

A Regulatory Case Study for the Development of Nanosensors

Tuesday, November 3, 2015



Dr. Kim Sapsford
FDA's Center for Devices and Radiological Health (CDRH)

This event will feature a Q&A segment with members of the public. Questions for the panel can be submitted to webinar@nnco.nano.gov from now until the end of the webinar at 1:00 pm. The moderator reserves the right to group similar questions and to omit questions that are either repetitive or not directly related to the topic.

Due to time constraints, it may not be possible to answer all questions.

>> **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.



Regulatory Case Study for the Development of Nanotechnology- enabled *In Vitro* Diagnostic Devices

Kim Sapsford, Ph.D.

Division of Microbiology Devices
Office of *In-vitro* Diagnostics and Radiological Health (OIR)
Center for Devices and Radiological Health (CDRH)

Tuesday, November 3rd 2015
NSI Webinar

>> **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.



Disclaimer

The contents of this presentation should not be considered as official position or policy of the U.S. Food & Drug Administration. The mention of trade names or manufacturers does not constitute endorsement.

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



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.



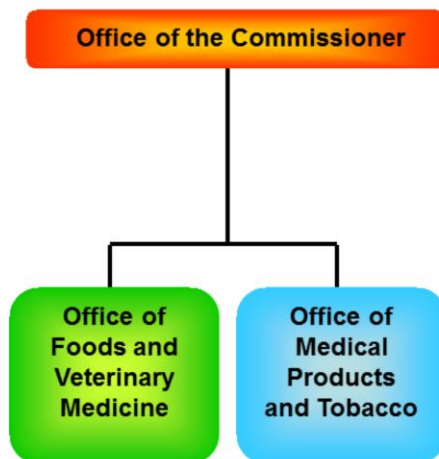
Overview

- Overview of FDA
- FDA/CDRH Medical Device Regulation
- *In Vitro* Diagnostic Devices
- Nanotechnology at FDA
- Case study – T2 Biosystems A Nanotechnology Enabled *In Vitro* Diagnostic Device
- CDRH Useful Links

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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.

Overview of US Food & Drug Administration (FDA)

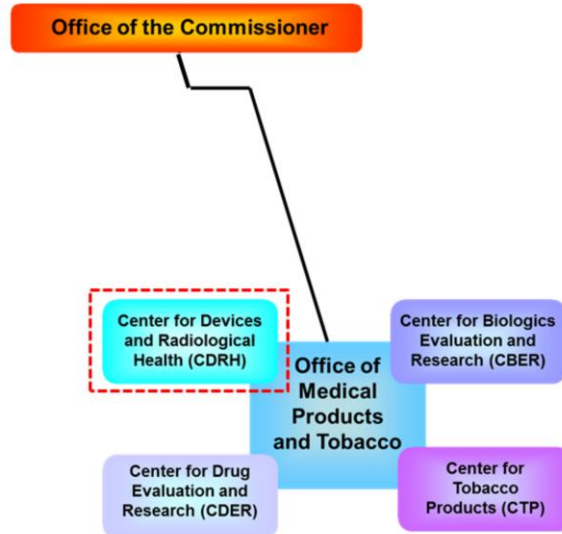


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<http://www.fda.gov/downloads/AboutFDA/CentersOffices/OrganizationCharts/UCM432556.pdf>

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.

Overview of FDA



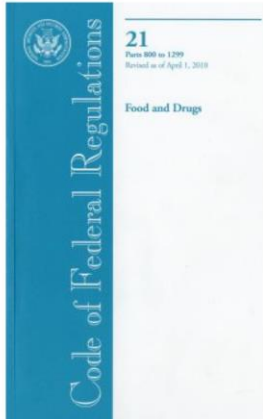
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<http://www.fda.gov/downloads/AboutFDA/CentersOffices/OrganizationCharts/UCM432556.pdf>

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.



Center for Devices and Radiological Health (CDRH)



- Federal Food, Drug and Cosmetic Act of 1938
- Medical Device Amendments 1976
- Code of Federal Regulations CFR – Most medical device and radiation-emitting product regulations are in Title 21 CFR Parts 800-1299

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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.

CDRH – What is a Device?

