>> **Stephen Lehrman:** Greetings. It is my pleasure to welcome you to today's webinar entitled: "A Regulatory Case Study for the Development of Nanosensors."

Our guest speaker is Dr. Kim Sapsford with the U.S. Food and Drug Administration (FDA). My name is Stephen Lehrman, and I'm with the National Nanotechnology Coordination Office, and I will be the moderator.

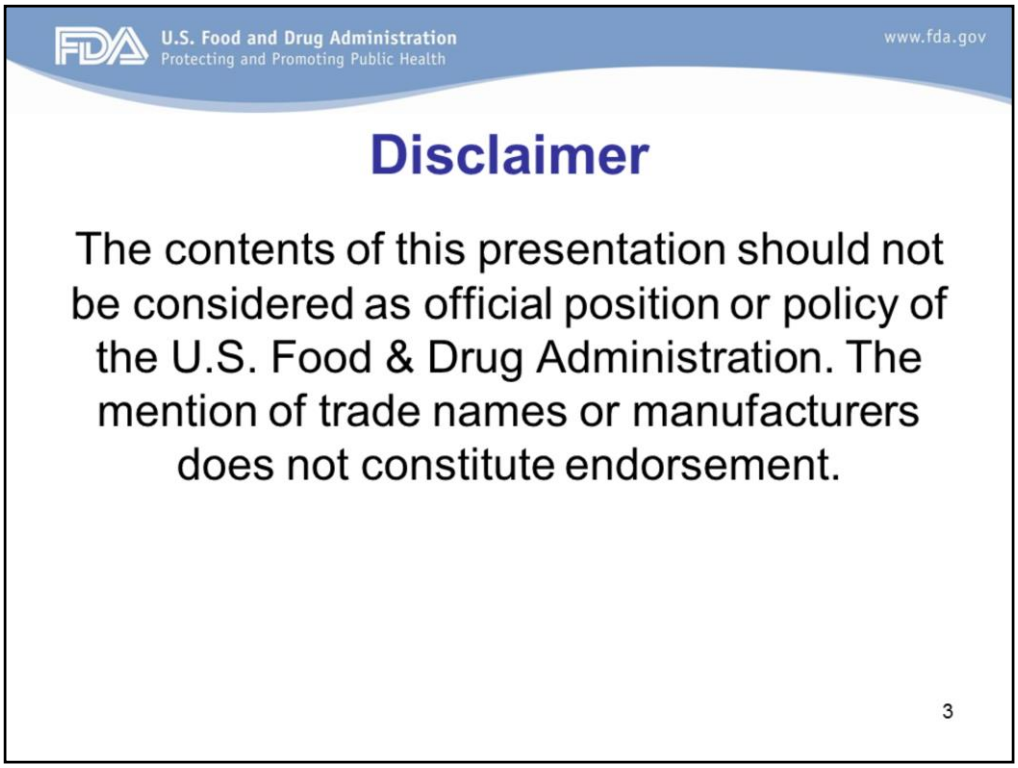
This webinar is part of the series in support of the Nanotechnology for Sensors and Sensors for Nanotechnology Signature Initiative, one of the five Signature Initiatives of the National Nanotechnology Initiative.

More information about the Signature Initiatives and the Federal resources supporting the development of nanosensors can be found at our website, nano.gov/sensorsnsiportal.

Dr. Sapsford is a premarket scientific reviewer at the Division of Microbiology Devices, Office of *In Vitro* Diagnostics and Radiological Health in the Center for Devices and Radiological Health (CDRH) at FDA.

Today's webinar will provide an overview of regulatory requirements for *in vitro* devices at FDA and a case study on a submission from a recently cleared *in vitro* nanotechnology-enabled sensor device. You are welcome to submit questions at webinar@nnco.nano.gov or using the "submit your questions here" window in the webinar interface. Now, please welcome Dr. Kim Sapsford.

>> **Kim Sapsford:** Thank you, Steve, for the introduction. Thank you all for joining the webinar today. I'd like to give a special thank you to the Nanotechnology Signature Initiative on sensors for inviting me to present today. I will present on a regulatory case study for the development of nanotechnology-enabled *in vitro* diagnostics sensors.



I have to start my presentation with a disclaimer that the contents of this presentation should not be considered as official position or policy of the U.S. FDA. And I wanted to add that the mention of specific products should not be considered an endorsement.

Acknowledgements

OIR/DMD

- Uwe Scherf
- Kristian Roth
- Patricia Conville
- DMD Staff

- Kevin Lorick - OIR

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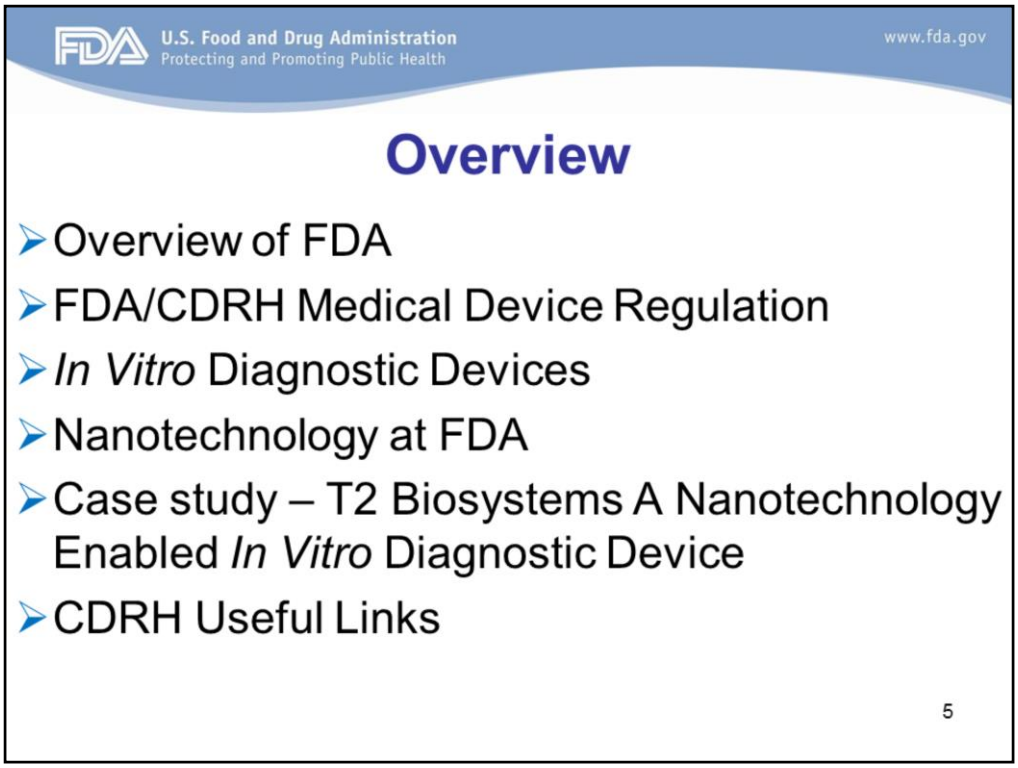
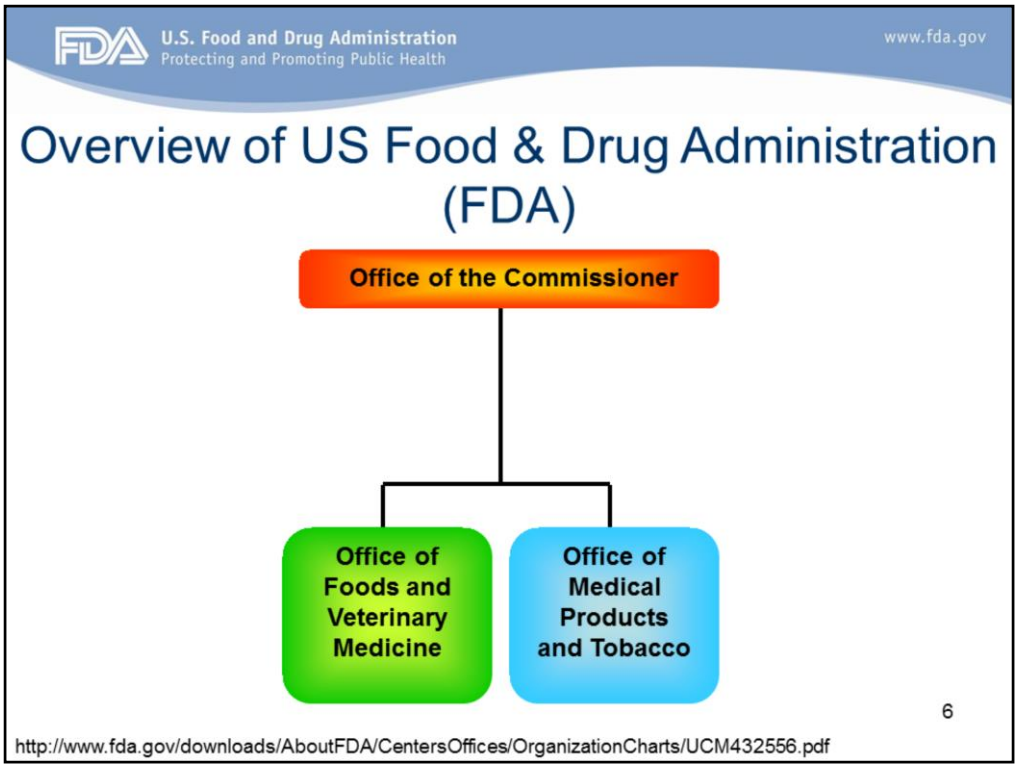
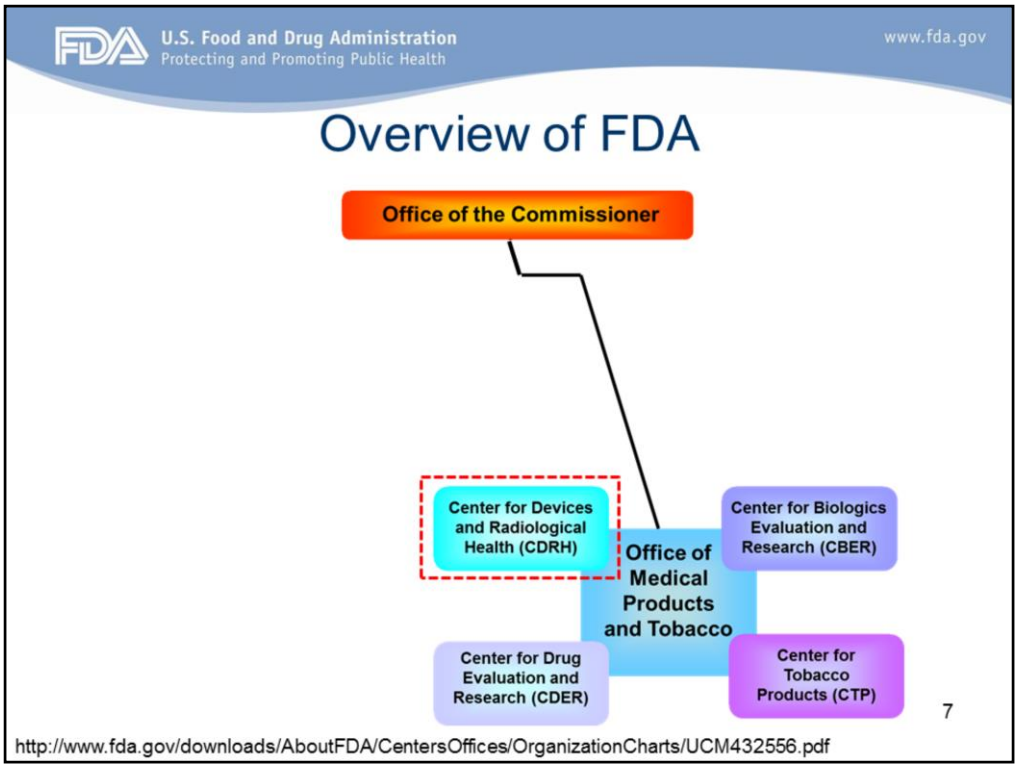
I would like to thank the Office of *In Vitro* Diagnostics and Radiological Health where I work and specifically: my Division Director, Uwe Scherf, from the Division of Microbiology Devices; my Branch Chief, Kristian Roth; and Patricia Conville who helped me prepare the slides today.



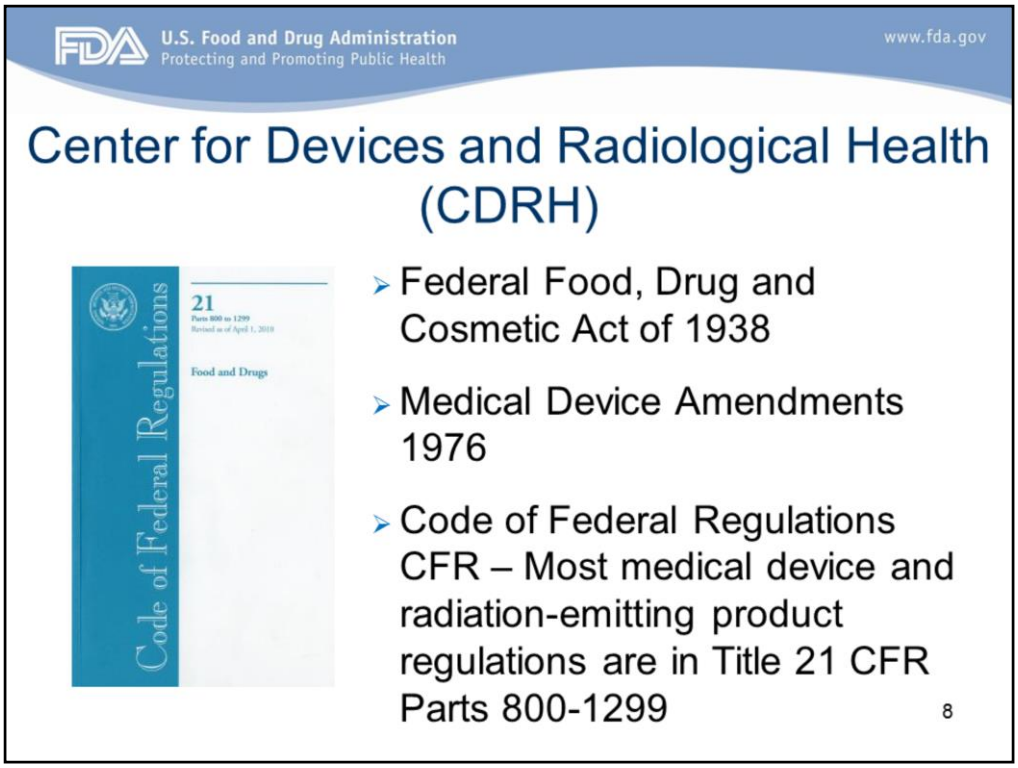
Here is an outline of my presentation: I'm going to give a brief overview of FDA. I'll then talk about FDA and CDRH medical device regulation. I'll then talk about *in vitro* diagnostic devices and nanotechnology at FDA, and then present the case study, which is on T2 Biosystems, a nanotechnology-enabled *in vitro* diagnostic device company. I will close the presentation with several CDRH links that will be useful for people developing these types of technologies.



To give you an overview of FDA, the agency is housed within Department of Health and Human Services, or HHS. The Office of the Commissioner oversees 12 main offices within the FDA. And the offices highlighted here are the two main offices that house the product-specific centers.

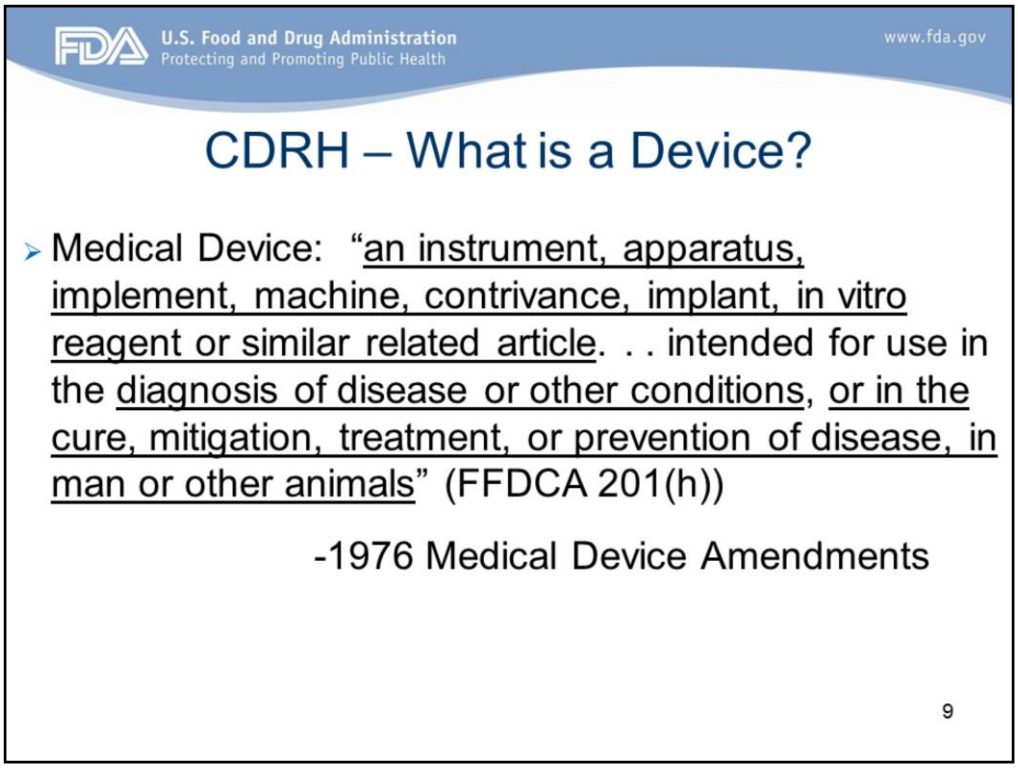


When it comes to *in vitro* diagnostics, these are mainly regulated by the Center for Devices and Radiological Health, which is in the Office of Medical Products and Tobacco. This office also houses the Center for Biologics Evaluation and Research, which is CBER; the Center for Tobacco Products, which is CTP; and the Center for Drug Evaluation and Research, which is CDER.

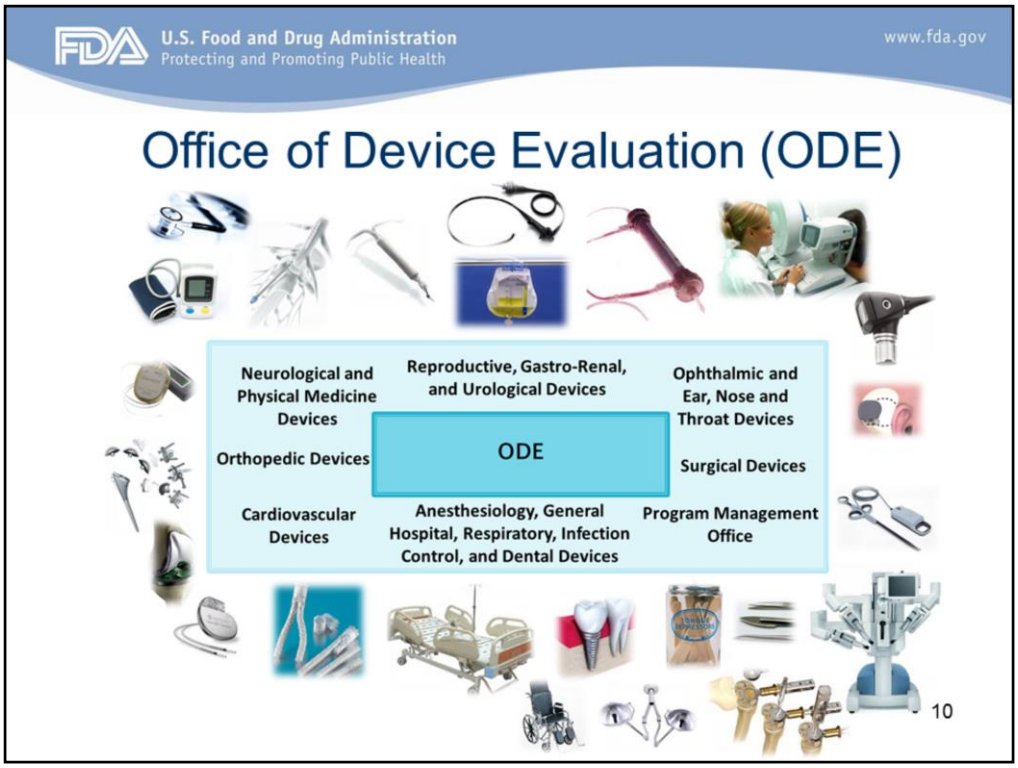


FDA authority comes from the Federal Food, Drug and Cosmetic (FD&C) Act of 1938; various Medical Device Amendments of 1976; the Modernization Act of 1997, 2002, and 2007; and finally the FDA Safety and Innovation Act of 2012. Under its rulemaking authority granted by Congress, FDA issues regulations and publishes them in the Code of Federal Regulations, or the CFR. It outlines the safety and effectiveness that binds all the studies that we ask for during our premarket review of devices.

