation. It's really important to implement a single testing protocol at all sites that are involved in the trial. Also, the sponsor should evaluate comparability of test results among the potential sites prior to initiating testing at those sites.

And the pre-analytical reagents and instrumentation should be considered to be part of the test system and these should be validated along with the IVD. So, for example, tools or reagents for a DNA extraction should be considered to be part of that test and they should be validated as such. Also for all the steps of the pre-analytical specimen handling and preparation, there should be detailed SOPs or protocols that are followed at each of those sites that perform any of these steps so that everybody who is getting you the specimen has analyzed it in the way that you need it so it's very comparable.

Okay this slide is listing recommendations for how to address that prescreening bias, which as I mentioned, it can happen when local screening is effectively a prescreen for identifying patients eligible for clinical trials, where they're only sending forward those patients who are eligible according to a local test, and you may be missing patients who would be negative according to that local test but have - or might be positive according to the test use in the trial. So recommendations: One, avoid enrolling subjects into a trial based on confirmation of local test results, if you can.

Two, ask the participating clinical sites to send forth specimens from all potential enrollees, not just the ones that were positive by their test. And three, when it's unavoidable, which is the case in certain situations and particularly in oncology, it's important to be aware of the potential for bias and evaluate whether the expected prevalence of the marker is being skewed by prescreening and then to develop approaches to address this selection bias.

Okay so the draft guidance also makes the point that it's important to know what analytical studies are likely to be necessary to support the IVD premarket submission and to plan ahead for those studies. Again: plan ahead, plan ahead, plan ahead. So, for example, if the analyte is potentially unstable, it might be necessary to take several samples. It can be from a small number

of clinical trial subjects but that will help you assess the stability. In general sponsors should collect and bank adequate samples from the clinical trial to be able to complete this full range of analytical studies that they anticipate having to do.

But it should be noted that not all analytical validation studies need to be done with the clinical trial specimens. But if you are going to do these, you know, with non-clinical trial specimens, it's important that the samples are from the same target population so we can reduce the chance for variability. And I'll also note that for some validation studies, it's possible to do them with contrived samples. And this is in cases when it's not possible to obtain the specimens for the particular marker, or something like that.

Okay so clearly banking specimens is really critical to being able to fully validate this IVD. And sponsors of the therapeutic trial, and Chris mentioned this in the beginning, that if you believe there's a need for a companion diagnostic or there may be need, then you should have a plan in place for banking the samples for future studies. Appendix two in the draft guidance goes into a lot of detail about specimen handling and this also includes a lot of information about banking specimens.

So here on this slide are just some of the highlights from the appendix. In the interest of time, I'll kind of run through these pretty quickly. Bank samples from the intent-to-diagnose population, not just the subjects who are enrolled. Make sure to consider accessibility to samples in foreign countries. It's also important to consider the informed consent policies for all uses of the samples, for example, making sure that retesting is covered. Thorough specimen annotation is needed and it's important to consider how stable the analyte is when you're storing those specimens because you may be better off storing a purified or extracted analyte.

Okay so another component that's really critical to successful companion diagnostic development is this issue of training versus validation set. Okay so the set of clinical samples used to design the IVD and establish that clinical decision point or cutoff is referred to as the training set. So testing should be conducted with the second set of independent clinical samples to validate that the chosen cutoff is the right one. This set is called the validation set. So for companion diagnostics, the validation set is generally made up of samples from the subjects who were screened for enrollment into that major efficacy trial. And for this reason, you really want to have your IVD design and assay cutoff established before the IVD is applied to these samples.

Sometimes after seeing the data, the sponsor will want to change the cutoff. So, for example, they may want to change it to include all of the responders. The changes are made based on the results from the validation set. Then effectively this becomes a new training set for the modified IVD and then the new cutoff should be validated with a different independent set of clinical samples. So okay.