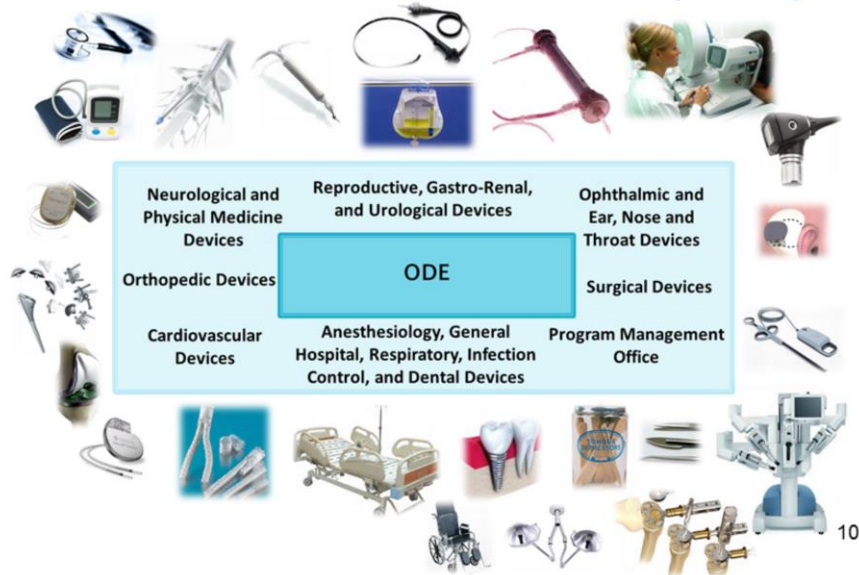
- Medical Device: “an instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent or similar related article. . . intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease, in man or other animals” (FFDCA 201(h))

-1976 Medical Device Amendments

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.



Office of Device Evaluation (ODE)



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.



Office of *In Vitro* Diagnostics and Radiological Health (OIR)



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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.

CDRH – What is a In Vitro Diagnostic (IVD)?

- In Vitro Diagnostic Devices (IVDs) are a subset of medical devices which are “reagents, instruments, and systems intended for use in the diagnosis of disease or other conditions, including a determination of the state of health, in order to cure, mitigate, treat, or prevent disease or its sequelae” (21 CFR 809.3)

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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 (*in vitro* diagnostic devices, or IVDs);
- Regulates radiological medical devices;
- Regulates radiation-emitting non-medical products;
- Implements the Mammography Quality Program authorized by the Federal Mammography Quality Standards Act of 1992; and
- Administers the federal law that supports the clinical laboratory community (the Clinical Laboratory Improvement Amendments—CLIA).
- OIR Link:
<http://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/InVitroDiagnostics/default.htm>

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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.

OIR – IVD Regulation

- Overview of IVD Regulation:
 - <http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/IVDRegulatoryAssistance/ucm123682.htm>
- A diagnostic device must be safe and effective for its Intended Use - 21 CFR 860.7
- The classification of an IVD is based on its benefit/risk profile which is determined based on a number of factors including the intended use of the device

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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 – Device Regulation

➤ Benefit/Risk based approach



Class I - Low likelihood of harm
register & list (21CFR §807)
General Controls

Class II - Moderate likelihood of harm or risk can be mitigated
Special Controls

Class III - High or unknown likelihood of harm
Significant Risk
Pre-market Approval

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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.

OIR – Intended Use

- For diagnostic devices Intended Use includes:
 - Target, disease and/or disease state being measured
 - Whether data is qualitative (e.g., +/-), quantitative (10^5 cfu/ml) or ordinal (Semi-quantitative)
 - The intended use population, e.g., adults with infection
 - The matrix being examined (e.g., blood, plasma, tissue, urine)
 - How the test is to be used (e.g., as an aid in diagnosis, risk assessment, prognosis, screening, determination of therapy, monitoring).

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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?

Premarket Review

- Submitted IVDs (devices) must establish adequate:
 - Analytical performance
 - Goal: establish the performance of the test and challenge the test
 - Examples of studies include:
 - Limit of Detection (Analytical Sensitivity)
 - Inclusivity (Reactivity)
 - Exclusivity (Analytical Specificity)
 - Precision/Reproducibility Studies (Test Variability)
 - Interferences (Endogenous/Exogenous)
 - Specimen Stability
 - Others

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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.