So personally, I see the Federal Food, Drug, and Cosmetic Act as outlining the FDA authority to regulate medical devices and the requirements that need to be met by law. The CFR contains the regulations developed by FDA to meet the requirements of the Federal Food, Drug, and Cosmetic Act.

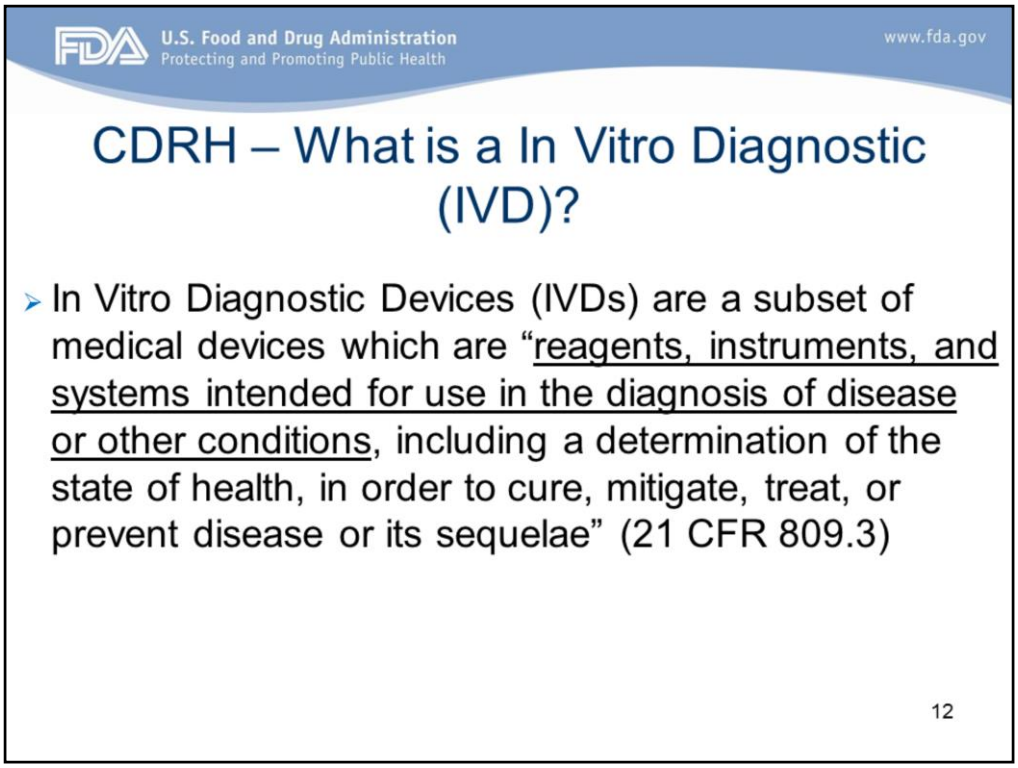


What is a device? It's an instrument, apparatus, implement, machine, contrivance, implant, *in vitro* reagent, or similar related article intended for use in the diagnosis of disease or other conditions or in the cure, mitigation, treatment, or prevention of disease in man or other animals. This is set out in the 1976 Medical Device Amendments Act.

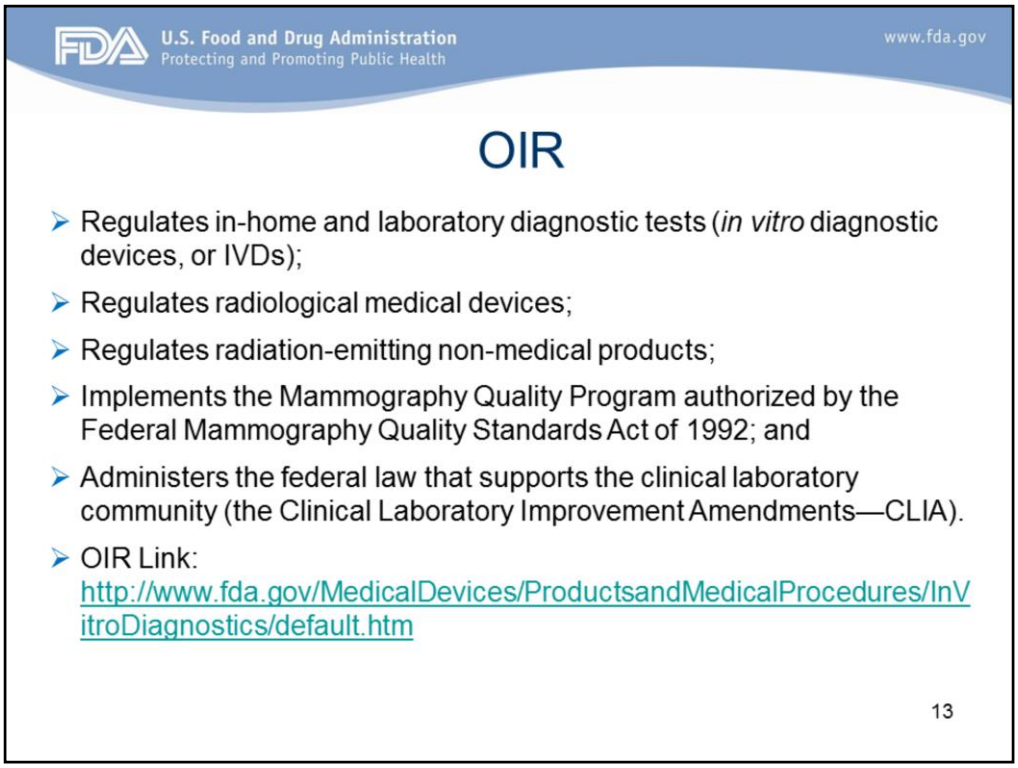


Within the Center for Devices and Radiological Health, we have two main offices that regulate the premarket submission of medical products. This includes the Office of Device Evaluation (ODE), and they regulate a wide range of medical devices, from simple tongue depressors to orthopedic devices and complex surgical devices, such as the Da Vinci surgical system for robotic surgery, which is shown here.

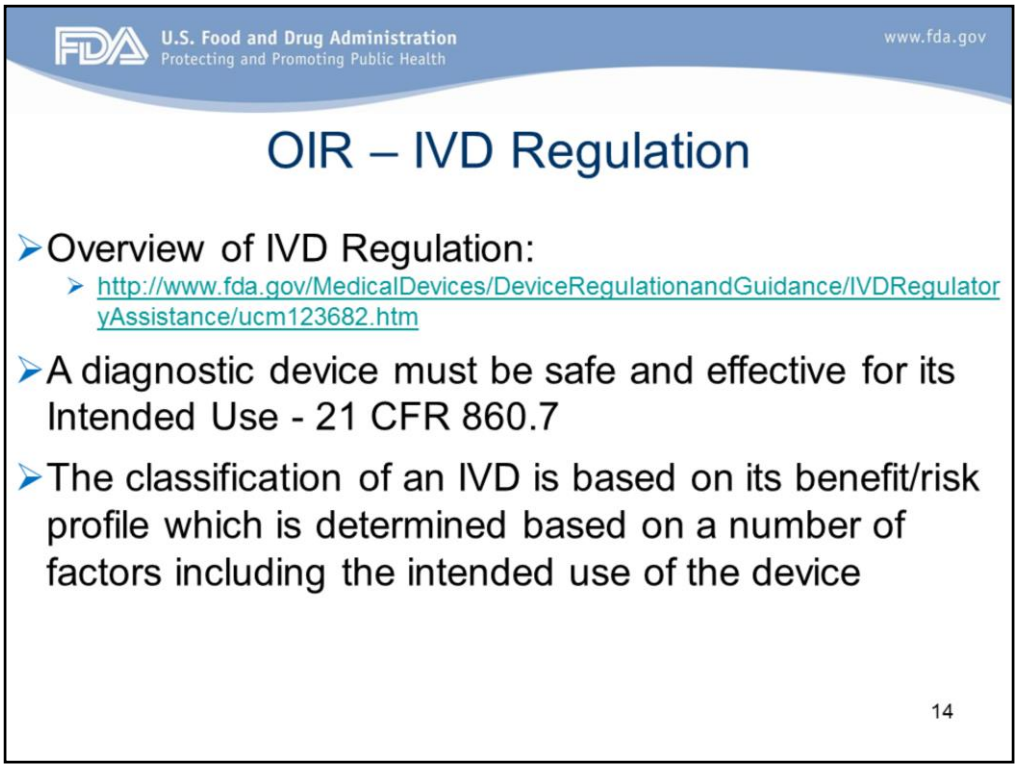
The other office is where I work: the Office of *In Vitro* Diagnostics and Radiological Health (OIR). OIR regulates a range of products specifically related to *in vitro* diagnostics and radiological devices. These include simple lateral flow test strips to *in vitro* diagnostics (IVDs) that incorporate complex clinical lab work stations and magnetic resonance imaging devices.



So what are *in vitro* diagnostic devices? They are a subset of medical devices, which are reagents, instruments, and systems intended for use in the diagnosis of disease or other conditions.



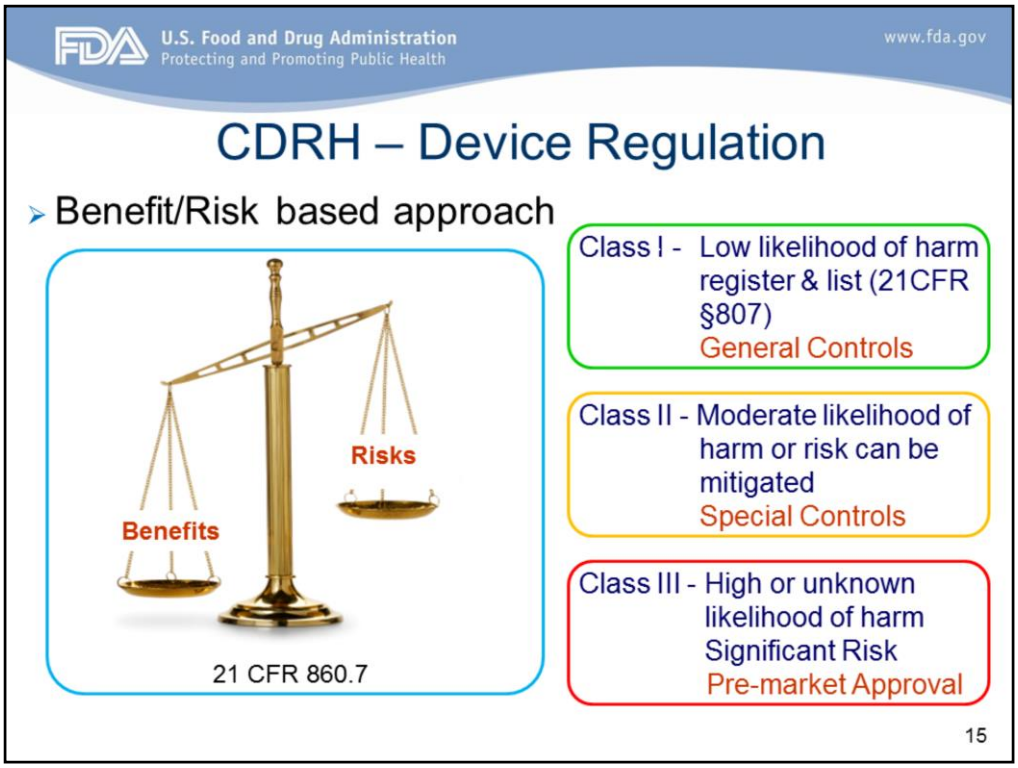
OIR regulates in-home and laboratory diagnostic tests or *in vitro* diagnostic devices. It also regulates radiological medical devices, and it also regulates radiation-emitting non-medical devices. I included a link that has a resource overview of OIR. It is a good resource to find out about the office.



I have also given a link to an overview of IVD regulation. A diagnosis device must be safe and effective for its intended use, and this is outlined in the 21 CFR 860.7. That's the Code of Federal Regulations.

It asks the questions: are there probable benefits to health from the device that can outweigh any risks? Also, is there reasonable assurance based on valid scientific evidence that the use of the device in the target population will provide clinically significant results?

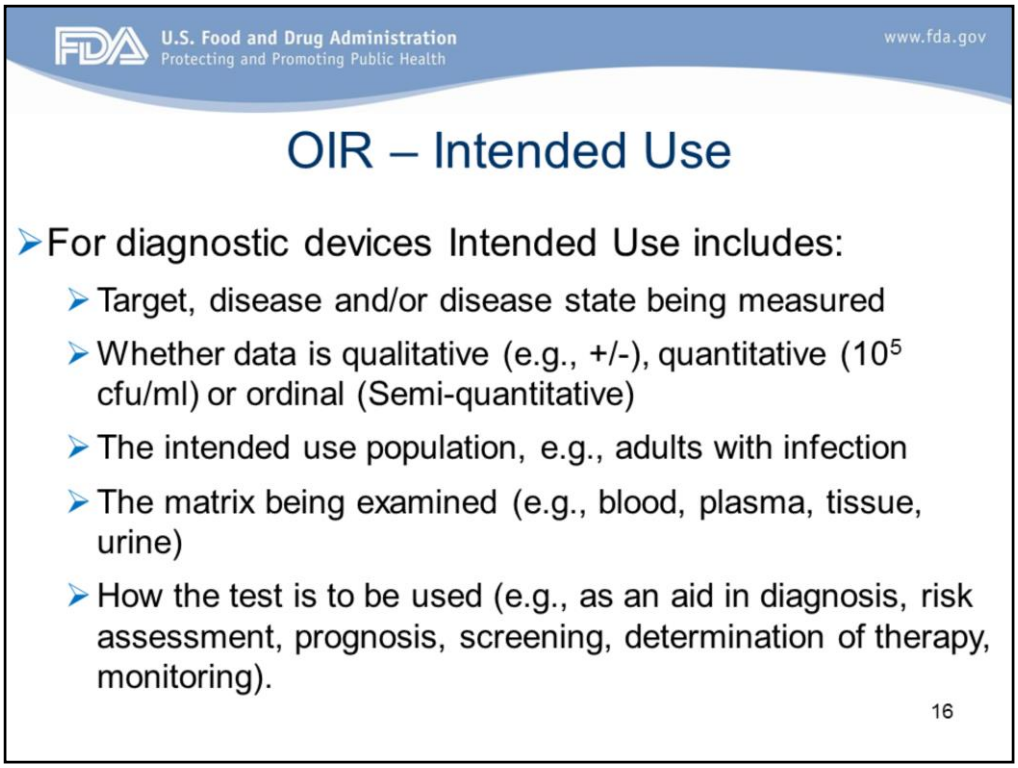
Valid scientific evidence that we evaluate during our review of IVDs must have benefits that outweigh the risks and results that are clinically significant.



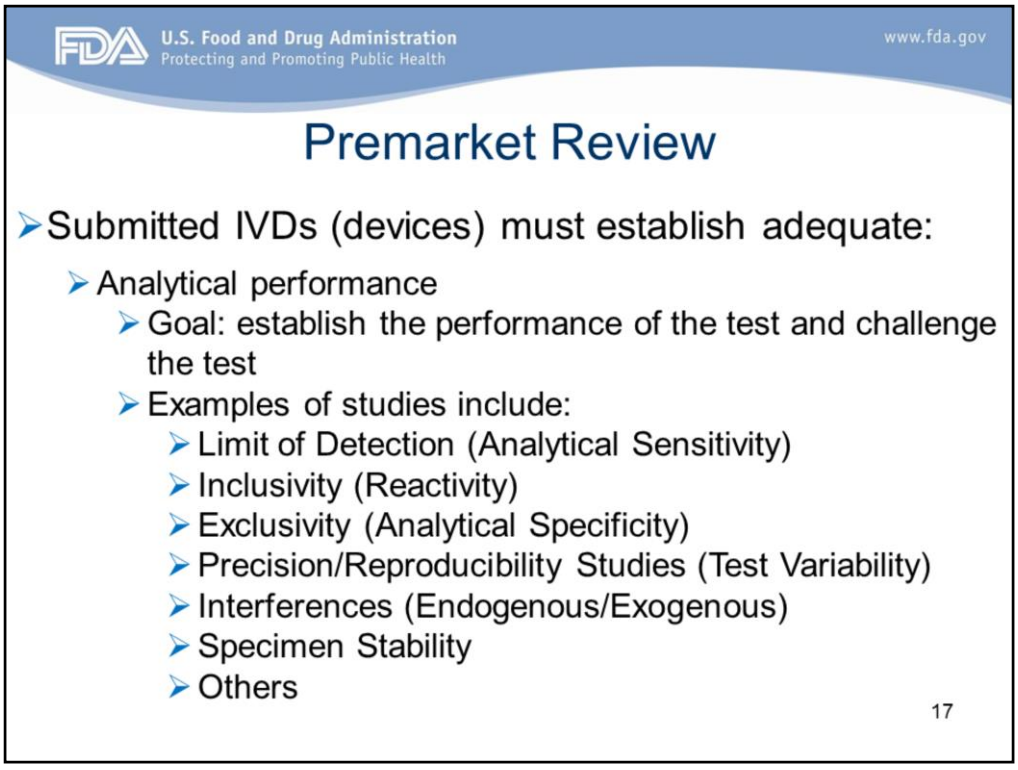
CDRH uses a risk-based approach when it regulates devices. The devices are classified into three classes. Class I is low likelihood of harm, and devices are just required to list and follow general controls. Class II devices are considered moderate likelihood of harm or risk that can be mitigated through the use of special controls. These types of devices typically require pre-market submissions to the FDA. Class III are high or unknown likelihood of harm, and these are considered significant risk devices that require a PMA or a pre-market approval submission to the FDA.

The classification of the IVD is determined based on a number of factors including the intended use of the device and its associated risk.

As I mentioned, Class II and Class III require pre-market submissions to FDA and clearance or approval before they can be legally marketed in the U.S. In the Division of Microbiology, we establish safety and effectiveness based on analytical and clinical data that's provided by the submitter in support of the device. This depends on the class of that device.

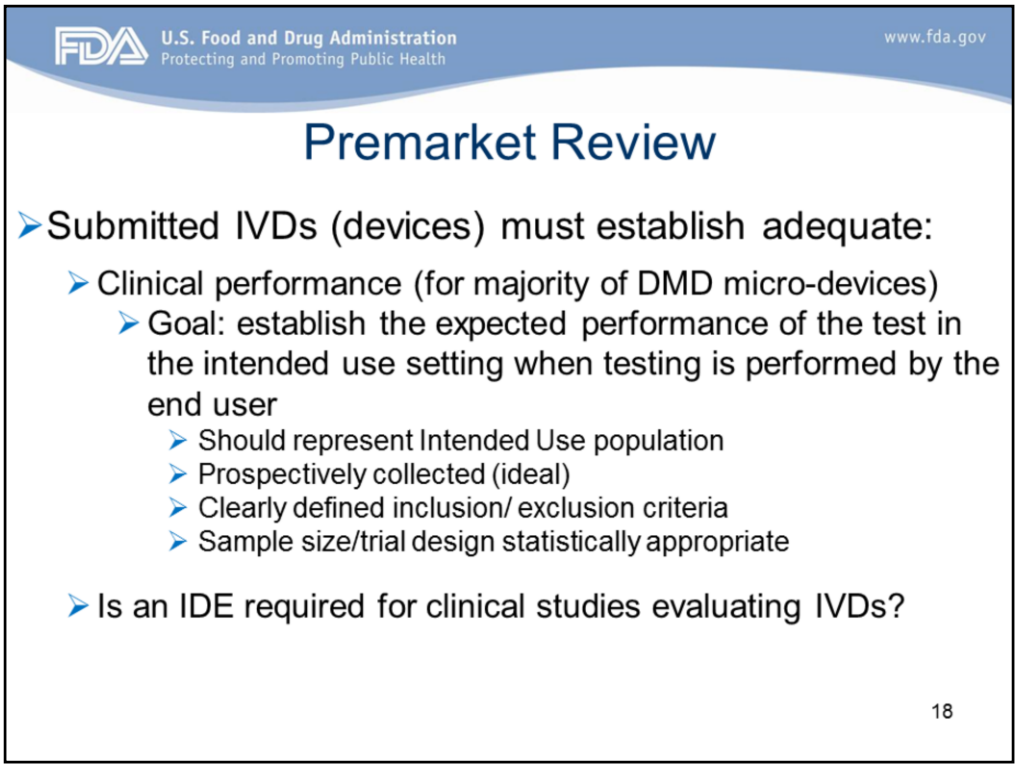


As I mentioned, the intended use of the device is a key component in determining the device classification. It should include the target disease or disease state that's being measured, whether the data is reported as qualitative, quantitative, or semi-quantitative; the intended use population, for example: adults with infection; and the matrix being examined. In this case, are you taking blood, plasma, tissue, or urine specimens from the patient? And then how is the test being used: is it an aid in diagnosis, a risk assessment? Or is it used for prognosis, screening, determination, therapy, or monitoring?