And we also know that other types of changes might happen as well. They could be changes in reagent configurations or instruments or platforms and they can also happen pretty late in the IVD development or in the co-development program. And so in these cases, to determine whether this new test has a very similar performance to the previous test, the sponsor might need to do what's called - or typically will need to do what's called a bridging study.

So a bridging study is a statistical plan to assess concordance and discordance between two tests using the same samples from the clinical trial. So an analysis study takes into account discordance, missing samples, and effect on

drug efficacy. The retest population really needs to be representative of the intended use population for the IVD and it should adequately reflect the characteristics that could affect the test performance because reanalysis of the trial is potentially biased if this retest population isn't representative. So there should be a plan to analyze the worst case scenario for missing data with a sensitivity analysis.

Okay so that's lots of general advice and many of you may be wondering how to implement this advice in your specific codevelopment program because there's always going to be product specific considerations that feed into the plan. So our advice is basically: as soon as you know that there is co-development intent, use the pre-submission program for feedback about specific IVD issues.

So a pre-sub is a formal written request from the sponsor to FDA requesting FDA feedback. And it's an opportunity to ask questions and have discussions with the IVD review teams about the product development. Questions could be related to clinical protocols or analytical studies or the appropriate regulatory pathway for the IVD. The co-development draft guidance provides some links and additional information about the pre-sub program. And again please use this process to come talk to us as early as possible. The goal is really for IVD development to be as efficient as possible and not slow down the development of the therapeutic product, which is usually further along at the point where the IVD gets involved.

Okay so now we're switching gears to go over the recommendations for coordinating the review of the IVD and the therapeutic product again with the goal of contemporaneous approval. Okay so here are the different submission types. You have the new drug application for the drugs, the NDA, the biologics license application for the biologics and the companion diagnostic

will likely be class three and require a premarket application. But we do have information in there about other potential pathways.

The statutory timelines differ for the therapeutic products and the IVDs, but in practice the IVD review is going to be kept on track with the therapeutic product review timeline so that both products can then come into the market at the same time. And in some cases, those therapeutic product timelines are shortened even further such as for expedited review or accelerated approval and that can create a real crunch on the IVD side of things. But there are some things that we do and that the sponsors can do to help out in those cases.

One is IVD priority review. So generally FDA has granted priority review status to the companion diagnostic submissions and this is particularly true when the companion diagnostic is the first-of-a-kind. Another thing that helps is the modular PMA process where - so this is where modules are submitted as they are completed and not waiting until all the clinical data is there to submit everything as a complete package. So this process basically gives FDA a head start in reviewing the IVD and this allows any issues that are found along the way to be identified and addressed. The last module that comes in is the clinical data and that's basically timed with the start of the review of the drug as well.

Okay so with respect to the manufacturing inspection, FDA tries to schedule this as early as possible for companion diagnostics so they have time to address any findings from those inspections before the deadline. It's really helpful for FDA to have this module as early as possible so that all the necessary documentation can be in place ahead of the inspection. Okay so there's also the BIMO, or bioresearch monitoring, inspections and these are the inspections of the clinical investigations. It's extremely helpful for us for the FDA if the BIMO information is organized in the PMA either in its own

section or somehow identified as BIMO information. And the types of BIMO information are detailed in the guidance.

It may also be necessary to set up a master file. For example, maybe the therapeutic product company has proprietary information but this information is relevant to the IVD review. So in the IVD application, it can reference this master file to get to this information. So if you think this is going to be the case, it's good to set those up. Likewise, it's good to set up these letters of authorization ahead of time or as the products come in so that each one can refer to the other. So it's authorizing basically the other applicants to refer to the NDA or the BLA or the PMA in support of the other applicant's product. So again there's some letters examples provided in the appendix.