Premarket Review

- Submitted IVDs (devices) must establish adequate:
 - Clinical performance (for majority of DMD micro-devices)
 - Goal: establish the expected performance of the test in the intended use setting when testing is performed by the end user
 - Should represent Intended Use population
 - Prospectively collected (ideal)
 - Clearly defined inclusion/ exclusion criteria
 - Sample size/trial design statistically appropriate
 - Is an IDE required for clinical studies evaluating IVDs?

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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.

Investigational Device Exemptions (IDEs)

- An IDE allows an investigational device to be used in a clinical study in order to collect safety and effectiveness data to support PMA or 510(k) submission.
- An IDE permits devices 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.

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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.

Investigational Device Exemptions (IDEs)

- Many IVD clinical investigations are exempt from IDE requirements 21 CFR 812.2(c) (but NOT Institutional Review Boards) **IF:**
 - test is noninvasive
 - test does not introduce energy into a subject
 - test results not returned to patient/physician
 - test does not require an invasive sampling procedure that presents significant risk

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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.

Premarket Review

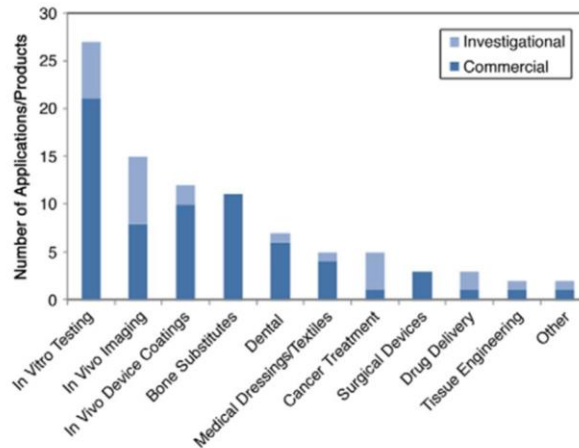
- All IVDs (devices) must establish adequate:
 - Labeling (21 § CFR 809.10)
 - Adequate instructions for use
 - Intended use, directions for use, warnings, limitations, interpretation of results, performance summary

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.

Nanotechnology at FDA

Medical Uses for Confirmed and Likely Nanomedicine Devices – 2013

Etheridge et al., *Nanomedicine: Nanotechnology, Biology and Medicine*, 9, 2013, 1–14.



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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.

Nanotechnology at FDA

www.sciencemag.org SCIENCE VOL 336 20 APRIL 2012

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POLICYFORUM

SCIENCE AND REGULATION

FDA's Approach to Regulation of Products of Nanotechnology

Margaret A. Hamburg

works (14–18). FDA does not categorically judge all products containing nanomaterials or otherwise involving the application of nanotechnology as intrinsically benign or harmful. As with other emerging technologies, advances in both basic and applied nanotechnology science may be unpredictable, rapid, and unevenly distributed across product applications and risk management tools. Therefore, the optimal regulatory approach is iterative, adaptive, and flexible (19, 20). It is iterative by developing and delivering incremental components of a regulatory system, such as guidances specific to product areas, each as warranted and when ready. It is adaptive by providing a mechanism, within statutory constraints, to change the rules, presumptions, or pathways for these regulatory components, in light of new information gained from research or from experience in regulating earlier products. And it is flexible by using all available means, ranging from workshops to consultations to guidances to rules, in order to match the burden of regulation to its need. To that end, FDA's regulatory approach will feature the following attributes:

A broadly inclusive initial approach may become more nuanced in light of experience, scientific information, and public input.

limited ability to evaluate product safety before its entry into commerce. Instead, FDA must rely on publicly available or voluntarily submitted information and on postmarket enforcement activities. In some of these cases, the law requires that information relied on in establishing safety be publicly available. In all cases, FDA encourages industry to provide safety information to FDA before taking their products to market. Such information can help FDA to advise companies and to carry out any necessary postmarketing safety oversight.

Technical advice and guidance to industry. FDA's recent draft guidance (8) on considerations for identifying products containing nanomaterials is intended to provide greater regulatory clarity to industry. As needed, FDA will develop additional product-specific guidance documents related to the use of nanomaterials in FDA-regulated products to assist industry to meet their regulatory and statutory obligations. These guidances may address interpretation of relevant statutory and regulatory standards and can provide guidance on the technical data needed to meet those standards.