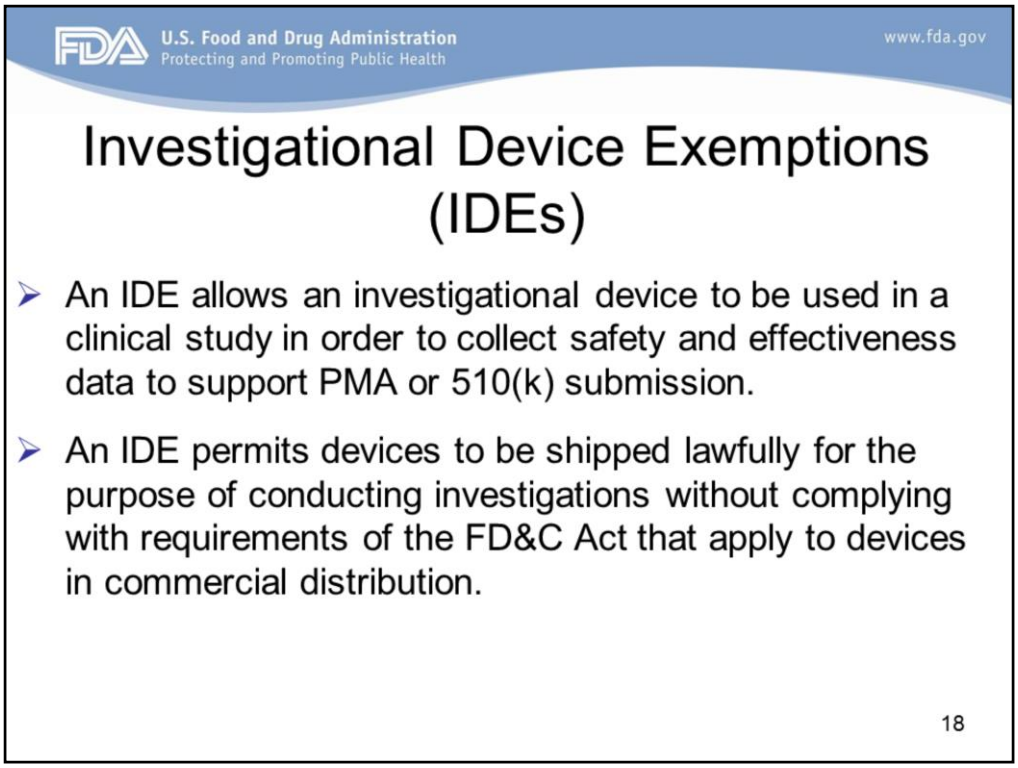


During the pre-market review, the IVD must provide reasonable evidence of the safety and effectiveness for the intended use. This is either directly, in the case of a PMA, or a *de novo* pre-market approval or through demonstration of substantial equivalence to a legally marketed device for a 510(k) pre-market submission.

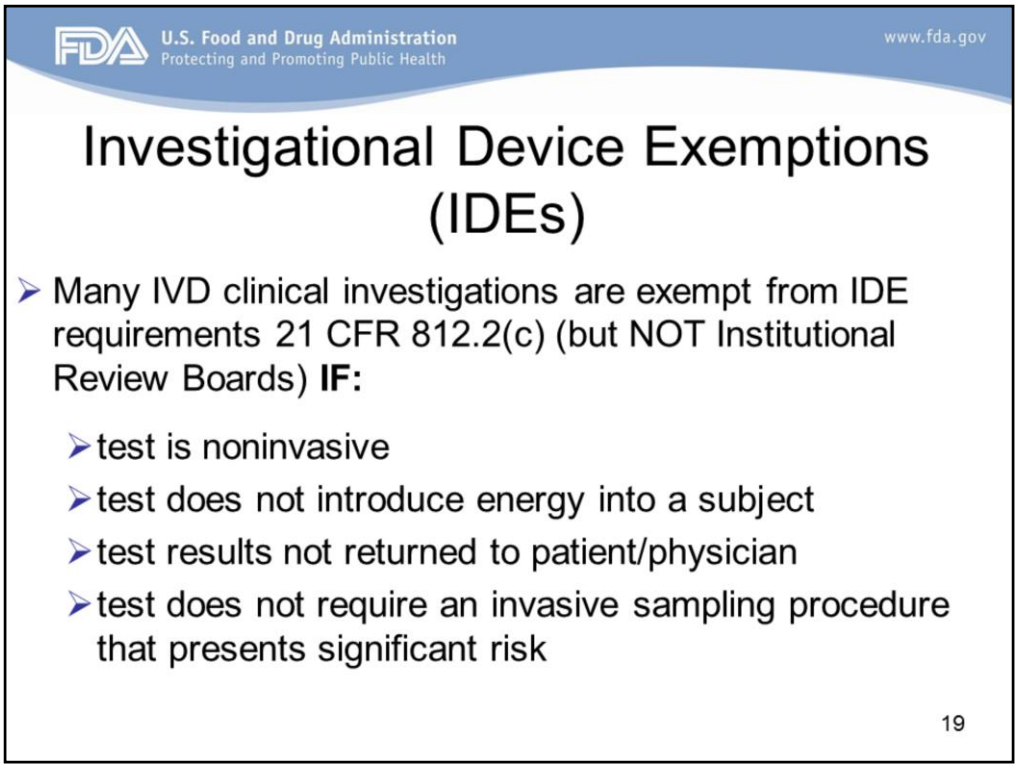
We evaluate analytical and clinical performance that is submitted in support of the pre-market review of a particular device. So for analytical performance, the goal of these studies is to establish the performance of the test and to challenge the test. Examples of studies include the limit of detection, the inclusivity, the exclusivity, the precision/reproducibility studies, interference studies, specimen stability, and some other studies. You will see more details of this as we go through the case study presented later.



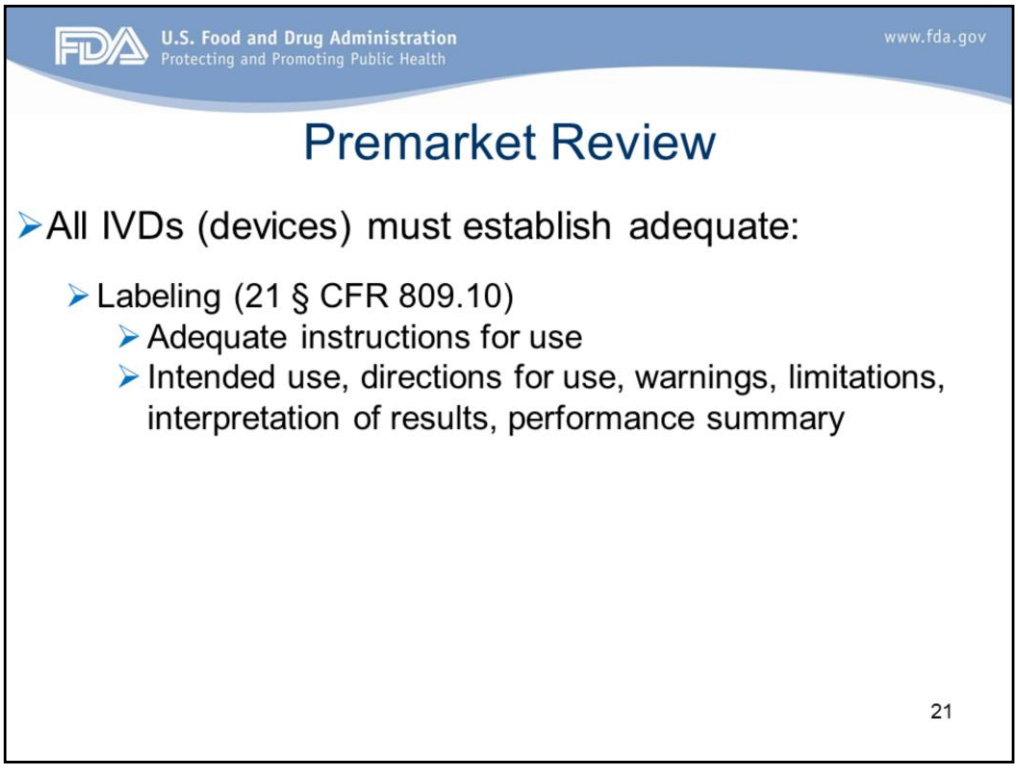
As I mentioned, in the Office of *In Vitro* Diagnostics and Radiological Health, we analyze the clinical performance. The goal is to establish the expected performance of the test in the intended setting when testing is performed by the end user. So this study should represent the intended use population. Ideally, it should use prospectively collected specimens. It should have clearly defined inclusion and exclusion criteria. And the sample size and trial design should be statistically appropriate.



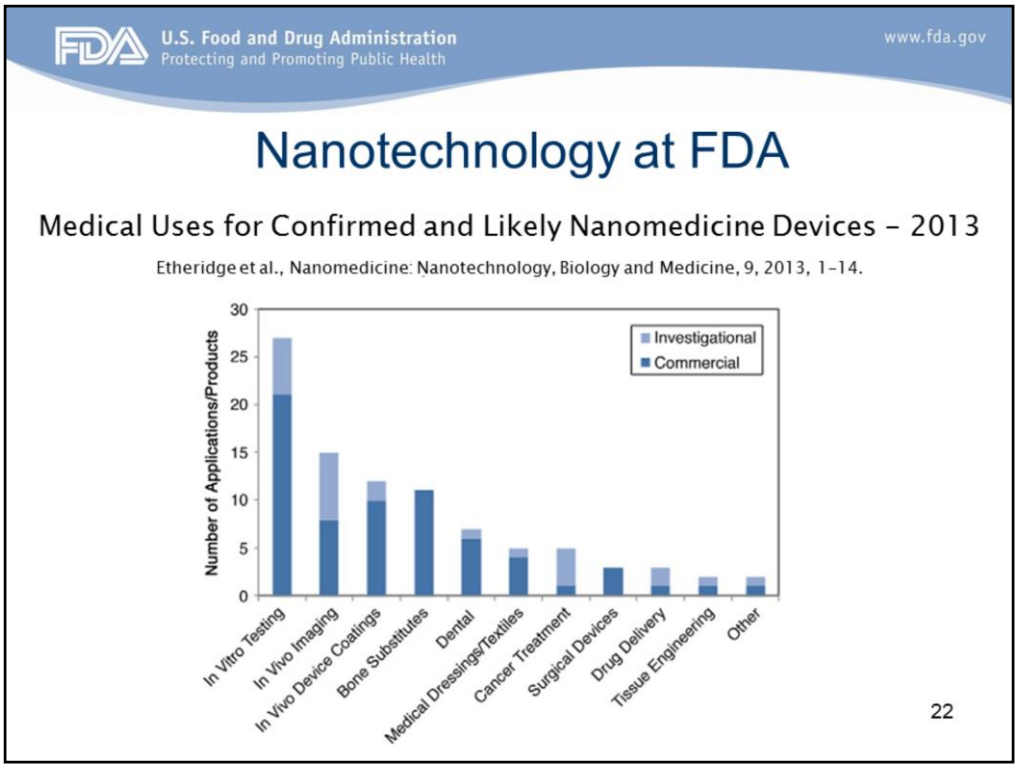
One of the questions we often get asked in the Division of Microbiology is whether an investigational device exemption (IDE) is required for clinical studies involving a pre-market IVD. For IDEs, an investigational device must be used in a clinical study in order to collect safety and effectiveness data in support of a PMA or a 510(k) submission. The IDE permits the device to be shipped lawfully for the purpose of conducting investigations without complying with requirements of the FD&C Act that apply to devices in commercial distribution.



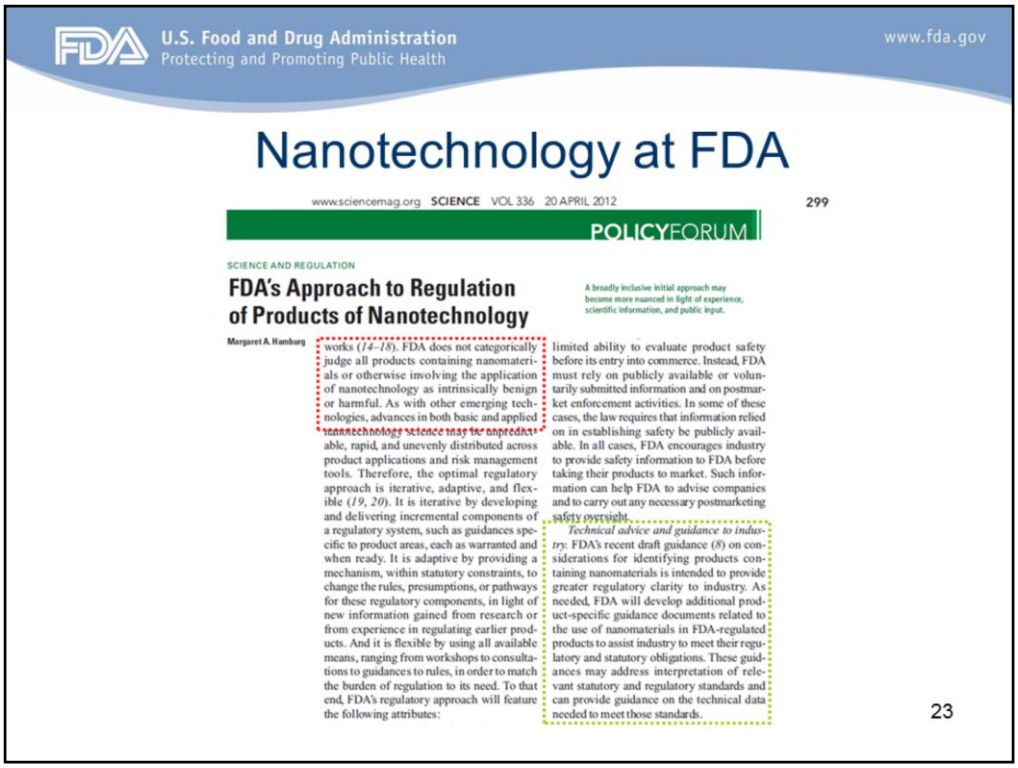
In the case of IVDs, many clinical investigations can be exempt from IDE requirements, although they are not exempt from institutional review boards. They can be exempt if the test is non-invasive, the test does not introduce energy into a subject, the test results are not returned to the patient or the doctor, and the test does not require an invasive sampling procedure that presents significant risk to the patient.



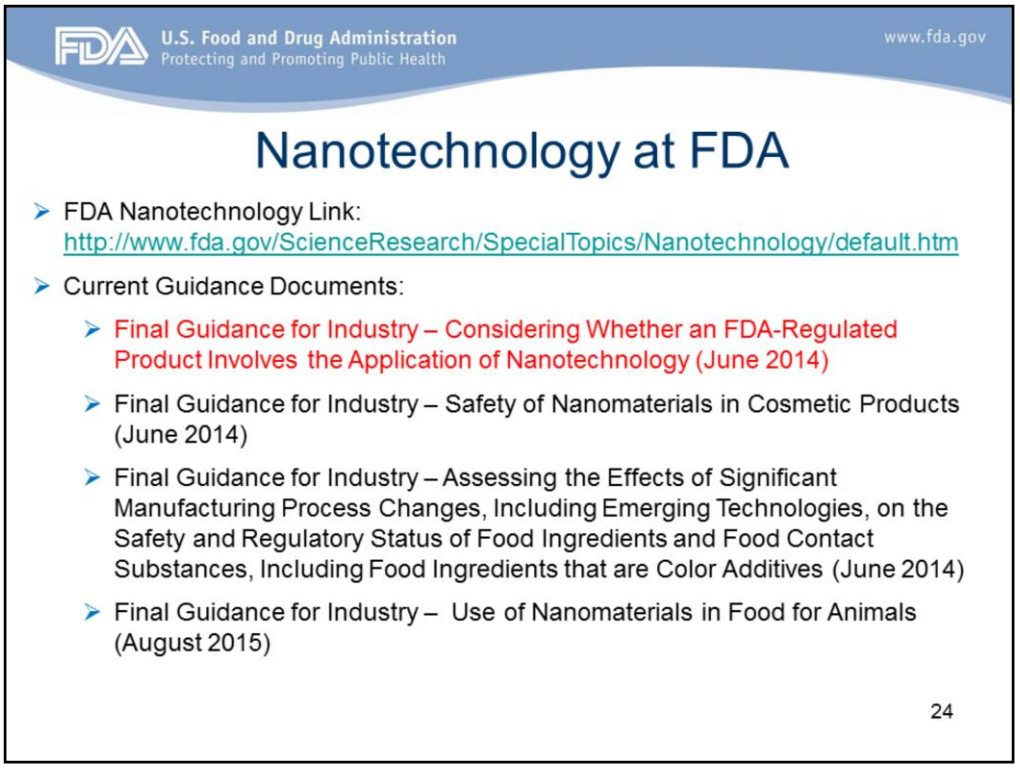
In addition we also review the labeling of the device. This is outlined in CFR 809.10. The labeling should include adequate instructions for use. It should include intended use of the device, the directions for use, any warnings and limitations associated with the test, interpretation of results, and also a performance summary.



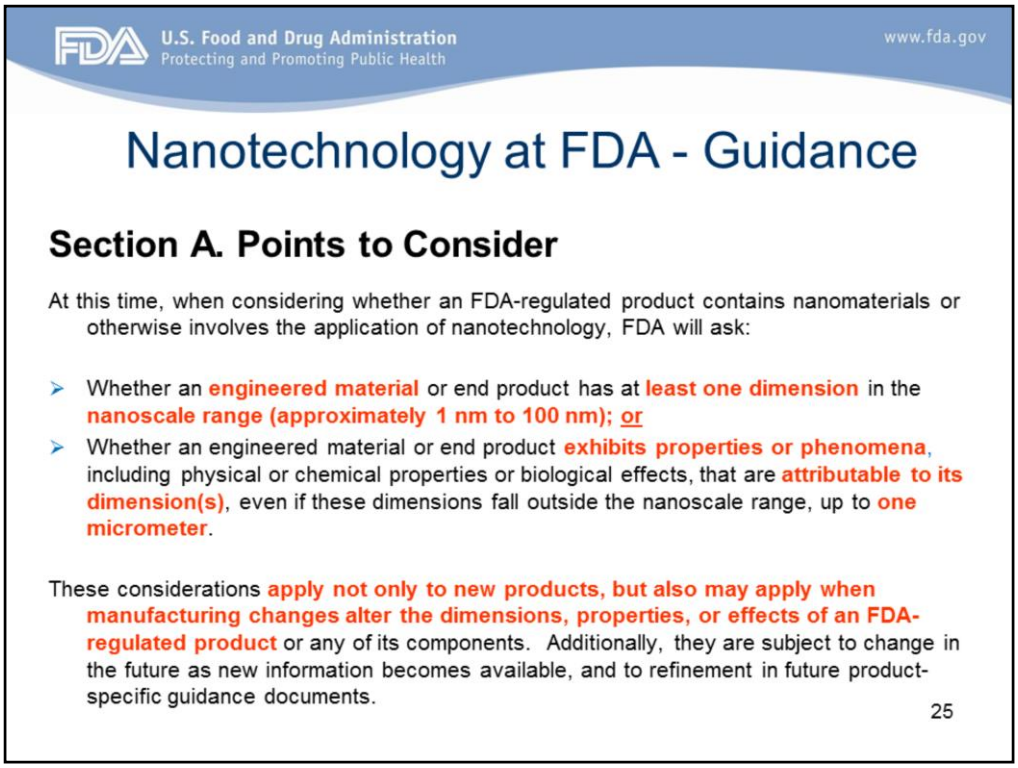
Now I want to talk about nanotechnology at FDA. This is a really nice review paper that appeared in *Nanomedicine: Nanotechnology, Biology and Medicine* in 2013. It outlines the investigational and commercial medical products that are already out there that use nanotechnology in some form. And you can see that *in vitro* testing and *in vivo* imaging are the two highest areas where nanotechnology is used in medical products.