All right so moving on to labeling. Okay so the draft guidance it reiterates the point that was made in the companion diagnostic final guidance that Chris mentioned in the beginning and that is that the two labels need to be consistent with each other. So as an example, if a drug's indicated for a population that has a particular spectrum of gene variants, the companion diagnostic should generally be indicated for the detection of all those variants in that spectrum. The guidance also discusses that there are several types of claims that could be generated for a companion diagnostic and that the claims - these claims are usually based on how the IVD was used in the major efficacy trial.

First, prediction claims. So a prediction claim would be supported by evidence that the benefit accrues to, only to, or primarily to a population that's defined by that IVD result, or evidence that serious adverse reactions are confined to that population defined by the IVD result. So prediction claims, they require information about both test positive and test negative. And so it's not possible to support a prediction claim for the IVD if you've only tested the test positive - or sorry, if you've only enrolled the test positive or the test negative because

you - in these cases you just don't have information about the safety and efficacy of the population that's not treated.

So trial designs like that, where only the test positive subjects or only the test negative subjects are selected for enrollment in a trial, they typically support companion diagnostic claims for patient selection. And then the final category of monitoring claims, the guidance really doesn't go into the trial designs needed to support this. So you should discuss those types of claims with the agency directly.

Okay so the final topic before we open it up for Q&A is post marketing considerations and this is short and sweet. The first point I want to make is that we recommend that sponsors - therapeutic product sponsors consult with FDA when they're designing their post marketing studies that might involve companion diagnostics. And then the next point is pretty straightforward, hopefully. If you - for adverse event reporting, so, report IVD reportable events to the IVD center; therapeutic product reportable events to the therapeutic product center. And if it's not clear or if both products could have contributed to the reportable event, report it to both centers.

Okay so let's sum up here with some key points. Use a clinical trial strategy that provides evidence for both the therapeutic product and the IVD. Read the enrichment guidance because it goes into much more depth on the trial designs that are appropriate for these studies. Interact with the FDA early and often. IVD sponsors can use the pre-sub program at any time in the process. Plan ahead. Collect clinical trial specimens and annotate and store them well because they will be needed for additional analytical validation studies and bridging studies or in the cases of when you're just learning about the biomarker, retrospective - perspective retrospective studies as well.

So the therapeutic product sponsors are encouraged to engage with the IVD partner as soon as possible in this process. The trial sponsor should determine what the IDE requirements are that apply to the investigational IVD that they're using in their trial and fulfill them. It's really important to complete the analytical validation studies before using the test in the trial. And it's recommended to use the test with market ready performance in the pivotal trials.

Okay so I'll end with this complex slide. So even a simplified view of co-development, it's really a complex to figure. And I think that's the nature of this co-development process because you're trying to weave these two distinct processes into one and get across the same finish line. So for IVDs, you need to think about whether you need an IDE submission, completing your analytical studies before using the test in the trial. You need to validate a new version of the test and lock it down again before continuing on. So it's these arrows that are going in and out of this analytical validation studies. And you may need a bridging study if the final version that you're putting before the FDA is not the same as what was used in the study.

So again use the pre-submission process at any point along this continuum to engage with the agency. On the therapeutic product side, it's much more linear, at least as compared to IVD development. So there are more regular meetings between FDA and the sponsor at the different phases. And these meetings are a great time to discuss incorporating the companion diagnostic strategy into the therapeutic product development.

Okay so with that, I will remind you that the docket's open until mid-October. We hope that you'll submit comments and help us finalize this draft. I want to point that - point out that although we did a pretty deep - a pretty comprehensive walkthrough today that the draft guidance contains a lot of

other points that we haven't raised that are also important for successful co-development. And so we encourage you to take a deep dive and give us your comments on all aspects of the draft guidance that are important to you. Okay so thank you for your attention. We'll now turn it over to Q&A and I - we have colleagues from the - from all three centers that have been involved in this. Other people were involved as well. It was a great group effort. I think we can open it up for questions now.

Coordinator: Thank you and to ask a question…

Irene Aihie: Thanks Pamela.