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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.



Nanotechnology at FDA

- FDA Nanotechnology Link:
<http://www.fda.gov/ScienceResearch/SpecialTopics/Nanotechnology/default.htm>
- Current Guidance Documents:
 - **Final Guidance for Industry – Considering Whether an FDA-Regulated Product Involves the Application of Nanotechnology (June 2014)**
 - Final Guidance for Industry – Safety of Nanomaterials in Cosmetic Products (June 2014)
 - Final Guidance for Industry – Assessing the Effects of Significant Manufacturing Process Changes, Including Emerging Technologies, on the Safety and Regulatory Status of Food Ingredients and Food Contact Substances, Including Food Ingredients that are Color Additives (June 2014)
 - Final Guidance for Industry – Use of Nanomaterials in Food for Animals (August 2015)

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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.

Nanotechnology at FDA - Guidance

Section A. Points to Consider

At this time, when considering whether an FDA-regulated product contains nanomaterials or otherwise involves the application of nanotechnology, FDA will ask:

- Whether an **engineered material** or end product has at **least one dimension** in the **nanoscale range (approximately 1 nm to 100 nm)**; **or**
- Whether an engineered material or end product **exhibits properties or phenomena**, including physical or chemical properties or biological effects, that are **attributable to its dimension(s)**, even if these dimensions fall outside the nanoscale range, up to **one micrometer**.

These considerations **apply not only to new products, but also may apply when manufacturing changes alter the dimensions, properties, or effects of an FDA-regulated product** or any of its components. Additionally, they are subject to change in the future as new information becomes available, and to refinement in future product-specific guidance documents.

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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.

Nanotechnology at OIR

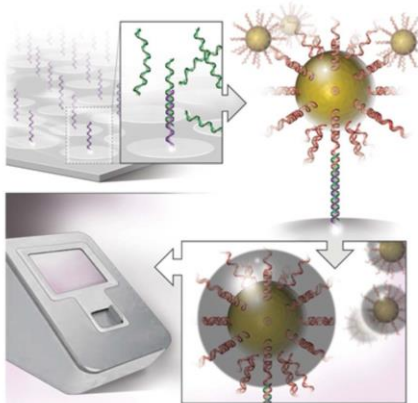
Nanomaterial	Device Type
Gold NPs	Ebola, Pregnancy Tests, Glucose, Gram-positive Blood Culture Pathogens, Gram-negative Blood Culture Pathogens, Enteric Pathogens, <i>Clostridium difficile</i> , <i>Staphylococcus</i> Blood Culture, Respiratory Viruses, Warfarin Metabolism, Cytochrome P450 CYP2C19 Drug Metabolizing Test, and F5/F2/MTHFR biomarkers in thrombophilia
DNA barcode	Breast cancer Prognostic gene assay
Magnetic NPs	Candida (fungal) test, and CellSearch Circulating Tumor Cell Kit

Nanoparticles

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.

Infectious Disease Nanotechnology at OIR

Nanosphere – Verigene Platform



Kim, Rutka and Chan., NEJM, 2010, 363, 2434.
<http://www.nanosphere.us/products/verigene-instruments>

Number of FDA-cleared diagnostic tests:

- > Respiratory Viruses
- > Gram-positive Blood Culture Pathogens
- > Gram-negative Blood Culture Pathogens
- > Enteric Pathogens
- > *Clostridium difficile*
- > *Staphylococcus sp.* Blood Culture

- > Warfarin Metabolism*
- > Cytochrome P450 CYP2C19 Drug Metabolizing Test*
- > F5/F2/MTHFR – Thrombophilia*

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*Not infectious disease

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.

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.cnb.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.