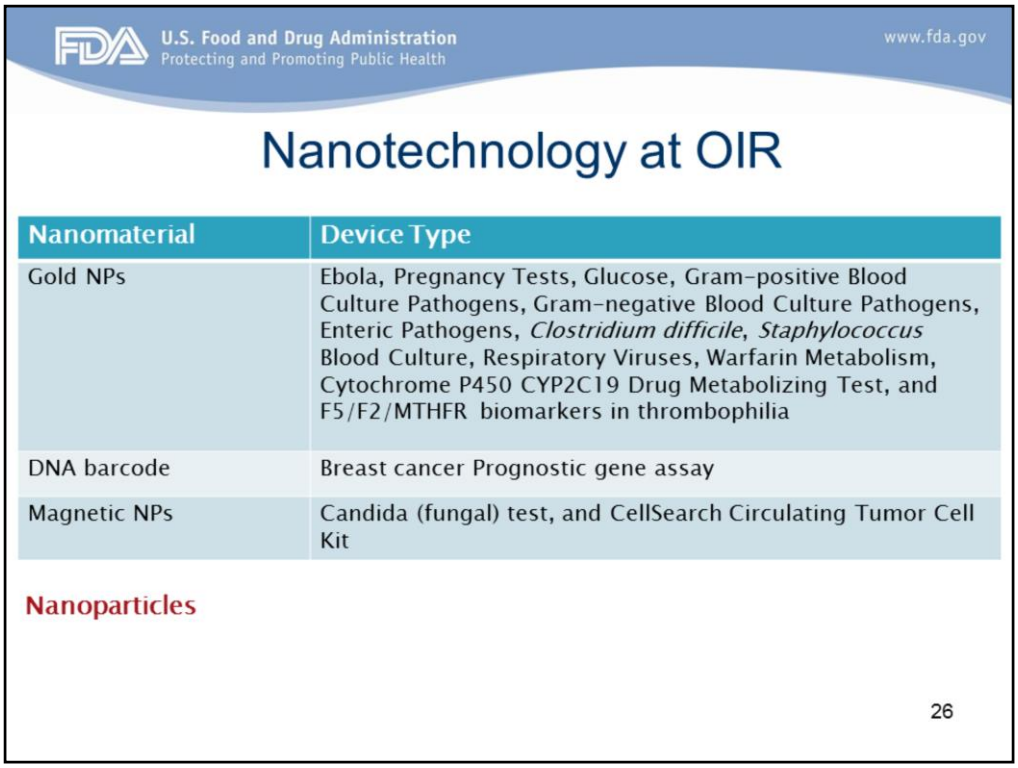
I also wanted to highlight a paper that was published in the journal *Science* in 2012 by our then commissioner Margaret Hamburg. The paper outlines that the FDA does not categorically judge all products containing nanomaterials, or otherwise involving the application of nanotechnology, as intrinsically benign or harmful. That's important as we review these devices.



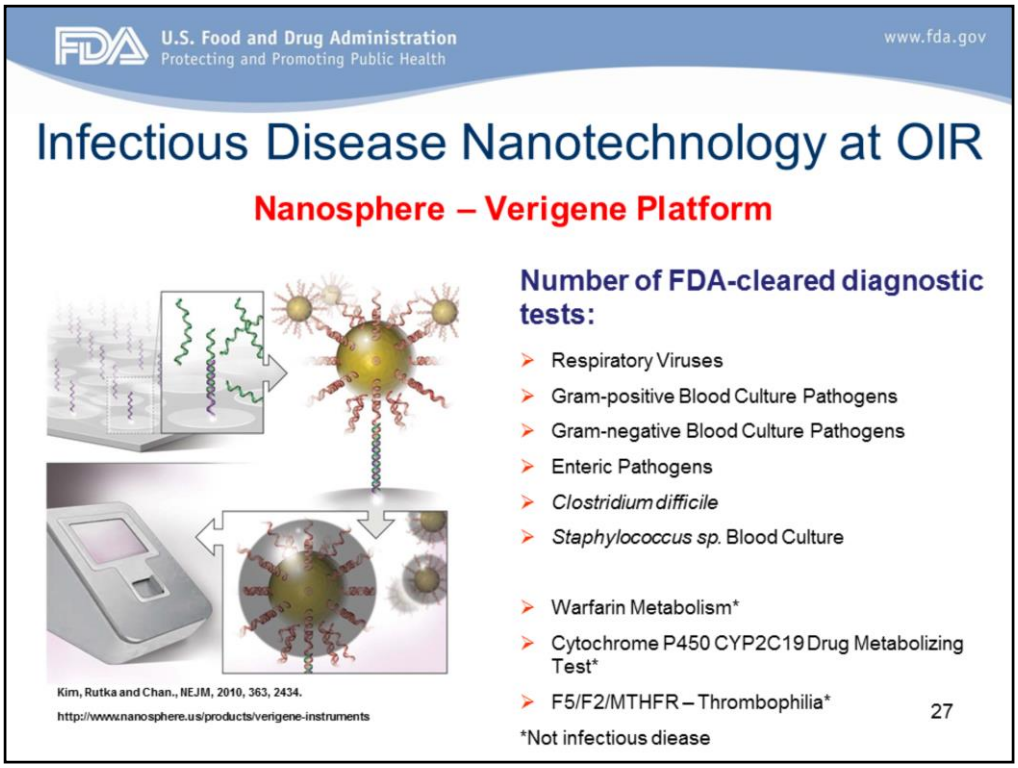
The link here includes information on current nanotechnology research that's ongoing within FDA and also provides links to published guidance documents related to nanotechnology. We currently have four final guidance documents published. These guidance documents highlight FDA's current thinking on this particular topic and often provide recommendations on appropriate studies required to determine or establish safety and effectiveness of the product covered by the guidance document. The guidance in red is the only nano-specific document related to devices that's published.



FDA does not have a formal definition for nanotechnology. Instead, we use points to consider. This is outlined in that guidance document that was highlighted in red on the previous slide. At this time, when considering whether an FDA-regulated product contains nanomaterials or otherwise involves the application of nanotechnology, we will ask whether the device contains an engineered material that has one dimension in the nanoscale range, which is approximately 1 to 100 nanometers, or has attributes or properties or phenomena including physical or chemical properties or biological effects attributed to its dimension(s) up to one micrometer.



We have a number of already approved or cleared devices that contain nanotechnology; for example a number of products contain gold nanoparticles. There is also a DNA barcoding device, and a couple of devices that use magnetic nanoparticles including the one that I'm going to talk about today.



Just to give you an idea, this is Nanosphere's Verigene® platform that uses gold nanoparticles that are coated with DNA. It binds the target sequence, which is then captured on the surface of the Verigene® platform. It uses a silver nitrate reduction reaction to amplify the signal. The company claims to have some sensitivity equivalent to PCR without having to do an amplification reaction.

This platform has a number of FDA-cleared diagnostic tests, including tests for respiratory disease, gram-positive blood culture pathogens, gram-negative blood culture pathogens, enteric pathogens, *clostridium difficile*, and *streptococcus* blood culture.

U.S. Food and Drug Administration
Protecting and Promoting Public Health
www.fda.gov

Infectious Disease Nanotechnology at OIR

Ebola Emergency Use Authorization (EUA)

- Rapid Antigen tests for Ebola
- Gold Nanoparticles allow visual interpretation of the test

Corgenix – ReEBOV™ Antigen Rapid Test

http://media.npr.org/assets/img/2015/02/20/ebola-text_custom-727e85f774c392fd2a807a9223ae6454fe009424-s1100-c15.jpg

OraSure – OraQuick® Ebola Rapid Antigen Test

http://fm.cnbc.com/applications/cnbc.com/resources/img/editorial/2015/06/12/102755340-oraquick.530x298.jpg?v=1434122806

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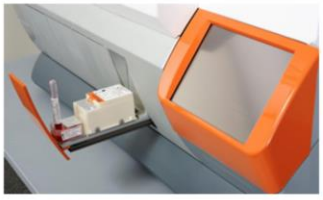
Under the current Ebola Emergency Use Authorization (EUA), we have a couple of simple lateral flow immunoassays for Ebola detection that use gold nanoparticles for visual interpretation of the test.

U.S. Food and Drug Administration
Protecting and Promoting Public Health
www.fda.gov

OIR Case Study – T2 Biosystems

http://www.t2biosystems.com/t2candida/

- The T2Candida Panel, performed on the T2Dx® Instrument, is a qualitative T2 Magnetic Resonance (T2MR®) molecular diagnostic assay for the detection of *Candida* species (listed below) from whole blood specimens from patients with signs and symptoms of invasive *Candida* infection
  - *Candida albicans* and/or *Candida tropicalis*
  - *Candida parapsilosis*
  - *Candida krusei* and/or *Candida glabrata*



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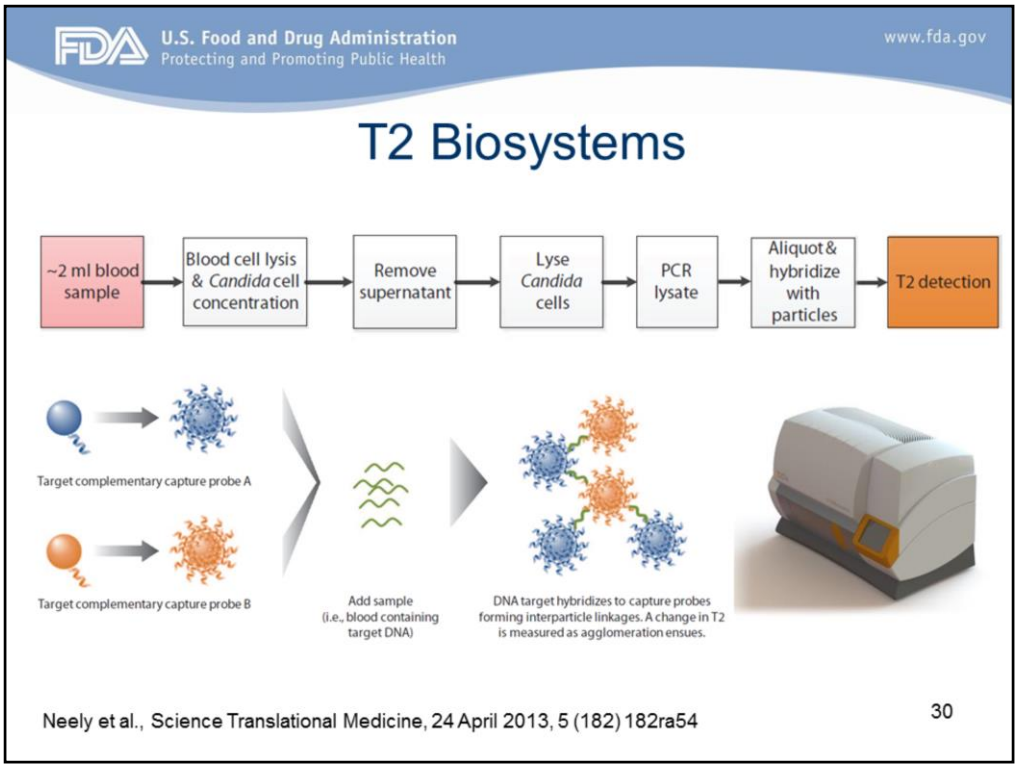
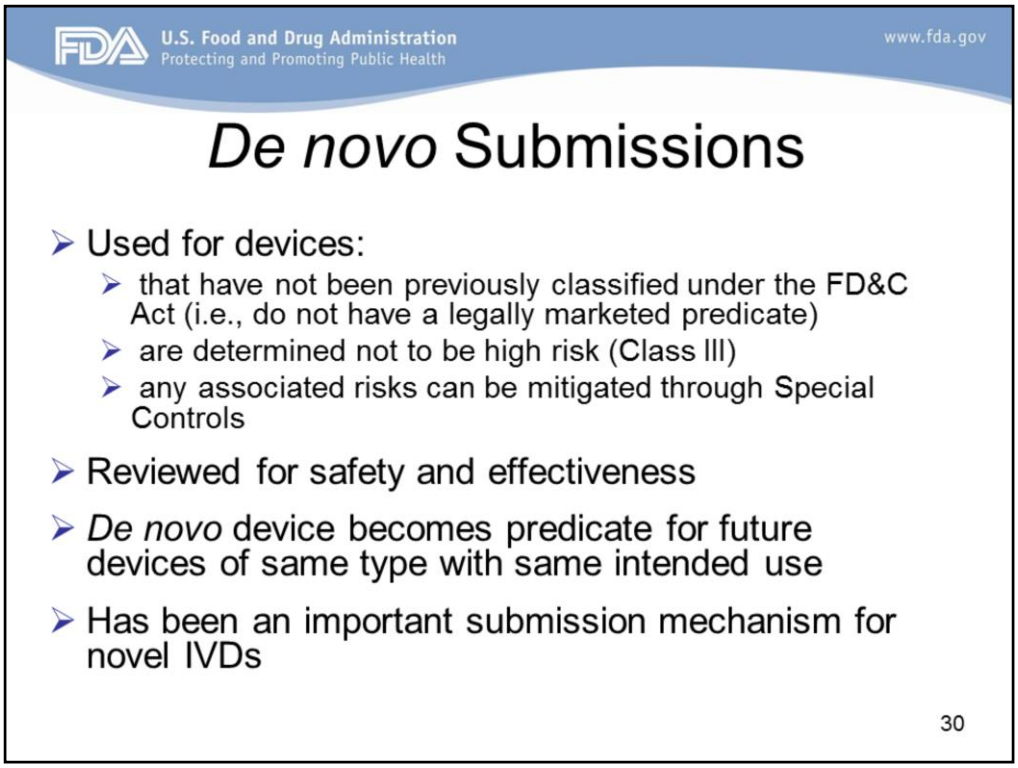
The case study in today's webinar is on T2 Biosystems. The company manufacturers a qualitative assay for the *Candida* species from whole blood of patients infected with *Candida*. It has a panel of five species that it can detect. As we go through this case study, although the assay involves the application of nanotechnology, it was treated during the pre-market review exactly how we would treat any IVD that does not involve the use of nanomaterials.

We look at the IVD as a whole system from collection of the specimen, detection, and the results. The IVD has to demonstrate that it's reproducible, performs as expected, and that it is safe and effective for its intended use.



Just to give you an overview of the technology, it takes a 2 ml blood sample. The end user adds the sample to the cartridge and the detection and PCR is all performed on the instrument.

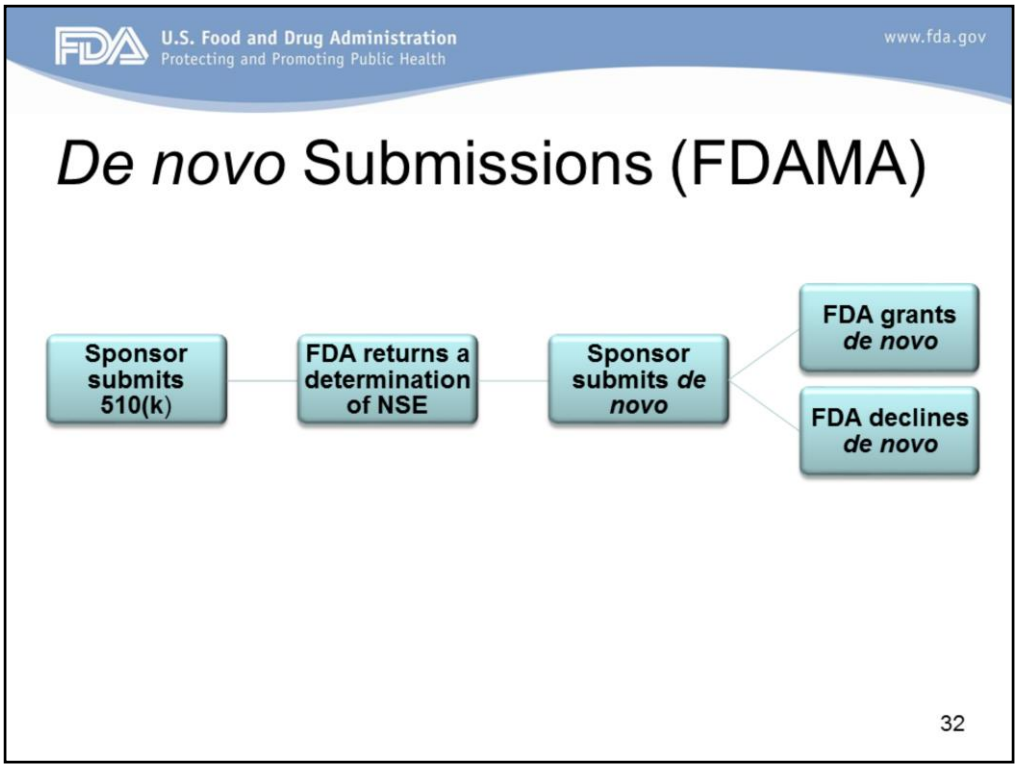
The blood cells in the sample are initially lysed and supernatant is removed. *Candida* cells are then lysed and PCR is performed on the sample. Super paramagnetic particles are added into the PCR product. The super paramagnetic particles are coated with species-specific DNA probes to the candidate species that are identified by the device. Clusters of particles affect the surrounding water molecules, and the instrument then detects this clustering by measuring a change in the T2 relaxation curve of the surrounding water molecules using magnetic resonance detection. That's how it detects the *Candida* species.



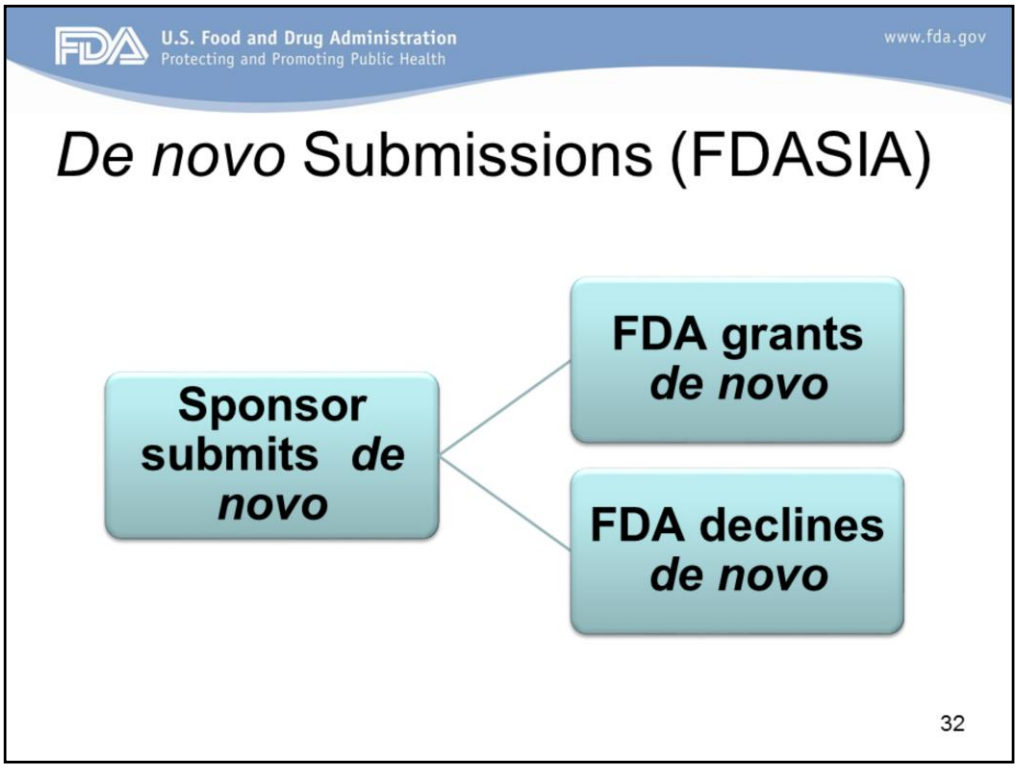
The T2 Biosystems *Candida* panel was determined to be a *de novo* submission because it detects the *Candida* organisms directly from whole blood. All our previous assays detect from a blood culture sample, i.e., the blood specimen is collected and then put into culture and the organisms are amplified before they are detected.

And so the *de novo* submission is used for devices that have not been previously classified under the Federal Food, Drug, and Cosmetic Act as there's legally no market predicate, and for devices that are determined not to be high risk (not Class III), and any associated risks can be mitigated through special controls.