Coordinator: …at this time please press star one. Please unmute your phone and clearly record your name at the prompt. To withdraw your question, please press star two. Once again at this time, please press star one to ask a question. One moment please for the first question. And we do have questions coming through. One moment please. The first question is from (David Rim). Sir your line is open.

(David Rimm): Thank you. I have a question. I didn't hear anything about absolute measurements. You talked about pre-specified cutoffs but are those cutoff values equal to any absolute measurement or is there any stipulation for comparison of a pre-specified cutoff to a universal standard?

(Liz): Pam did you hear that one?

Pamela Bradley: (Liz) I was going to let you take that one. Sorry for the silence…

(Liz): Okay. In that case, I'm not sure I exactly understand the question. So in terms of the cutoff, he wants to know how that corresponds with (unintelligible). I'm sorry is the questioner still there?

(David Rim): Yes I'm still here. The - I didn't realize the line was open. My - what I mean by a standard that is a cutoff could be a plus one or a plus two whereas a standard is a micrograms per ml or nanograms per ml, or microgram total protein. Some standard that could be reproduced by other sources or orthogonal methods, as opposed to an internally agreed upon and arbitrary cutoff.

(Liz): Yes so we would expect a cutoff, like plus one or plus two, if it was adequately explained how you got to that score. As you probably know, there are multiple ways to get to certain scores. We would also assess a cutoff that was a quantitative measurement or even a qualitative measurement of positive or negative if you had some kind of internal standard for understanding what positive and negative was. Does that answer your question?

(David Rim): So there's no reference standard to which these are required. That is, I'm concerned then that essentially a test could be analytically validated for reproducibility but not for so for precision but not for accuracy.

(Liz): So we would look for validations of accuracy as well as precision around the cutoff that you establish.

(David Rim): But accuracy infers that you can obtain the same result by an orthogonal method.

(Liz): So for us, accuracy would be in most cases comparisons to a truth, a reference method, a clinical manifestation. So we've done a number of these now and

this is - has not been an issue. In general, the accuracy ultimately pans out clinically by assessing what are the patients be selected actually pass the benefit intended. And the accuracy analytically is generally demonstrated against samples with a known value, whether that's a qualitative or a quantitative value or semi- quantitative.

Irene Aihie: We'll take our next question.

Coordinator: (Mark McCarthy) your line is open.

(Mark McCarthy): Hi. Thanks very much for taking the question. I'm not entirely certain that I understand some of the elements of timing and what appears to be an involvement of the question regarding the use of a clinical trial assay. The agency seems to be saying that the PMA or most of the time it'll be a PMA filing for a companion diagnostic will have to be completed but not necessarily approved prior to the commencement of the pivotal study for the therapeutic article. Assuming I've got that right, I'm trying to sort of square that with the idea of a clinical trial assay and I'm not aware of any stipulations that a CTA cannot be used during the clinical trial. I mean and I don't know if the bridging study is how you take the CTA, you know, out to approval. But can you at least say a little bit about the question of, you know, having the entire PMA file versus having the PMA approved before the commencement of the pivotal study and assuming that's the case, where the clinical trial assay fits into all this?

Pamela Bradley: Sure. This is Pam. I'll take a first crack and then turn it over to the room. So maybe I misspoke but the - you do not have to have a PMA file before you start the pivotal study. You - what we hope is that the test that's used in the pivotal study has market ready characteristics so that you really understand how that test performs. And you mentioned that going from the CTA to the

IVD that would be filed as a PMA. That process can be done using the bridging study to get from that CTA to the IVD. Does this answer your question?

(Mark McCarthy): Okay thank you. Appreciate it.

Christopher Leptak: Operator next question.

Coordinator: Thank you and before we take the next question, as a reminder questions are only taken over the phone today. If you'll please press star one to ask a question at this time. Our next question is from (Abdel Halene). Your line is open.

(Abdel Halene): Sure. Thank you. Actually I have four questions. Do I share all of them at once or one by one?