OIR Case Study – T2 Biosystems

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

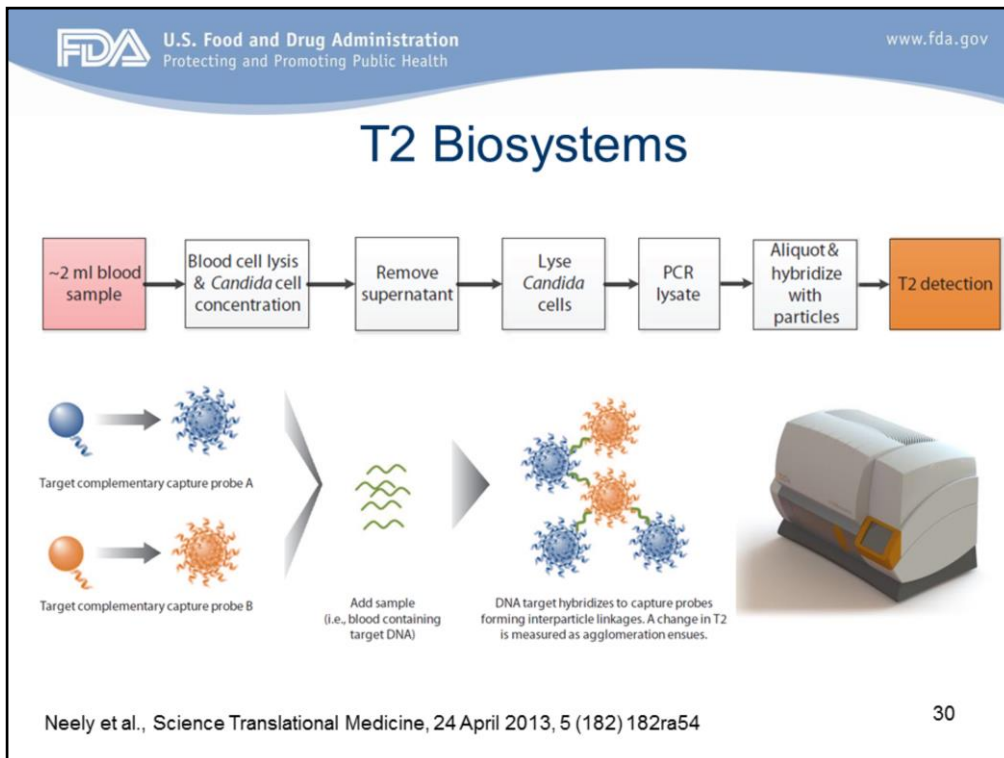
- The T2Candida Panel, performed on the T2Dx[®] Instrument, is a qualitative T2 Magnetic Resonance (T2MR[®]) molecular diagnostic assay for the detection of *Candida* species (listed below) from whole blood specimens from patients with signs and symptoms of invasive *Candida* infection
 - *Candida albicans*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

De novo Submissions

- Used for devices:
 - that have not been previously classified under the FD&C Act (i.e., do not have a legally marketed predicate)
 - are determined not to be high risk (Class III)
 - any associated risks can be mitigated through Special Controls
- Reviewed for safety and effectiveness
- *De novo* device becomes predicate for future devices of same type with same intended use
- Has been an important submission mechanism for novel IVDs

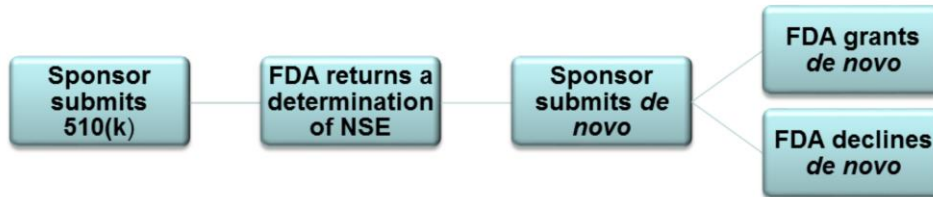
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The T2 Biosystems *Candida* panel was determined to be a *de novo* submission because it detects the *Candida* organisms directly from whole blood. All our previous assays detect from a blood culture sample, i.e., the blood specimen is collected and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