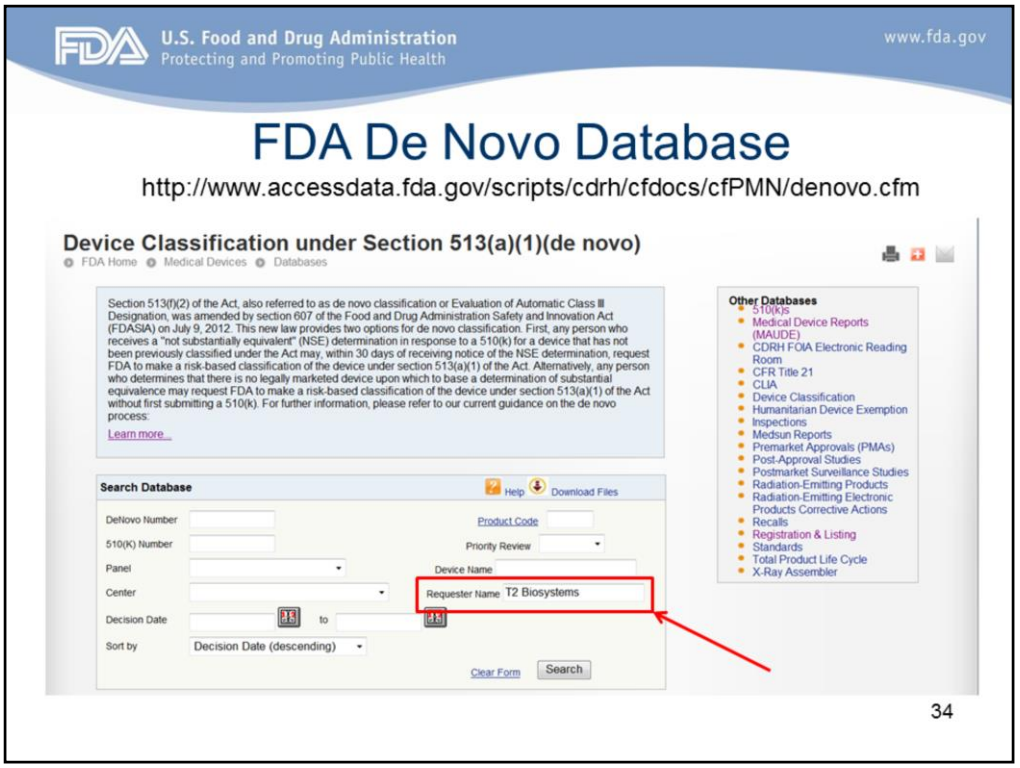
In the case of the *de novo* submissions, we review the safety and effectiveness of the device. The *de novo* device then becomes a predicate for any future devices of the same type or the same intended use. This has been a very important mechanism in our division for clearing novel *in vitro* diagnostics.



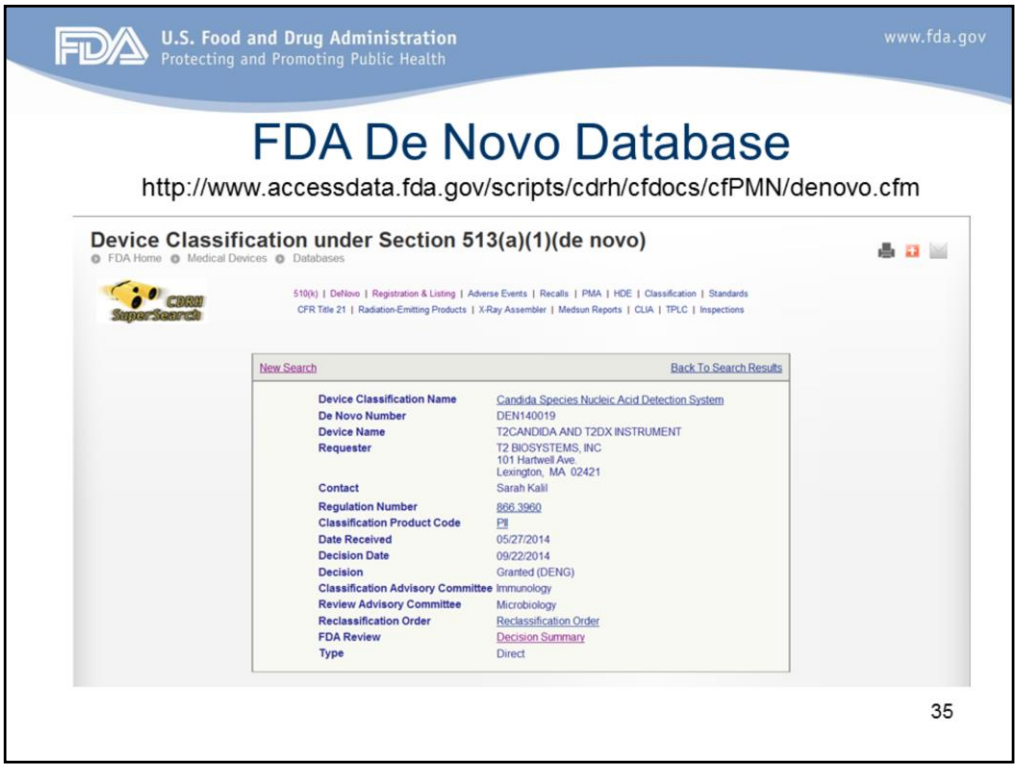
There are two options for submitting a *de novo*. Option 1 was established by the Medical Device Modernization Act. The sponsor submits a 510(k). The FDA will return a determination of "not substantially equivalent" for a previously marketed device and then the sponsor submits a *de novo*. The FDA can either grant the *de novo* or decline the *de novo* submission.



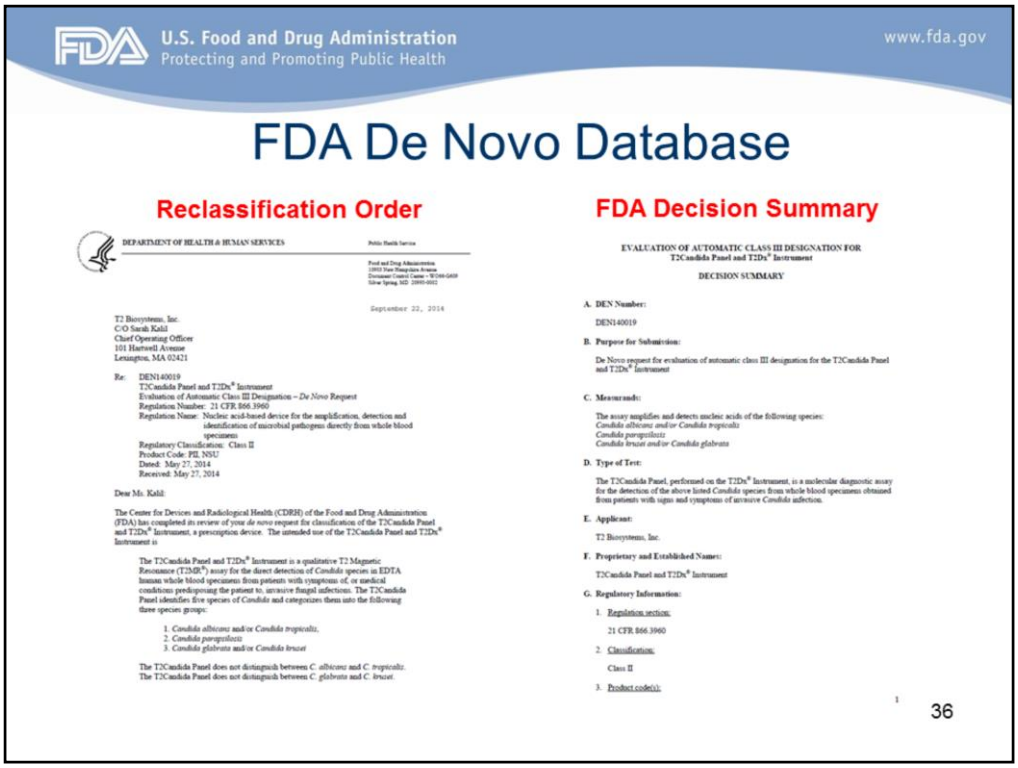
The second option is referred to as the direct *de novo* request. This came out of the Food and Drug Administration Safety and Innovation Act of 2012. Now the sponsor can make a *de novo* submission directly. The FDA can either grant or decline the *de novo* depending on our review of the data submitted to support it.



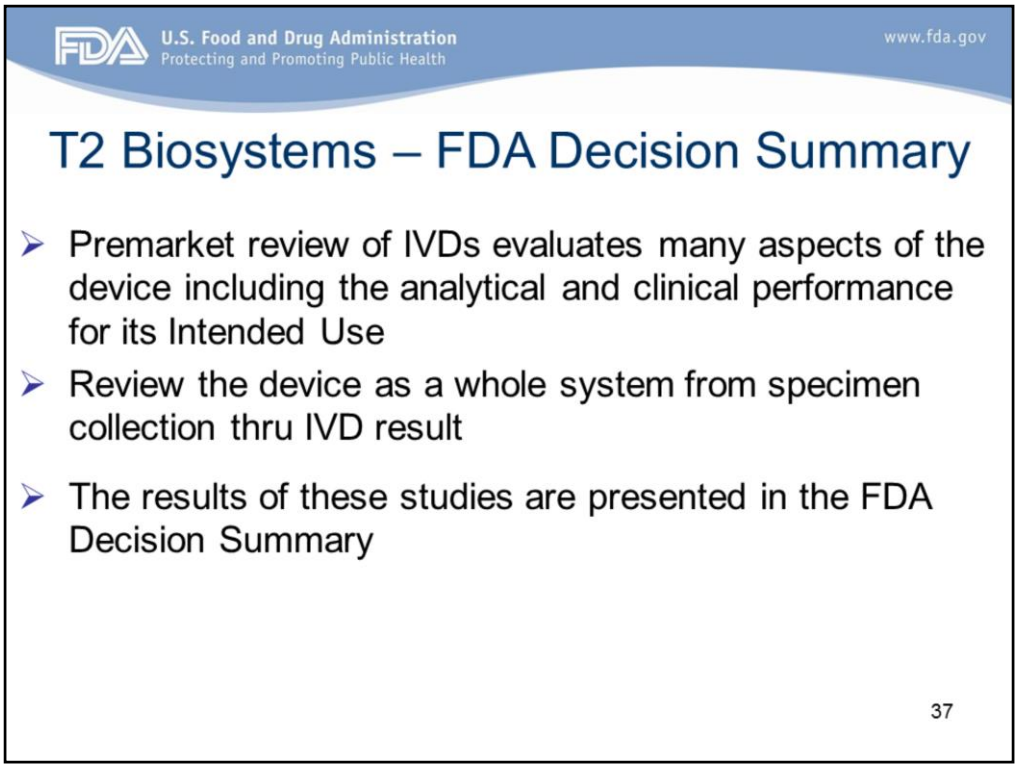
FDA has a *de novo* database where you can look up *de novo* submissions that have been cleared. If you go to the database, you can type in "T2 Biosystems" under the requester name.



If you hit search, it comes up with the T2 *Candida* and T2DX instrument. You can see this lists all the information about the device, and the link to the reclassification order and decision summary. FDA publishes our reclassification orders and decision summaries online.

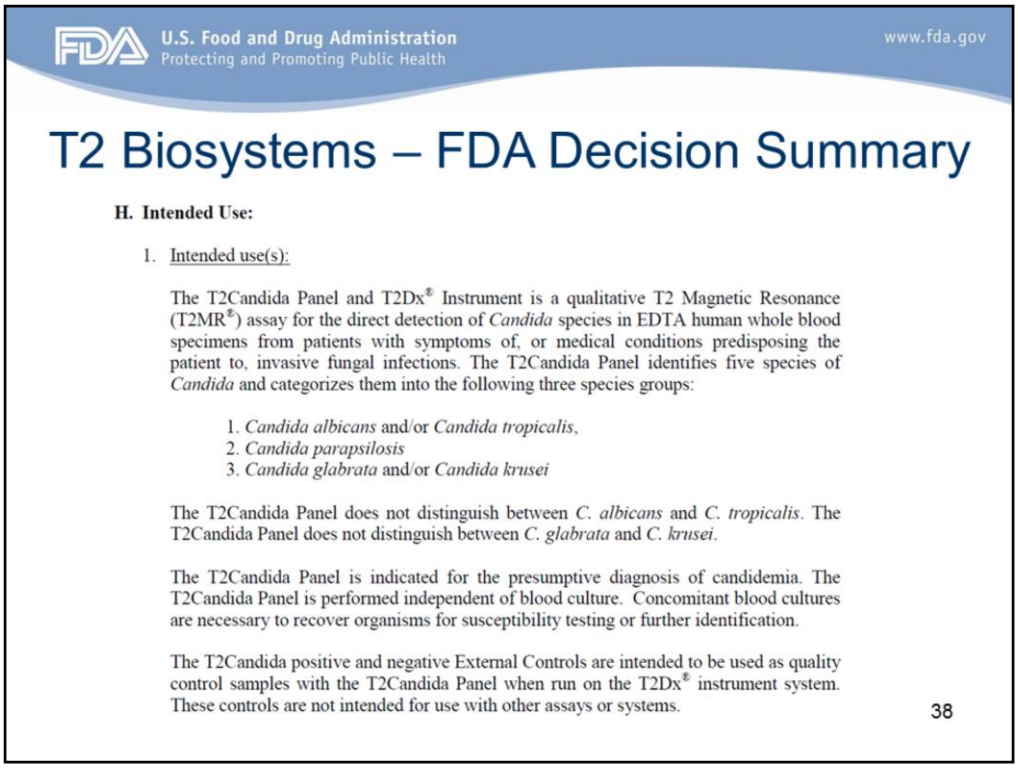


The reclassification order lists the special controls that are required under the *de novo* classification and that the submitter has to follow to demonstrate the device is safe and effective for its intended use. We also publish, and you can access, the decision summary.



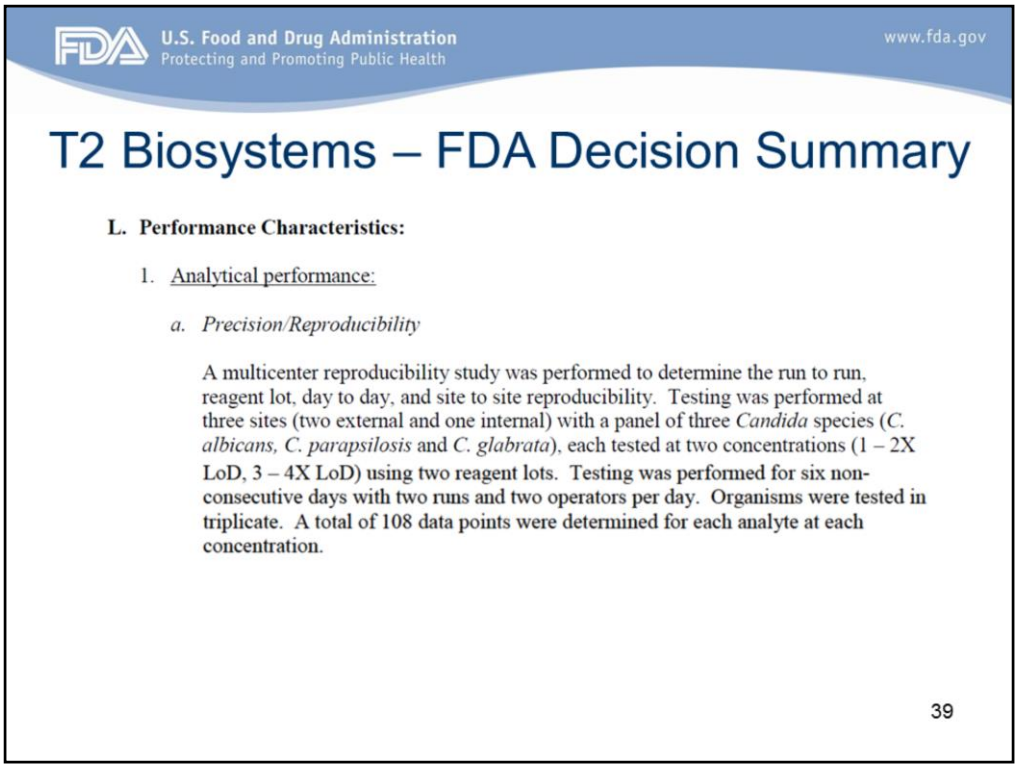
During the pre-market review of *in vitro* diagnostics, we evaluate many aspects the device including the analytical and clinical performance for its intended use. We review the device, as I mentioned, as a whole system from specimen collection through to the IVD result. The results of these studies are all presented and published in the FDA decision summary.

This is a very useful resource if you're interested in what studies were performed to support the approval or clearance of a particular device.



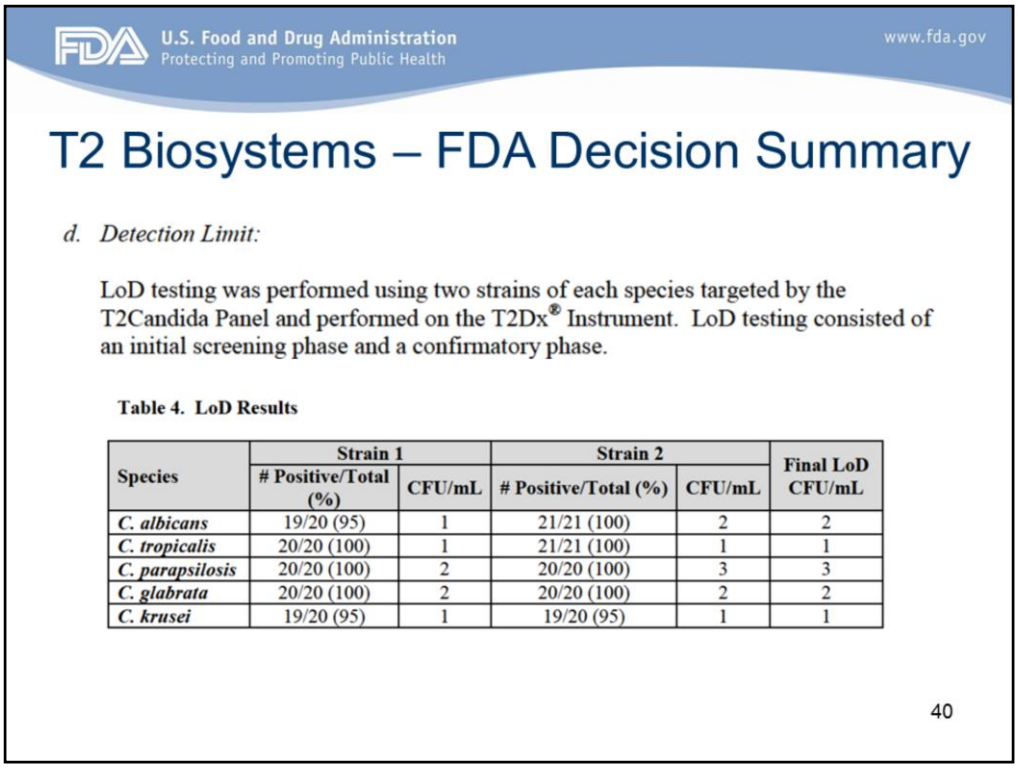
Now I'm going to go through some of the sections of the T2 Biosystems FDA decision summary. This is the intended use of the T2 *Candida* Panel. As I mentioned earlier, the intended use should list the target. And so you can see that the target is *Candida* species and it lists the five species that are recognized by the device, and they are categorized into three species groups. It tells you the assay and the qualitative detection. The intended use is for patients with symptoms or medical conditions predisposing them to invasive fungal infections.

The matrix being examined is EDTA human whole blood. How the test is used, this is a presumptive diagnosis of candidemia, or the fungal infection.

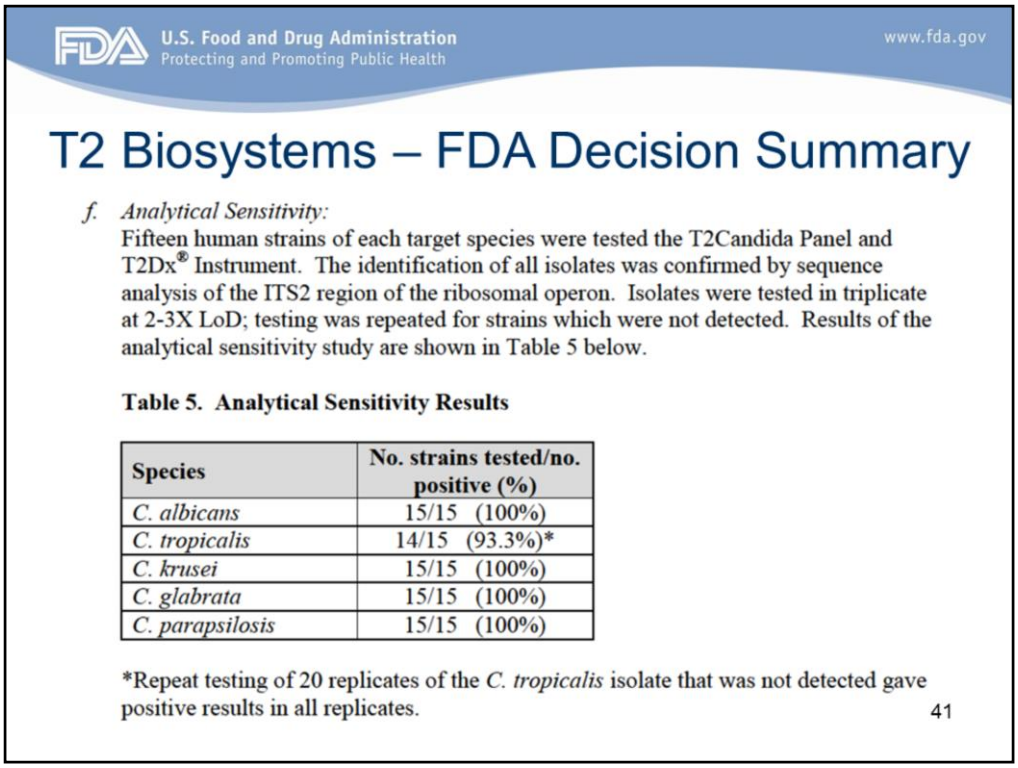


So I'm just going to go through some of the performance characteristics that we have evaluated during the pre-market review. We looked at analytical performance, and this includes a precision/reproducibility study. The goal of the precision/reproducibility study is to ensure that when the tests are performed by different laboratories in the hands of different operators on different days, they provide the same results when tested with the same specimen.