Christopher Leptak: How about prioritize them?

(Abdel Halene): Sure prioritize. All right so for my question slide number four and slide number 14, I believe the question is the two points are related. It was mentioned that you can enroll marker positive subjects only if the biomarker is known to be a predictable prognostic. So does this mean that the biomarker clinical qualification has to be done in a prior clinical trial where the clinical value is the biomarker can be elucidated and the cutoff can be established?

Mike Pacanowski: Hi. This is Mike Pacanowski. The confidence that a clinical trial can be conducted in a marker positive subset locations depends on a number of factors. There may be experimental evidence that would suggest only a certain subset of patients respond. There may be preliminary evidence from early phase clinical trials that suggest differential responses based on biomarker

status. So there's a number of different approaches to determine whether or not a marker positive trial should be conducted. So it doesn't necessarily rely only upon clinical evidence necessarily.

Christopher Leptak: And just to be clear, you had mentioned as part of your question qualification. So qualification has a very distinct meaning here at the FDA. And it involves biomarkers that are developed in a drug independent context through the formal biomarker qualification program. And just I'm not sure how you're using that term as part of the question but I just wanted to make that clarity.

(Abdel Halene): Yes I meant to prove that the biomarker is a predictable prognostic.

Christopher Leptak: So the biomarker development can occur within the IND context or through qualification. It wouldn't have to be qualified in a formal sense for it to be used in an IND setting in clinical trial.

(Abdel Halene): All right. So my next high priority question is about the bridging study. So there was not too much details but my question is I know it can be case by case from FDA perspective. But and as (unintelligible) figure when we do bridging study with CTA again this is to be marketed for IVD against the CTA, do we reanalyze samples with the CTA also at the time of bridging or we consider the initial data? And if we need to re-analyze because probably the samples have been aged and we established it can be an issue, what about if reanalysis with CTA results can be discarded from the initial results?

Christopher Leptak: Pam do you want to start?

Pamela Bradley: I was going to let (Liz) answer this one.

Elizabeth Mansfield: So I'm sorry the question was when do you need to the bridging study between…

(Abdel Halene): No. The question was if we - in your slide number 30, you mentioned the bridging study and I'm assuming you meant bridging of CTA clinical trial and assay which is to be marketed IVD. So and it happens most of the time now in pharmaceutical (unintelligible). So I'm asking as the final bridging do we test - do we need to reanalyze the samples with the CTA or we use the initial results from the CTA? Because reanalysis sometimes is needed if in the stability of the biomarker can be an issue. So the question is do we need to reanalyze and fully analyze and the results from reanalysis can be (unintelligible) from initial results which is set of samples we use - set of results.

Elizabeth Mansfield: Okay. I think I understand your question is do you need to rerun the CTA in the bridging assay…

(Abdel Halene): Yes.

(Liz): …when you're doing the bridging.

(Abdel Halene): Yes.

(Liz): I think it would generally be helpful if you did, but if you didn't have the samples or whatever, we can probably work with the original results.

(Abdel Halene): If we prefer to do actually reanalysis because of sample instability, especially if the study can take two or more years. So I'm asking - again my second part of question, if we reanalyze and we found the reanalysis data is not concordant with the initial results, which is it of the CTA results we'll use?

Elizabeth Mansfield: Well I suspect that would be an internal discussion with the FDA, and I - generally I think you probably want to use the results from when the samples were stable. But often when there's a stability issue, we have other ways to deal with bridging studies that don't necessarily use all of the original clinical samples.

Christopher Leptak: So we fully acknowledge that depending on when the co-development paradigm begins, especially if it's in the early phase, we expect, much like in the clinical program, that there's a maturation as you gather information and there's more scientific understanding. The same would be true under the buy site. So certainly we, you know, as the program moves forward, as it's successful and goes into phase three trials, also what we would like at the time of the phase three development is that the performance characteristics for the device are set and that there as Pam described sort of market ready. How you get there I think is a bit of a - there's a flexibility as the assay evolves and if there's any issues with stored samples.

(Abdel Halene): All right. Actually my question was for using CR. I'm asking about the clinical trial period of clinical trial with where CTT - CTA as (unintelligible) of this can be used for it.

Christopher Leptak: Right. So I know you had more questions but we have three other folks that are waiting to answer their questions. So if you don't mind, we'll move on to them. And just so folks know we were originally scheduled to stop at 2:00 but we're extending it given the technical difficulties earlier. But we do have a hard stop at 2:30.

(Abdel Halene): Sure.

Christopher Leptak: So I guess the next questioner.

Coordinator: Next question from (Eric Thomas). Your line is open.

(Eric Thomas): Hi. I have two questions. One, do you think you could expand a little bit about situations when you have a device that's considered non-significant risk and information needs to be submitted to the IND instead of an IDE? That's an area where it seems to be unclear what's in our company about what level of information is really necessary. Often we've submitted and we don't receive a response. So we're not entirely sure what the division is looking for there. That's the first question and then I can ask the second.

Christopher Leptak: Yes that one's hard to discuss in a very - in a general sense. Certainly if the device is initially considered to be a non-significant risk device, there are circumstances where the drug division would still like to know certain aspects about the device's performance in order to be able to interpret the trial from a drug perspective. What those characteristics are and when they would be required is very much context and case specific. But that information at least the way we work it out between the two product centers is that that device information could then come in under the IND at the request of the drug division and then we can consult with our device colleagues on whatever the information is that was submitted.

(Eric Thomas): So if I'm understanding the answer correctly it's really on only if the drug division requests that information. So say a risk determination request was put in and it comes back NSR. It's then usually generally acceptable then for the sponsor just to submit the protocol as per a typical study not including the device and just go forward?

Christopher Leptak: Yes it's hard because an initial qualification for the device may be non-significant risk but then as that program development matures something may change that classification to a significant risk or potentially. So the important thing is to make sure that you capture all the information so that if you do require it for the IDE in the future, you have it available. But in the interim, submitting it at the request of the direct division to the IND is probably the best approach.

(Liz): But if the IND - if they don't request it, you're not required to send it. It's only when…

Christopher Leptak: Right…

(Liz): …the drug division requests it and puts something in the IND (unintelligible).

Christopher Leptak: And maybe (unintelligible)…

(Eric Thomas): (Unintelligible) voluntarily ahead of time and weren't - it's ranged in terms of just having a few pages describing the general context of use to actually having like full validation. So okay.

Christopher Leptak: Right.

(Eric Thomas): That's really helpful. Thank you. And then my second question is regarding I know that the guidance, you know, promulgates using the market ready test in the phase three. Some cases - in some cases a test may be implemented in the phase three trial and then there are some improvements. Is the agency more open now to allowing concordance between two versions of the test if samples are being - can - shown to have concordance if they had to make some changes between the test employed in the phase three trial initially. Either it's

either done all retrospectively in terms of basically bridging between the two or having one portion run with one version of the test and the second run with the second version.

Pamela Bradley: So I'll start with just clarifying. We don't necessarily mean market ready test so much as market ready performance characteristics. And we understand that there are changes that happen after the trial is done to go to market.

(Eric Thomas): Okay.

Pamela Bradley: So maybe reagent configurations or things. So you don't have to have the test - the exact test that comes before the agencies and that's so when we say market ready I just want to clarify that that doesn't mean market ready test packaged up ready to go out.

(Eric Thomas): Okay.

Pamela Bradley: And then for the second part of your question, it's that bridging study. So if you do make changes then it's important to just show that the changes haven't affected the performance.

(Eric Thomas): Okay.

Pamela Bradley: In the sense of concordance and discordance, you're still very similar in that performance.