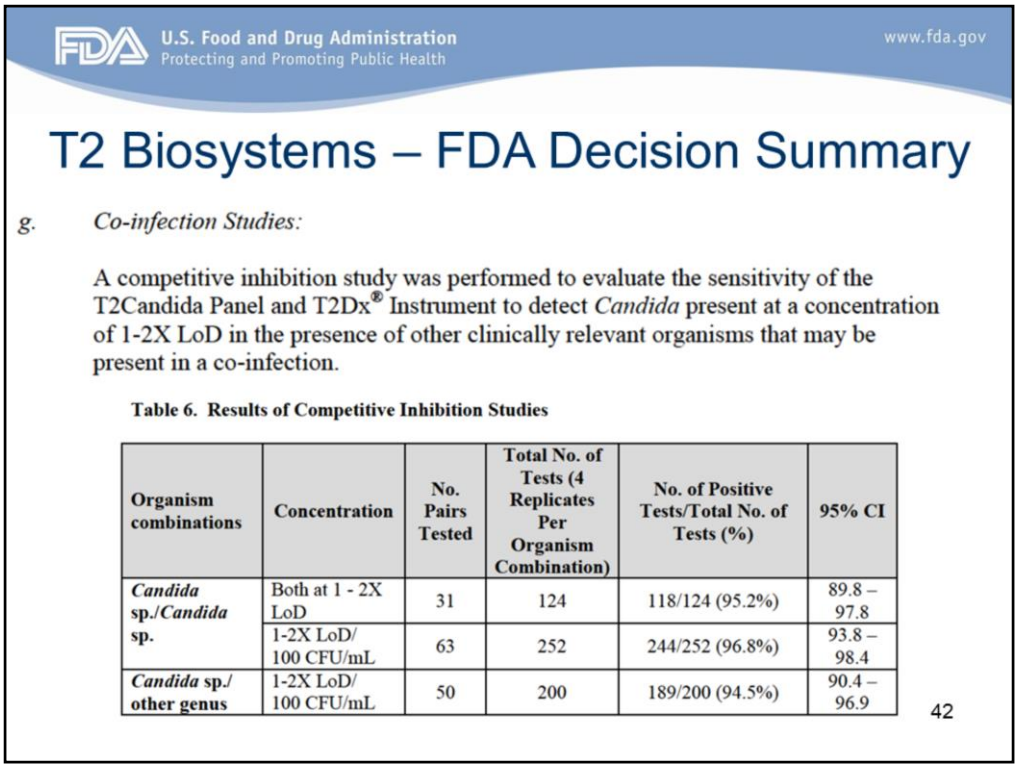
Typically for these studies, organisms are put into a clinical matrix, sent to three testing sites, and then tested in a blinded fashion using multiple operators and instruments. The summary of these studies is presented in the FDA decision summary.



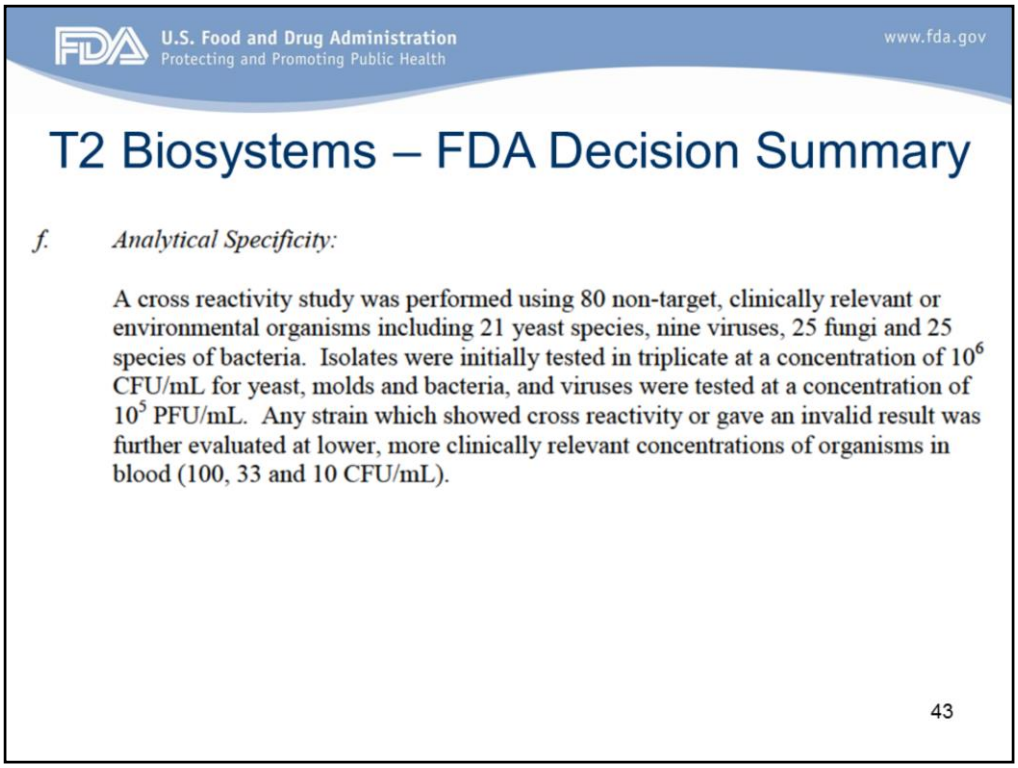
We also looked at the limit of detections of the device. We evaluate the tentative limit of detection (LoD) using a serial dilution of each of the targets, and then the limit of detection has been confirmed by generating a minimum of 20 samples spiked at the LoD. If you get 19 out of the 20 correct, then the tentative LoD is your confirmed LoD. This table just shows you the confirmed LoD for the different *Candida* species that are detected by the device. You can see that they looked at two different strains of each species. The final LoD was reported as the highest LoD that was measured between the different strains.



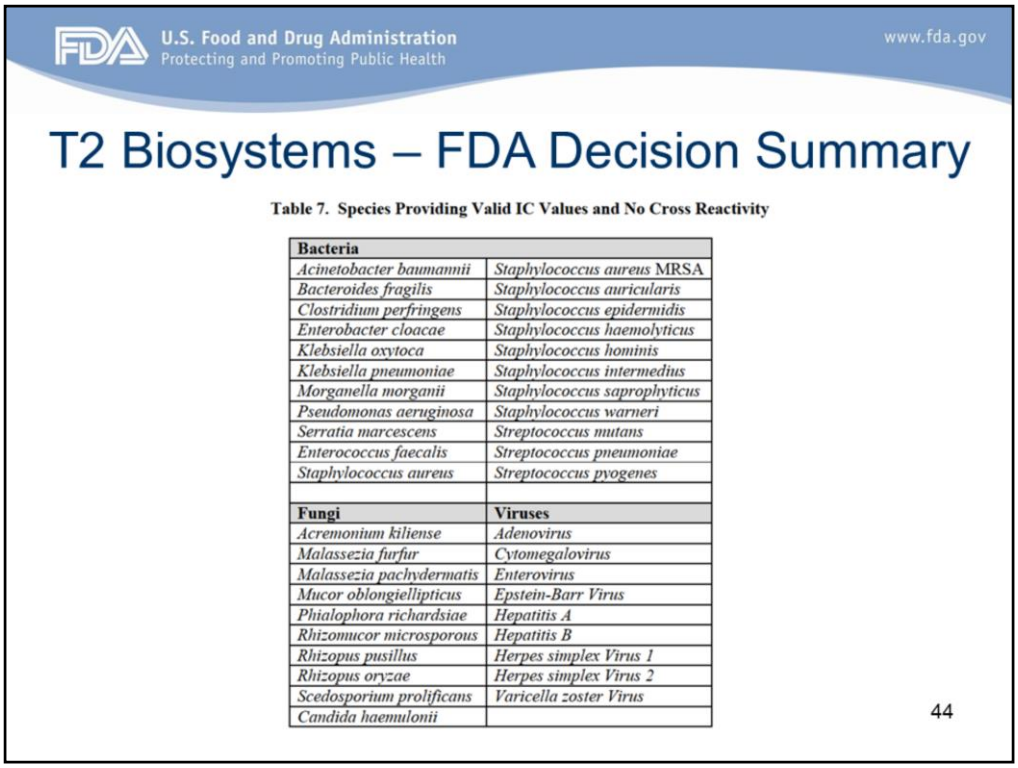
We also look at the analytical sensitivity of the device. This study is to demonstrate that the *in vitro* diagnostic device is able to detect various strains of the same species. In the case of the T2 Biosystems device, this is done for each of the five *Candida* species on the panel. They looked at 15 different human strains for each target species.



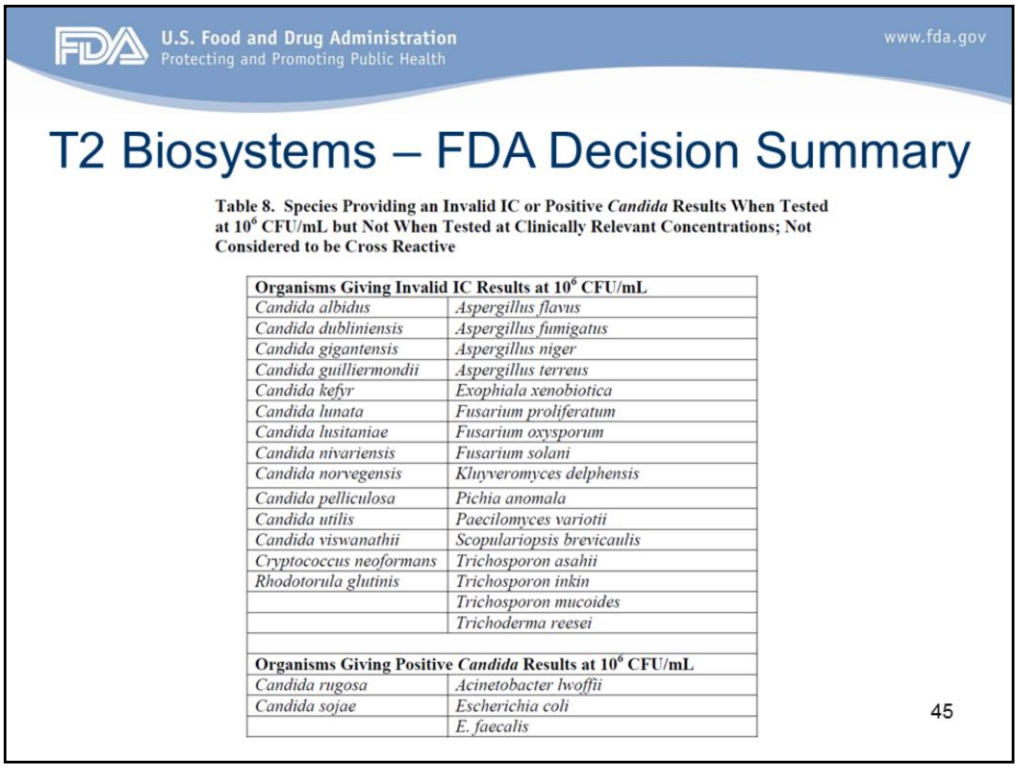
They also looked into co-infection studies. The competitive inhibition study was to demonstrate that *Candida* could be detected in samples that have other clinically relevant bacteria or other species of *Candida*. They looked at bacterial species such as *pseudomonas* and *streptococcus*.



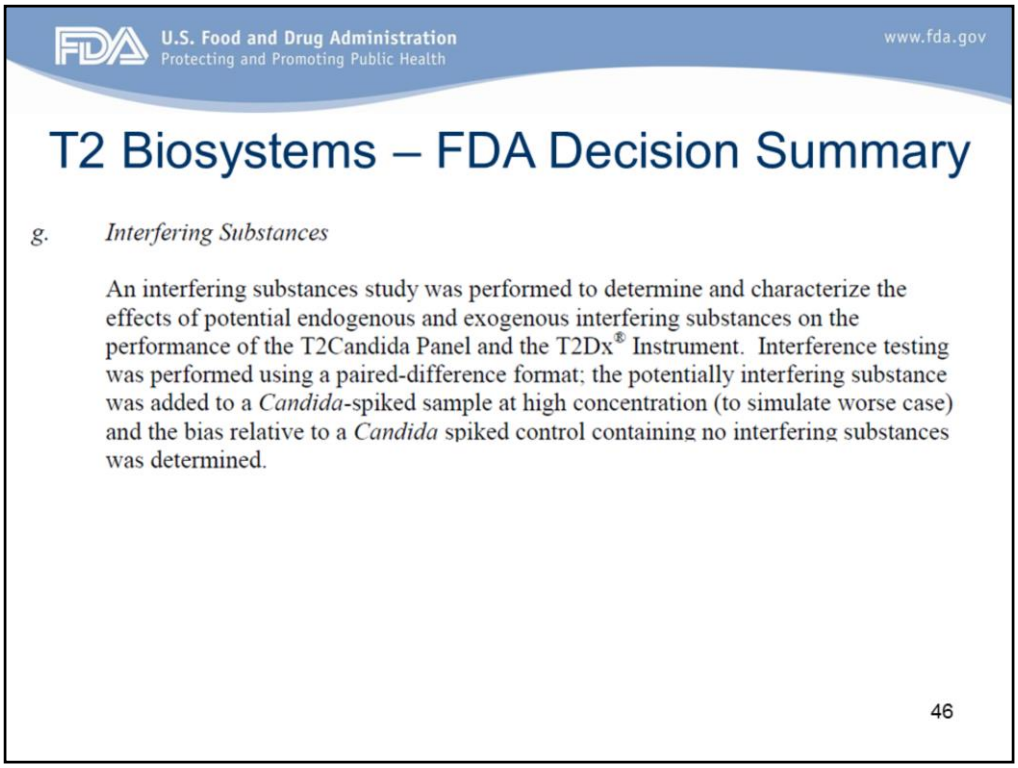
Another important criteria is analytical specificity. A cross-reactivity study evaluates whether the IVD gives a false positive result when non-pocketed species are present in the clinical specimen. This includes a wide range of clinically and environmentally relevant organisms, and the exact choice of organisms depends on the specific intended use of the device in question and the matrix that is being tested.



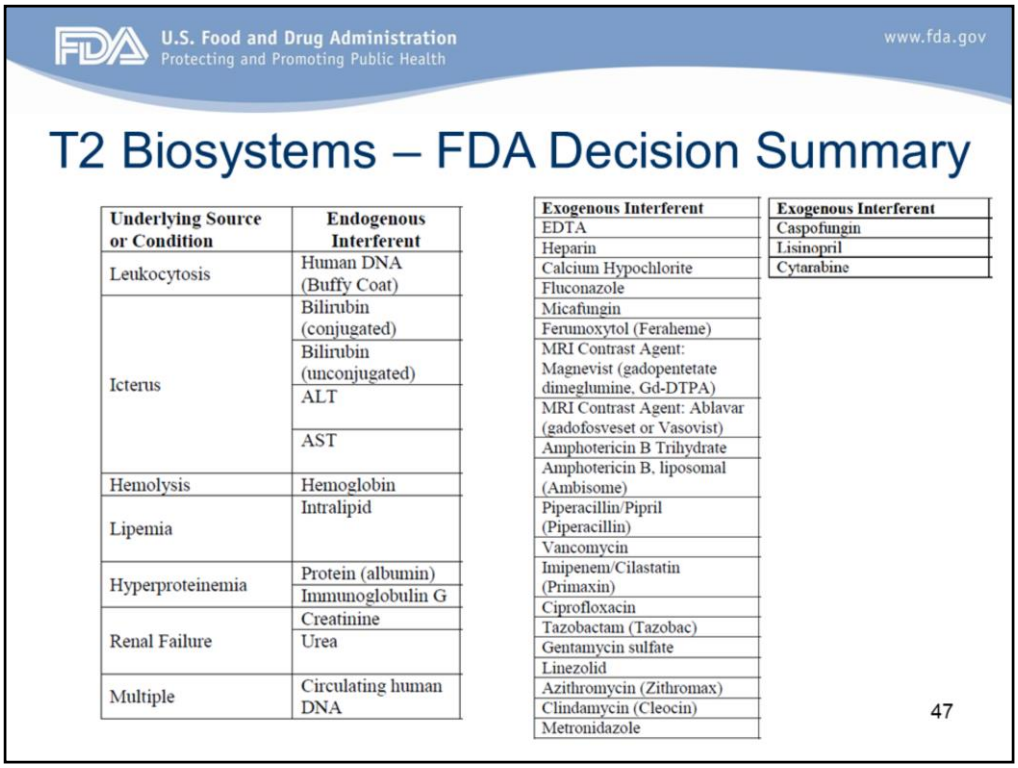
Here are the species that were studied for the T2 Biosystems device. Results from this study indicate no cross-reactivity.



This table highlights species that gave cross-reactivity at high levels when they were initially tested. When they were tested at clinically relevant levels, they were considered to not be cross-reactive with the test.



We also look at a number of interfering substances, which can be endogenously or exogenously interfering. They are not the same for every device, and they're dependent on the matrix. For T2 Biosystems, these were the materials that were evaluated as potential interferences.