Christopher Leptak: I mean if you think about the post-marketing setting, we realize technology changes and nothing is static that's one of the reasons for the drug label that we refer to the device as a FDA approved or a cleared test. We don't

list the specific test or model so that that way there is this opportunity for innovation improvement in the future.

(Eric Thomas): Okay. And well thank you very much both of you answers are really helpful. If - well I don't - I know there's another speaker. If also if you had any information to clarify about differences between complementary and companion diagnostics because complementary is a relatively new classification I'd appreciate hearing anything you guys have to offer on that. But I don't want to take the rest of the time as well. So thank you.

Christopher Leptak: Yes I think in the interest of time since that's a little bit off topic let's move onto the next questioner please.

Coordinator: The next question from (George Popper). Your line is open.

(George Popper): Thank you very much. So I have a question with respect to the next generation sequencing based IVDs. The recent draft guidance on the use of standards for the NGS based IVDs is restricted only to germ line diseases or variance. And I'm wondering for those cases where IVD devices are intended as a companion diagnostic for a somatic disease, what kind of guidance can CDRH do with respect to data standards?

Pamela Bradley: (Liz) do you want to take this one since it's NGS…

(Liz): Yes. This is (Liz). At the moment we have not published any guidance or draft guidance on that. We have held a public meeting on it where I think a lot of principles were elucidated. At this time, I would suggest that the test developer would talk with OIR through the pre-submission process to get that information.

(George Popper): Okay great.

(Liz): You can do that. Okay.

(George Popper): Thanks.

Christopher Leptak: And operator last question I guess.

Coordinator: Last question from (Julie Engel). Your line is open.

(Julie Engel): Hi. Thank you for taking my question. I just had a question about the use of RUOs in the clinical program. It sounds like there's flexibility in using those if they are labeled properly and if they are - if you plan to commercialize them then you would have to under - they would have to undergo the design control process. What about the use of class one assays in this same context? Would the same issues of labeling and validation apply or can they not be used in a clinical program?

(Liz): So this is (Liz). I don't think there would be any issue with using a class one device in a co-development context. Unfortunately, we haven't identified any case of - or maybe fortunately we haven't identified any cases in co-development where the device would have been considered class one. If such a thing were to happen, if we had not already classified the test I think we would have to go through the de novo classification process. In order to classify it as class one if we had already classified the test and then (unintelligible) class one, well I think we'd have to think about what we would do then in terms of how we would be able to refer to that test in labeling.

(Julie Engel): Okay thank you. I also had a second part of that question. We talk about if the possibility of a 510(k) or a de novo and the labeling of that would that also

include the therapeutic in those labels or just the device in the therapeutic label but not the therapeutic in the device label?

(Liz): Generally it's our intent for a companion diagnostic to mention the therapeutic name in the device label as well as the device name in the therapeutic…

(Julie Engel): Okay. That makes sense.

(Liz): …or for the existence of the device in the therapeutic one.

(Julie Engel): Okay thank you which makes sense. It just wasn't clear in the guidance. Thank you.

Christopher Leptak: All right well thank you everyone for sticking with us especially with the technical difficulties early on. Hopefully this was helpful to you. And again just to echo Pam's earlier comments, please if you have any comments please upload them into the public docket and those comments will be considered as we move the guidance to final in the future.

Coordinator: And we will now turn the meeting back over to Irene Aihie for closing remarks at this time.

Irene Aihie: Thank you. This is Irene Aihie. We appreciate your participation and thoughtful questions. Today's presentation and transcript will be made available on the CDRH line web page at www.fda.gov/training/cdrhlearn by Friday, August 26. Please submit draft guidance related comments to docket number FDA-2016-D-1703 by October 13, 2016. The docket can be found at www.federalregister.gov/A/2016-16735. If you have additional questions about the draft guidance document, please use the contact information

provided at the end of the slide presentation. As always, we appreciate your feedback and this concludes today's webinar.

Coordinator: Thank you for attending today's presentation. This does conclude the conference. You may disconnect at this time.

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