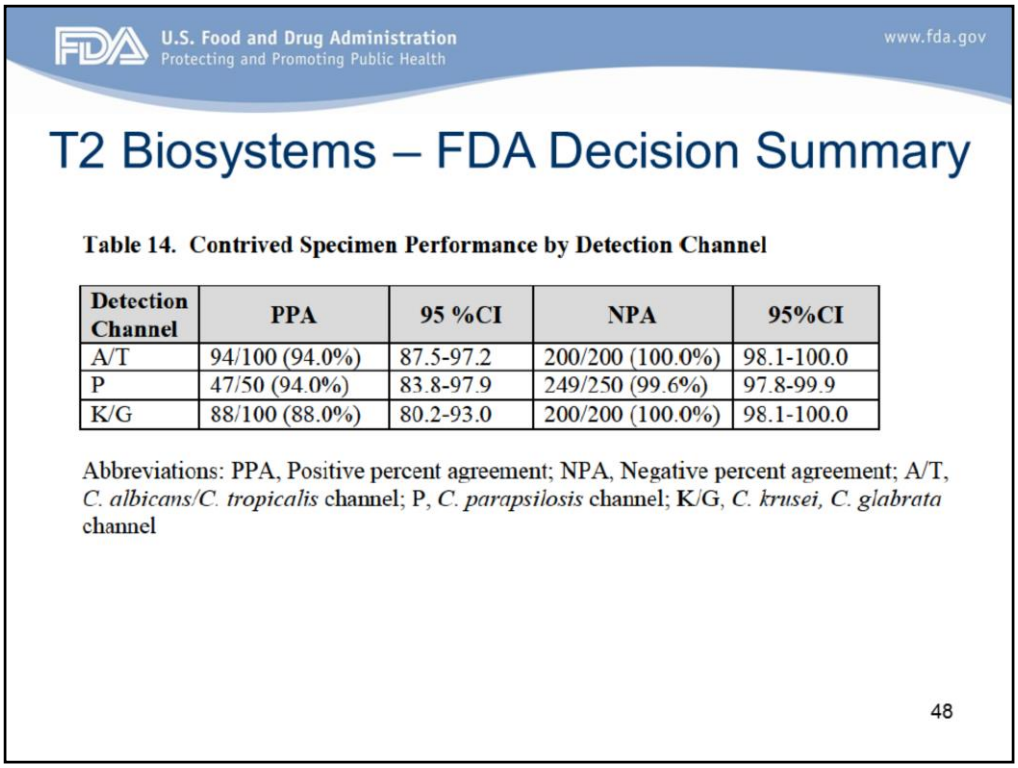


Underlying Source or Condition	Endogenous Interferent
Leukocytosis	Human DNA (Buffy Coat)
Icterus	Bilirubin (conjugated)
	Bilirubin (unconjugated)
	ALT
	AST
Hemolysis	Hemoglobin
Lipemia	Intralipid
Hyperproteinemia	Protein (albumin)
	Immunoglobulin G
Renal Failure	Creatinine
	Urea
Multiple	Circulating human DNA

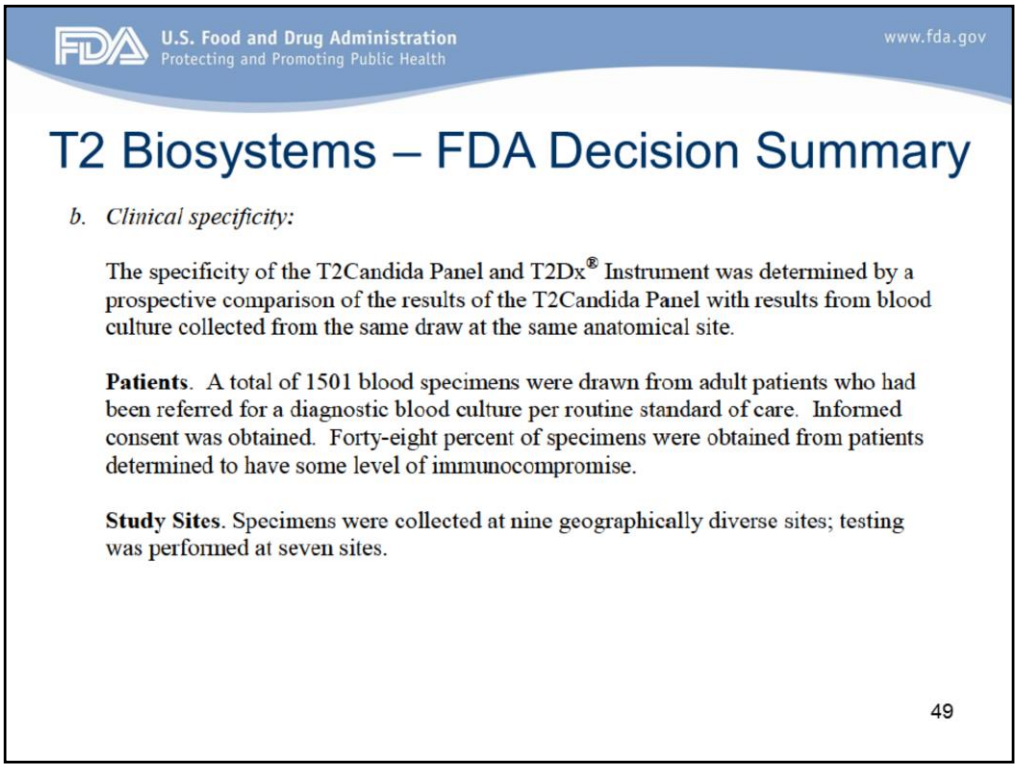
Exogenous Interferent
EDTA
Heparin
Calcium Hypochlorite
Fluconazole
Micafungin
Ferumoxytol (Feraheme)
MRI Contrast Agent: Magnevist (gadopentetate dimeglumine, Gd-DTPA)
MRI Contrast Agent: Ablavar (gadofosveset or Vasovist)
Amphotericin B Trihydrate
Amphotericin B, liposomal (Ambisome)
Piperacillin/Pipril (Piperacillin)
Vancomycin
Imipenem/Cilastatin (Primaxin)
Ciprofloxacin
Tazobactam (Tazobac)
Gentamycin sulfate
Linezolid
Azithromycin (Zithromax)
Clindamycin (Cleocin)
Metronidazole

Exogenous Interferent
Caspofungin
Lisinopril
Cytarabine

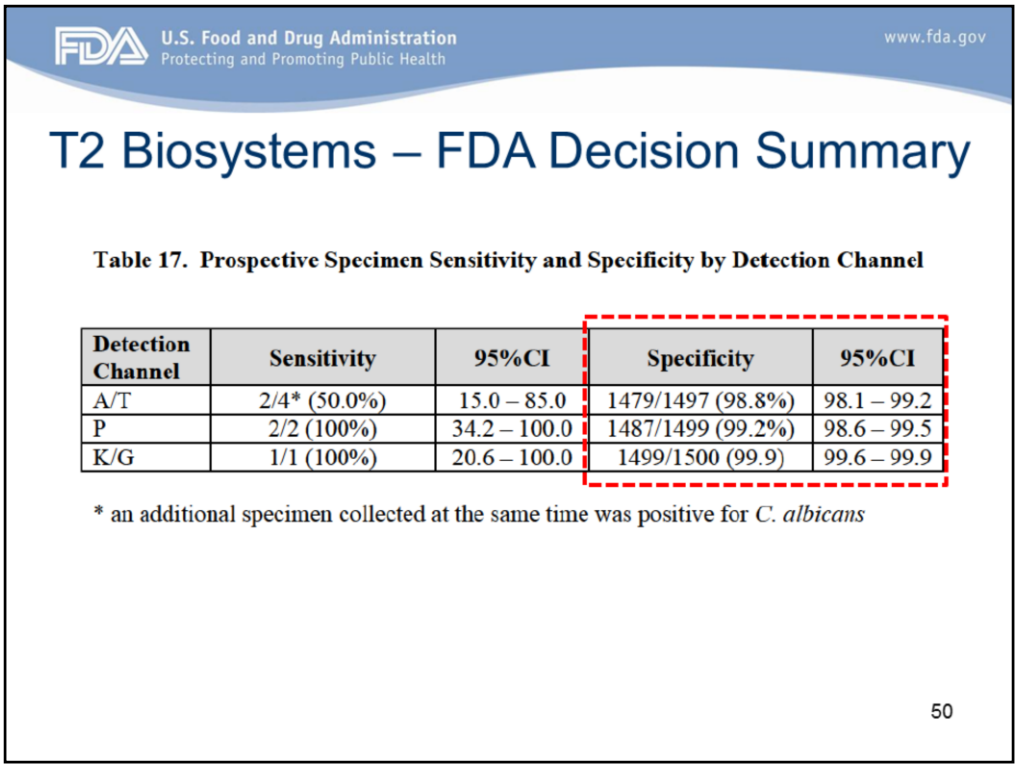
This is just a subsection of all the analytical studies that were performed by T2 Biosystems during their submission. If you're interested in finding out about some of the other analytical studies, I suggest that you follow the link and look at the full FDA decision summary. Analytical studies include the evaluation of the assay cut-off, carryover and cross-contamination studies, specimen stability studies, reagent stability studies including storage and shipping, and internal and external control selection, whose performance was evaluated during reproducibility and clinical studies.



As I mentioned, we also look at the clinical performance of the device. Because of the low prevalence of *Candida*, the clinical positive percent agreement was actually evaluated in contrived samples. This shows you the positive percent agreement for this particular device using these contrived samples.



We also evaluated the specificity, which is determined in a clinical study using prospectively collected specimens. The performance was compared to results from blood culture, which is considered the gold standard. They looked at a total of 1501 blood specimens that were drawn from adult patients who had been referred for diagnostic blood culture per routine standard of care.

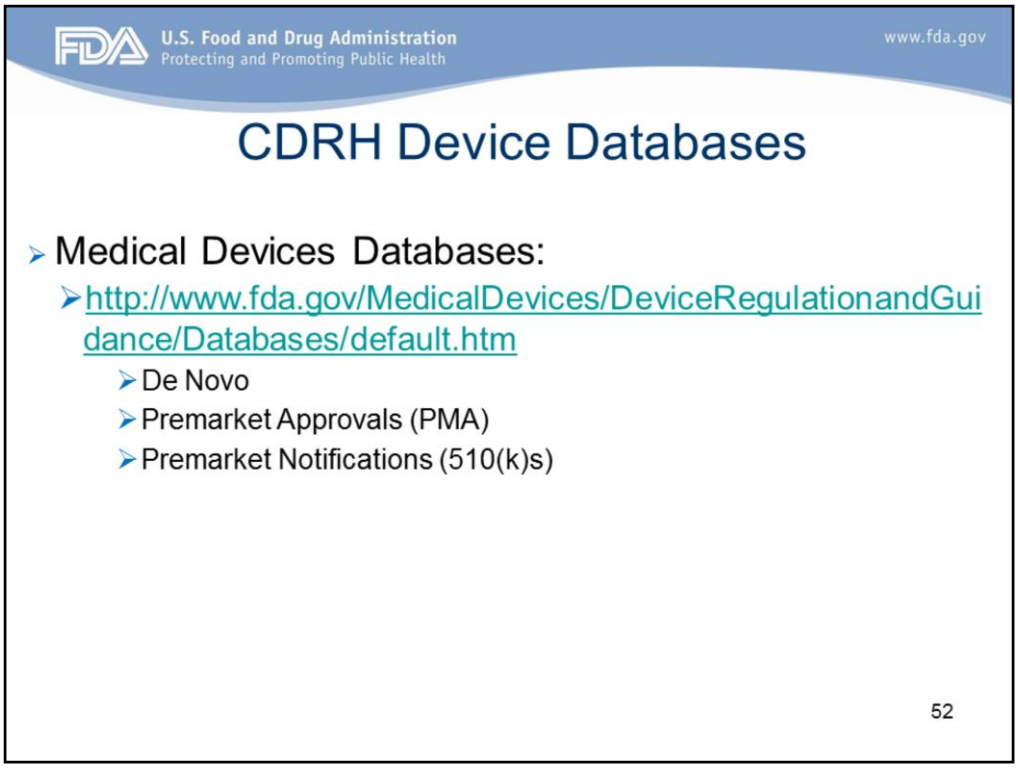


You can see here the results of the specificity study using the prospectively collected specimens.

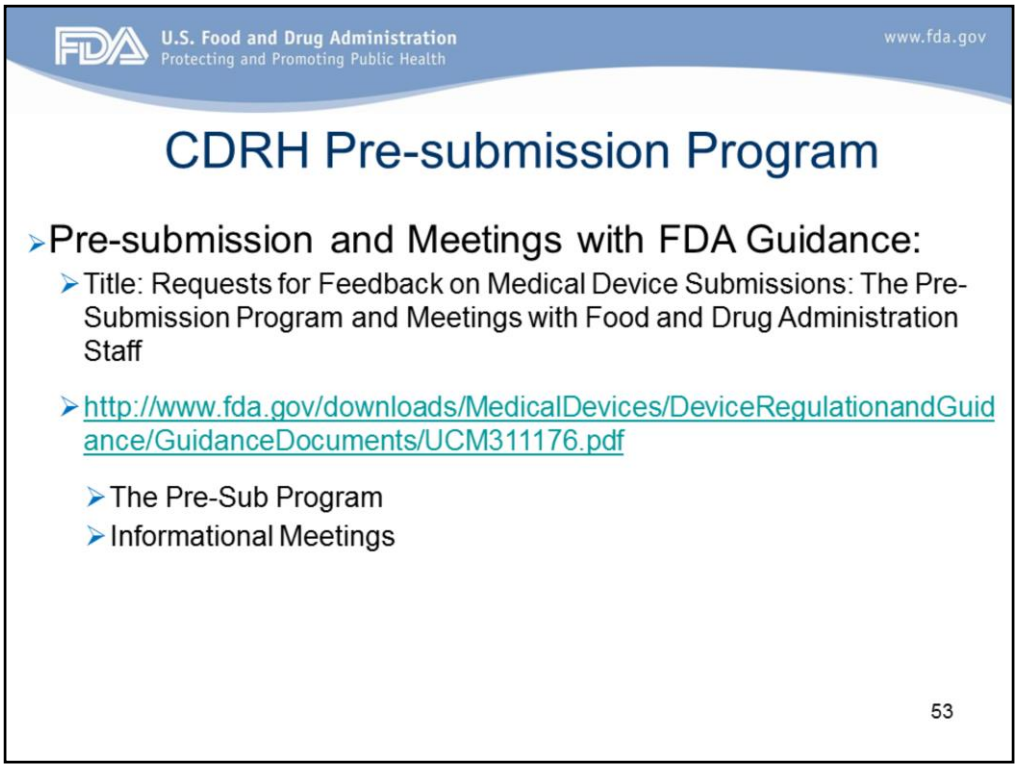
Again, this is all outlined in the final FDA decision summary. I just wanted to finish off the presentation with some useful links to CDRH for anybody who's developing these types of assays.

The Division of Industry and Consumer Education has a link that's a good resource if you are looking for information about FDA in general.

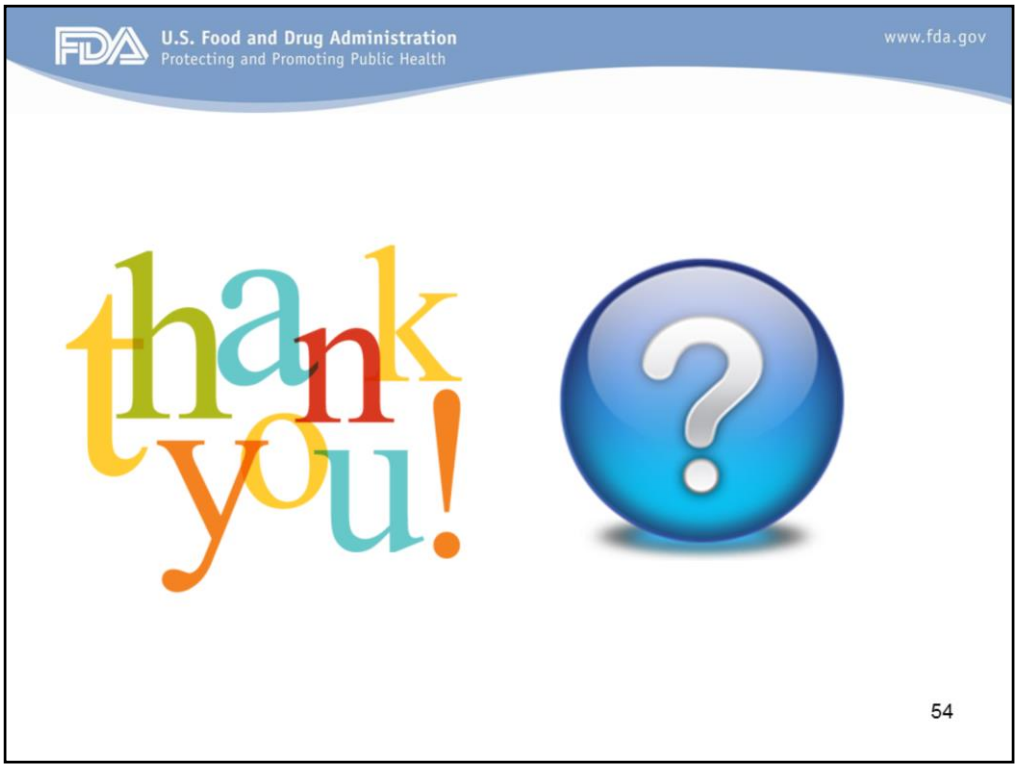
Then we have the device advice page, which is a comprehensive regulatory assistance website. It has some links to presentations. It will give you background into regulatory issues related to devices.



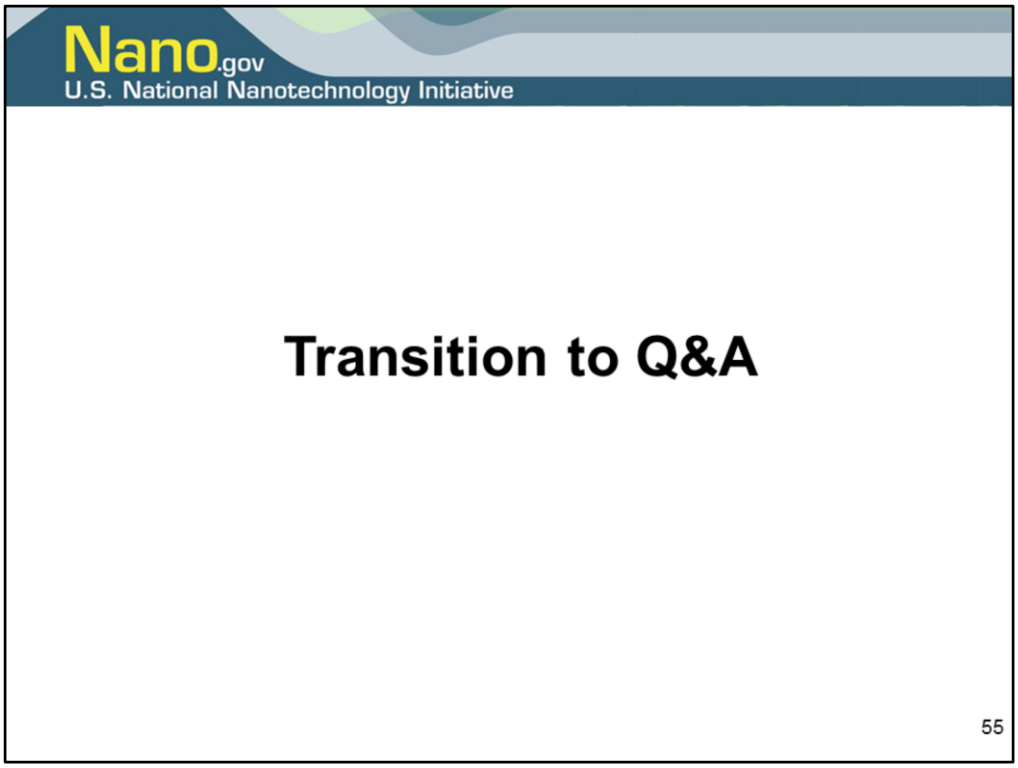
Then there are the medical device databases. We have a number of databases. They can be found at this website. There are links to the *de novo* pre-market approval and the pre-market notifications or the 510(k) submissions. From these links, you can access the decision summaries, which will give you an idea of how a specific device's studies were performed to support its approval or clearance. So they're very useful databases to search.



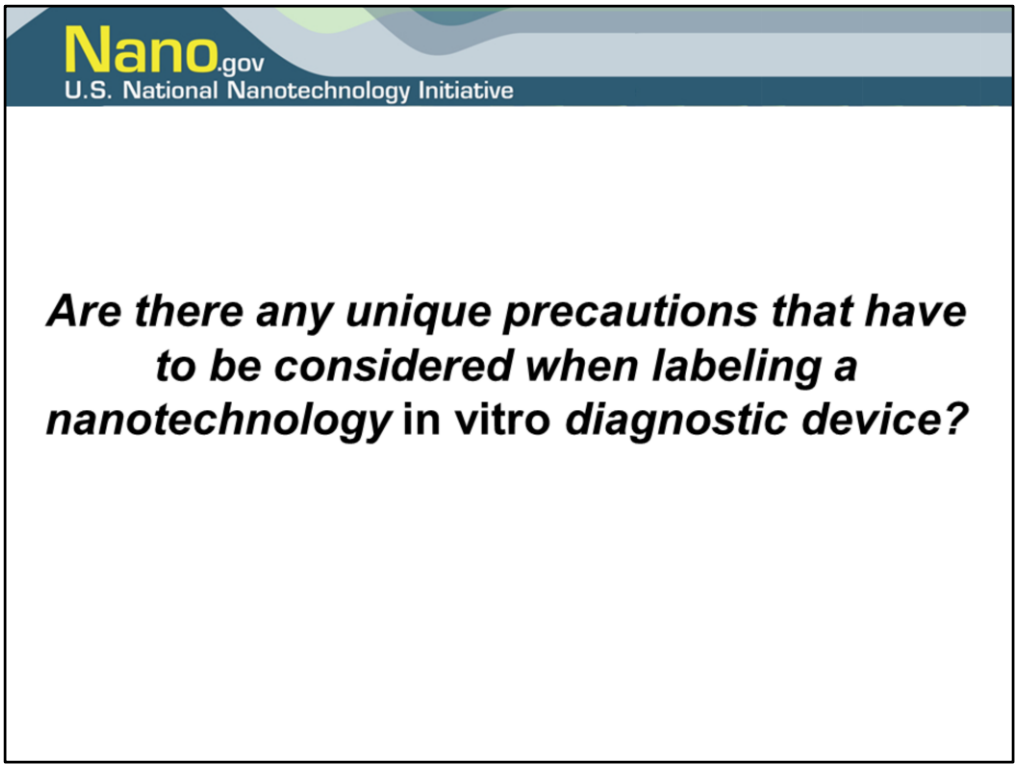
I want to finish with the CDRH pre-submission program. This is a free interaction with FDA, and there are various different types. There are informational meetings that you can request or the actual pre-submission program. This is a link to the guidance document that outlines this interaction with FDA. It's a mechanism by which you can submit questions about the device that you're developing, and you can get specific feedback related to your particular device that you describe in the submission to us. It's an invaluable resource, and it can be done at any stage of the device development.



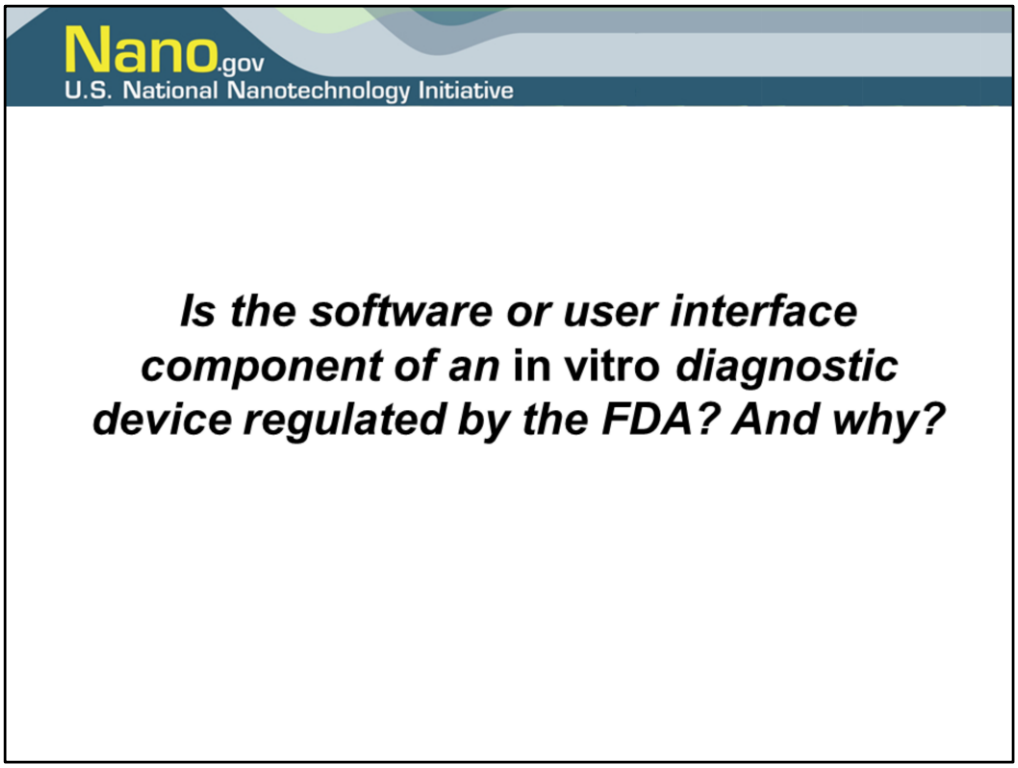
This concludes my presentation. Thank you all for listening. I'm happy to answer any questions.



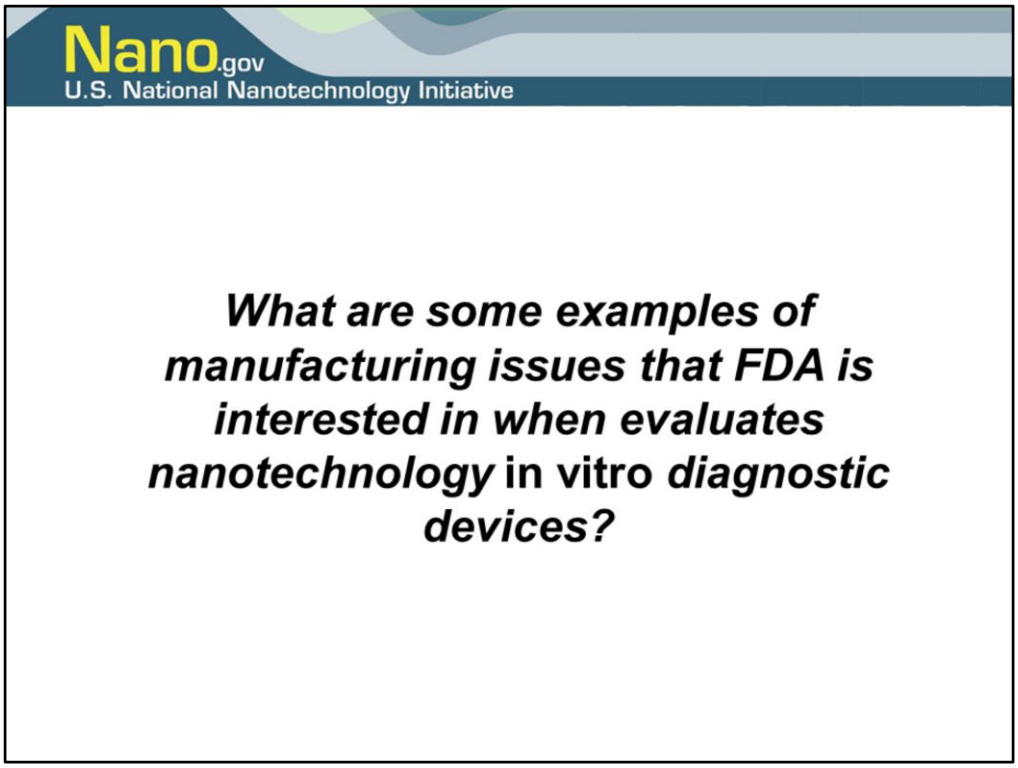
>> **Stephen Lehrman:** Thank you, Kim, for an excellent presentation. I would like to remind our audience that they can submit questions via email at webinar@nnco.nano.gov or in the "submit your questions here" window in the webinar interface. Now we're going to go ahead and turn to our first question.



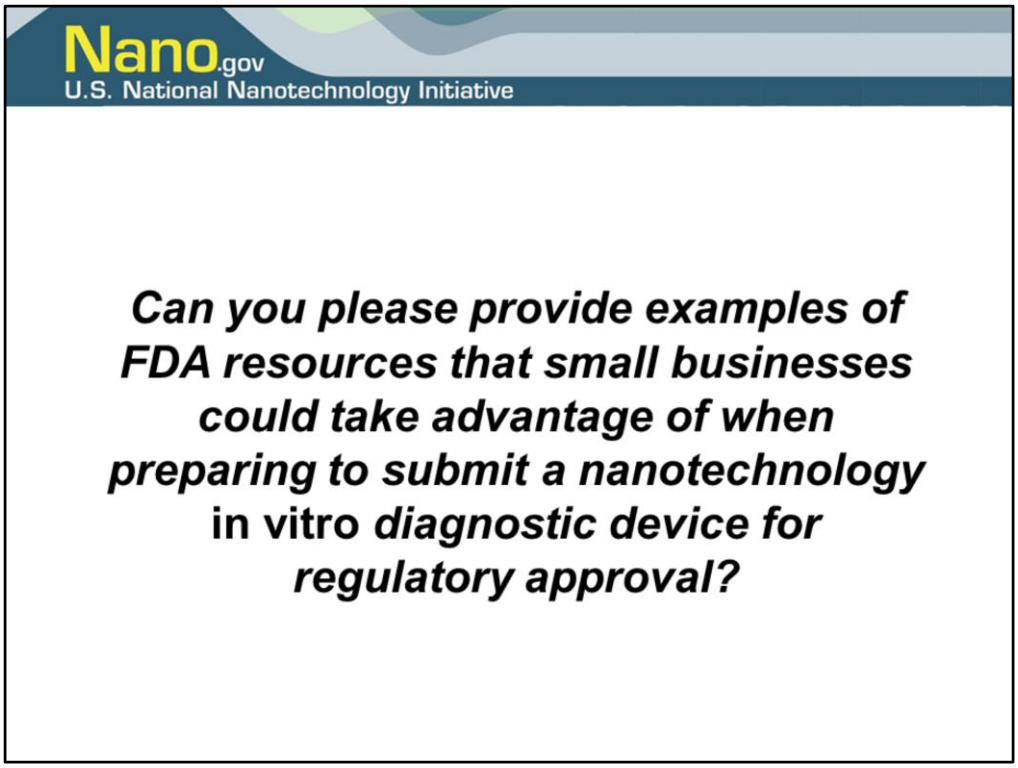
>> Kim Sapsford: Really, this depends on the nanomaterial that you will be using in your in vitro diagnostic device. Precautions would be to look at the labeling to make sure that there's appropriate disposal of any material that's considered a hazard, for example.



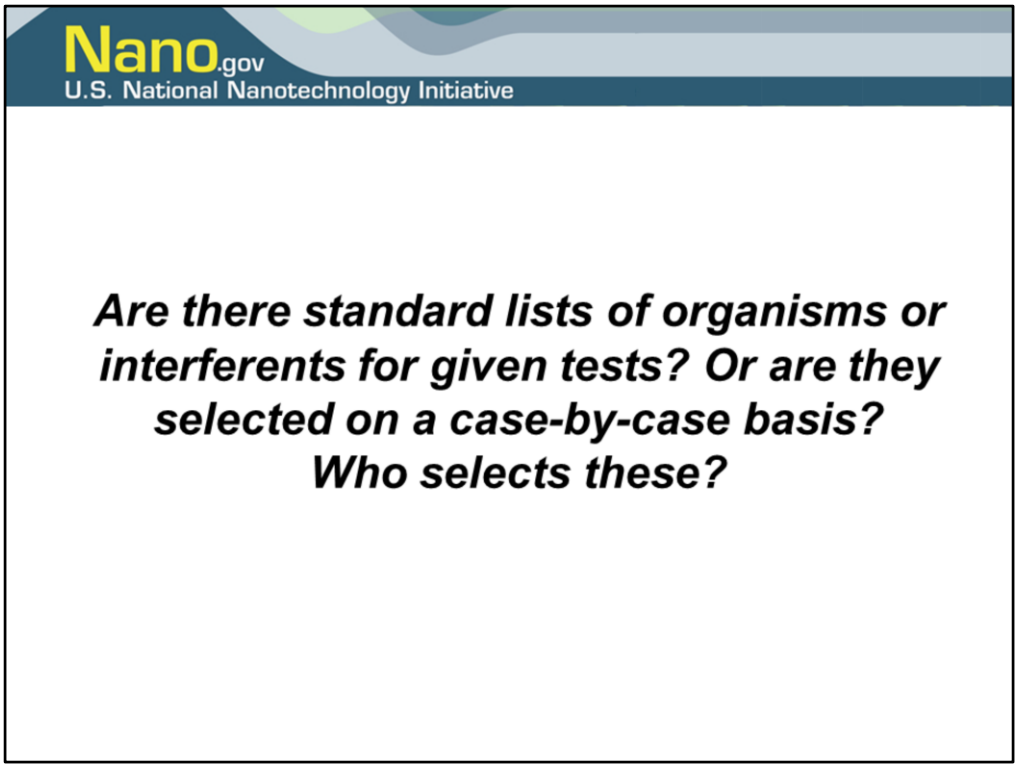
As I mentioned in the presentation, we review the system as a whole and this includes any software that's essential to the device and user interface. These are all evaluated as part of our review, and they are evaluated during the clinical study, actually, where it's used by the end user.



One of the issues with manufacturing nanomaterials is producing a reproducible product. This is really evaluated during the reproducibility study where we are looking at your in vitro diagnostic device and making sure it produces the expected result. One of the things we look at in the reproducibility study is different lots of materials that can pick up any manufacturing issues. We don't have specific manufacturing questions that we ask during our 510(k) pre-market review. We do have manufacturing questions that are asked during review of a PMA or a Class III device.



I want to highlight again the pre-submission process that's available to anybody who wants to, not just small businesses, but anybody who wants to receive feedback on their particular device. It's free, so it's useful for a small business that may not have lots of funding. Also, the DICE Web site that I highlighted at the end of my talk is also a useful resource for small businesses. That's actually tailored for small businesses and it's a way to ask general questions or even specific questions about the regulatory review process.



Depending on the analyte, there are some lists that are standardized to an extent, but there is no one list that works for everything – it will depend on the specific intended use and specimen type of the device. If there is a device that has already received clearance/approval from FDA that has a similar intended use/specimen type to the proposed device, then the FDA Decision Summary is a good starting point to see what organisms/interferents were evaluated in the past. The CLSI guidance document EP07-A2, Interference Testing in Clinical Chemistry, is also a good reference for a list of potential interferents. For feedback specific to a proposed device I would recommend a pre-submission be submitted to the agency. Ultimately the FDA review branch assembles experienced FDA employees (e.g., medical officers, scientists, and laboratorians) that review the proposed device to determine which organisms and interferents should be evaluated during the pre-market review. When a submission comes in, a company has typically already conducted studies. When the list of interfering substances or microorganisms are not sufficient to support that the device can be safely and effectively used in a clinical scenario (as was done for similar devices), additional substances or organisms are added to the list.

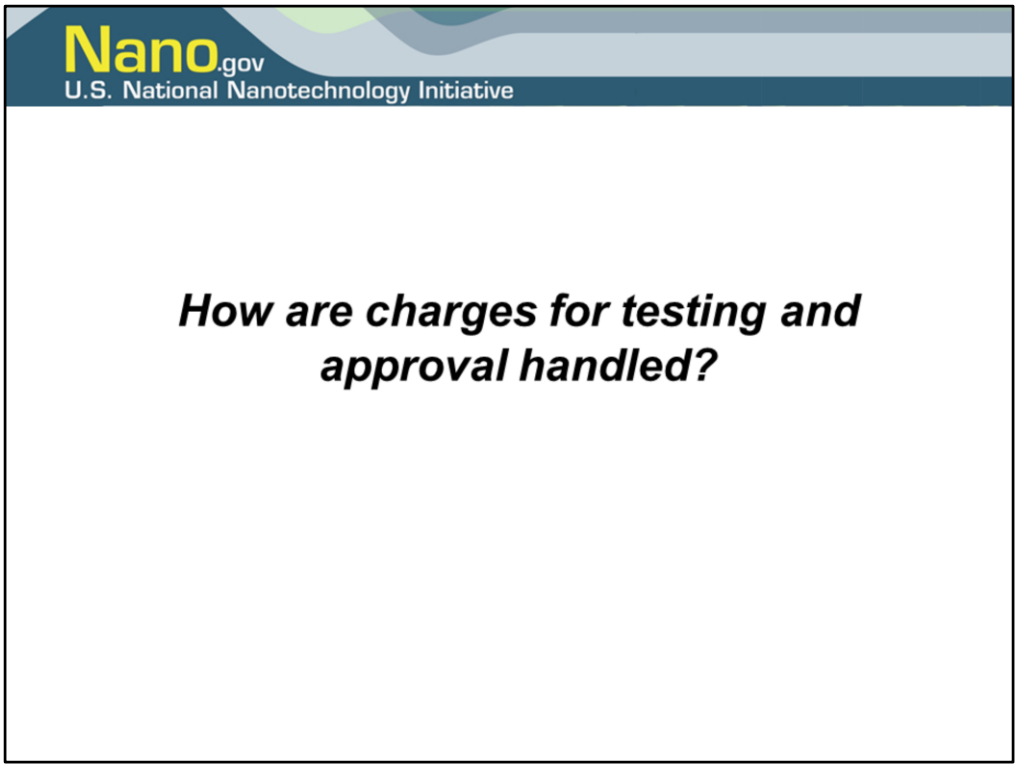
Typically, we look for the following:

- Microbial Cross-Reactivity/Interference: To validate that the risk of a false positive result due to cross-reactivity or false negative result due to interference is unlikely, studies are conducted using a panel of well characterized, clinically relevant organisms commonly found in the specimen type claimed in the intended use.
- Interfering Substances: Interfering substances should be tested based on their commonality of use, and their potential for interference with any component of the assay technology (e.g., interaction with an assay reagent; production of a interfering signal) or modification of a phenotype by direct interaction with the analyte in a way that could interfere with analyte detection (e.g., metabolic induction of extracellular polymeric substances or induction of a membrane-protective stress-response such as aggregation).

When considering possible interfering substances for your device, you should evaluate each component of the assay technology. The following are examples of scenarios where representative interfering substances should be considered (e.g., autofluorescent compounds for fluorescent detection devices; chelating agents for metal enzyme dependent assays; blood for colorimetric assays that require visual identification of antibody-captured red nanoparticles; viscosity-increasing agents for devices that require accurate liquid transfer).

Preparation of interfering substances should be conducted with the intent to mimic residual clinical material. Rationale

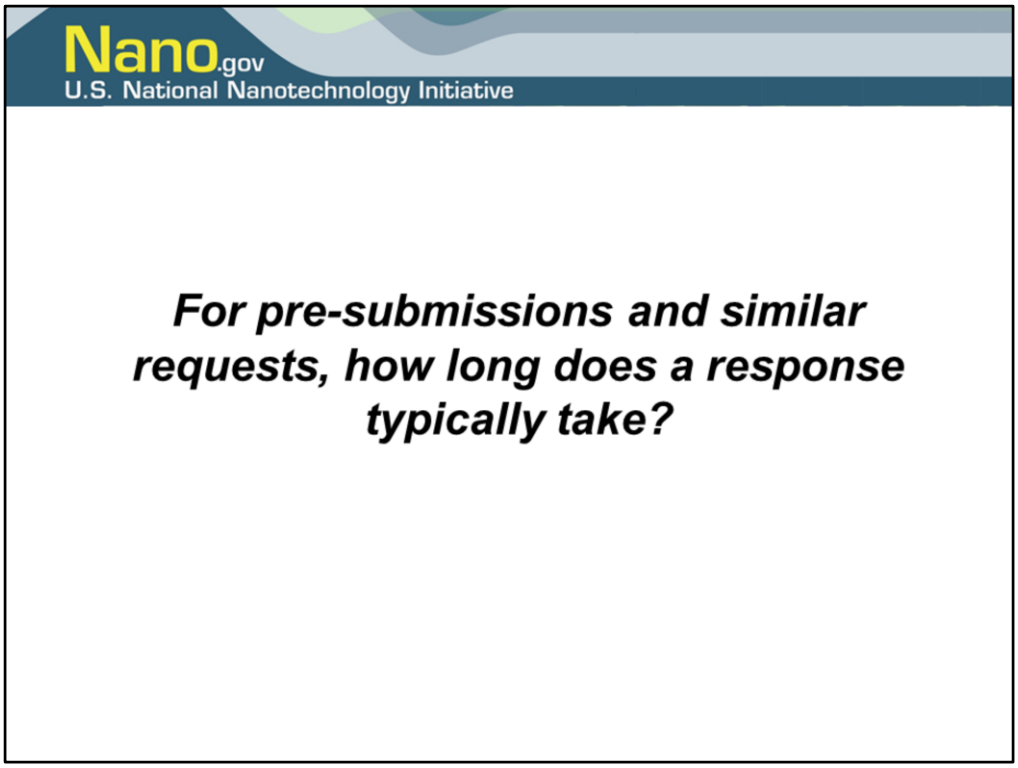
should be presented in the submission as to why any particular material is tested for interference in the context of the concentration it is expected to be found in a clinical specimen.



The only charges associated with an FDA submission for clearance or approval of a device are listed at the following website:

http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/Overview/ucm310929.htm

There are no charges associated with a pre-submission.



A pre-submission is typically handled and feedback provided within 75 calendar days from when the submission was first received and logged into the Document Control Center (DCC).

For more information on pre-submissions, please see the following link:

http://www.fda.gov/downloads/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm311176.pdf

For more information on goals from the Medical Device User Fee Amendments of 2012 (MDUFA), see the following link:

http://www.fda.gov/downloads/MedicalDevices/NewsEvents/WorkshopsConferences/ucm295454.pdf

FDA should be notified of significant modifications to a device that is cleared through the 510(k) process and all modifications for a device that is approved through the PMA process. In order to aid in making these determinations, the documents at the following links can be helpful:

510(k):http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm080235.htm

PMA: http://www.fda.gov/RegulatoryInformation/Guidances/ucm089274.htm]

>> Stephen Lehrman: Thank you, Kim. If there are no further questions, I think we're going to wrap up a little bit early. We want to thank Dr. Kim Sapsford for her great presentation and also thank our audience for attending this webinar. In a few weeks, we will post the transcript and the presentation slides from this webinar on the nano.gov website. The next National Nanotechnology Initiative webinar, entitled "Applications of Nanoinformatics", is scheduled for Thursday, November 12th from 12 noon to 1:00 p.m. This webinar will include several case studies on using specific nanoinformatics tools and principles to address nanotechnology-related environmental, health, and safety questions. More information on this webinar, including registration information, is available at www.nano.gov/publicwebinars. With that, thank you again. This concludes today's webinar.