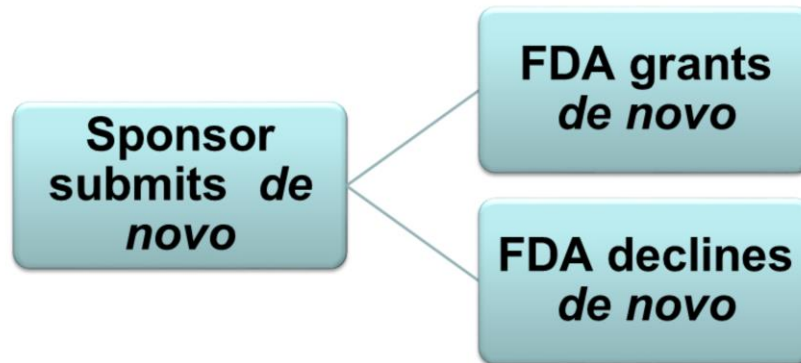
In the case of the *de novo* submissions, we review the safety and effectiveness of the device. The *de novo* device then becomes a predicate for any future devices of the same type or the same intended use. This has been a very important mechanism in our division for clearing novel *in vitro* diagnostics.

De novo Submissions (FDAMA)



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.

De novo Submissions (FDASIA)



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

FDA De Novo Database

<http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMN/denovo.cfm>

Device Classification under Section 513(a)(1)(de novo)

FDA Home Medical Devices Databases

Section 513(f)(2) of the Act, also referred to as de novo classification or Evaluation of Automatic Class III Designation, was amended by section 607 of the Food and Drug Administration Safety and Innovation Act (FDASIA) on July 9, 2012. This new law provides two options for de novo classification. First, any person who receives a "not substantially equivalent" (NSE) determination in response to a 510(k) for a device that has not been previously classified under the Act may, within 30 days of receiving notice of the NSE determination, request FDA to make a risk-based classification of the device under section 513(a)(1) of the Act. Alternatively, any person who determines that there is no legally marketed device upon which to base a determination of substantial equivalence may request FDA to make a risk-based classification of the device under section 513(a)(1) of the Act without first submitting a 510(k). For further information, please refer to our current guidance on the de novo process. [Learn more...](#)

Other Databases

- 510(k)s
- Medical Device Reports (MAUDE)
- CDRH FOIA Electronic Reading Room
- CFR Title 21
- CLIA
- Device Classification
- Humanitarian Device Exemption
- Inspections
- Medsun Reports
- Premarket Approvals (PMAs)
- Post-Approval Studies
- Postmarket Surveillance Studies
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- Standards
- Total Product Life Cycle
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DeNovo Number Product Code

510(K) Number Priority Review

Panel Device Name

Center Requester Name T2 Biosystems

Decision Date to

Sort by Decision Date (descending)

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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.

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

FDA De Novo Database

http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMN/denovo.cfm

Device Classification under Section 513(a)(1)(de novo)

FDA Home Medical Devices Databases

510(k) | De Novo | Registration & Listing | Adverse Events | Recalls | PMA | HDE | Classification | Standards
 CFR Title 21 | Radiation-Emitting Products | X-Ray Assembler | Mdsun Reports | CLIA | TPLC | Inspections

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Device Classification Name	Candida Species Nucleic Acid Detection System
De Novo Number	DEN140019
Device Name	T2CANDIDA AND T2DX INSTRUMENT
Requester	T2 BIOSYSTEMS, INC 101 Hartwell Ave Lexington, MA 02421
Contact	Sarah Kall
Regulation Number	866.3960
Classification Product Code	PI
Date Received	05/27/2014
Decision Date	09/22/2014
Decision	Granted (DENG)
Classification Advisory Committee	Immunology
Review Advisory Committee	Microbiology
Reclassification Order	Reclassification Order
FDA Review	Decision Summary
Type	Direct

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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.



FDA De Novo Database

Reclassification Order

FDA Decision Summary



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
1015 New Hampshire Avenue
Silver Spring, MD 20910
Phone: (301) 796-6000

September 22, 2014

T2 Biosystems, Inc.
c/o Sarah Kahl
Chief Operating Officer
101 Harvard Avenue
Lexington, MA 02421

Re: DEN140019
T2Candida Panel and T2Dn[®] Instrument
Evaluation of Automatic Class III Designation – De Novo Request
Regulation Number: 21 CFR 866.3960
Regulation Name: Nucleic acid-based device for the amplification, detection and identification of microbial pathogens directly from whole blood specimens
Regulatory Classification: Class II
Product Code: P01, NSU
Dated: May 27, 2014
Received: May 27, 2014

Dear Ms. Kahl:

The Center for Devices and Radiological Health (CDRH) of the Food and Drug Administration (FDA) has completed its review of your de novo request for classification of the T2Candida Panel and T2Dn[®] Instrument, a prescription device. The intended use of the T2Candida Panel and T2Dn[®] Instrument is:

The T2Candida Panel and T2Dn[®] Instrument is a qualitative T2 Magnetic Resonance (T2MR[®]) assay for the direct detection of *Candida* species in EDTA human whole blood specimens from patients with symptoms of, or medical conditions predisposing the patient to, invasive fungal infections. The T2Candida Panel identifies five species of *Candida* and categorizes them into the following three species groups:

1. *Candida albicans* and/or *Candida tropicalis*,
2. *Candida parapsilosis*,
3. *Candida glabrata* and/or *Candida brucei*

The T2Candida Panel does not distinguish between *C. albicans* and *C. tropicalis*. The T2Candida Panel does not distinguish between *C. glabrata* and *C. brucei*.

EVALUATION OF AUTOMATIC CLASS III DESIGNATION FOR T2Candida Panel and T2Dn[®] Instrument

DECISION SUMMARY

- A. DEN Number:
DEN140019
- B. Purpose for Submission:
De Novo request for evaluation of automatic class III designation for the T2Candida Panel and T2Dn[®] Instrument
- C. Measurements:
The assay amplifies and detects nucleic acids of the following species:
Candida albicans and/or *Candida tropicalis*;
Candida parapsilosis;
Candida brucei and/or *Candida glabrata*
- D. Type of Test:
The T2Candida Panel, performed on the T2Dn[®] Instrument, is a molecular diagnostic assay for the detection of the above listed *Candida* species from whole blood specimens obtained from patients with signs and symptoms of invasive *Candida* infection.
- E. Applicant:
T2 Biosystems, Inc.
- F. Proprietary and Established Names:
T2Candida Panel and T2Dn[®] Instrument
- G. Regulatory Information:
1. Regulation section:
21 CFR 866.3960
 2. Classification:
Class II
 3. Product code(s):

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.

T2 Biosystems – FDA Decision Summary

- Premarket review of IVDs evaluates many aspects of the device including the analytical and clinical performance for its Intended Use
- Review the device as a whole system from specimen collection thru IVD result
- The results of these studies are presented in the FDA Decision Summary

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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.

T2 Biosystems – FDA Decision Summary

H. Intended Use:

1. Intended use(s):

The T2Candida Panel and T2Dx[®] Instrument is a qualitative T2 Magnetic Resonance (T2MR[®]) assay for the direct detection of *Candida* species in EDTA human whole blood specimens from patients with symptoms of, or medical conditions predisposing the patient to, invasive fungal infections. The T2Candida Panel identifies five species of *Candida* and categorizes them into the following three species groups:

1. *Candida albicans* and/or *Candida tropicalis*,
2. *Candida parapsilosis*
3. *Candida glabrata* and/or *Candida krusei*

The T2Candida Panel does not distinguish between *C. albicans* and *C. tropicalis*. The T2Candida Panel does not distinguish between *C. glabrata* and *C. krusei*.

The T2Candida Panel is indicated for the presumptive diagnosis of candidemia. The T2Candida Panel is performed independent of blood culture. Concomitant blood cultures are necessary to recover organisms for susceptibility testing or further identification.

The T2Candida positive and negative External Controls are intended to be used as quality control samples with the T2Candida Panel when run on the T2Dx[®] instrument system. These controls are not intended for use with other assays or systems.

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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.

T2 Biosystems – FDA Decision Summary

L. Performance Characteristics:

1. Analytical performance:

a. *Precision/Reproducibility*

A multicenter reproducibility study was performed to determine the run to run, reagent lot, day to day, and site to site reproducibility. Testing was performed at three sites (two external and one internal) with a panel of three *Candida* species (*C. albicans*, *C. parapsilosis* and *C. glabrata*), each tested at two concentrations (1 – 2X LoD, 3 – 4X LoD) using two reagent lots. Testing was performed for six non-consecutive days with two runs and two operators per day. Organisms were tested in triplicate. A total of 108 data points were determined for each analyte at each concentration.

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.

T2 Biosystems – FDA Decision Summary

d. Detection Limit:

LoD testing was performed using two strains of each species targeted by the T2Candida Panel and performed on the T2Dx[®] Instrument. LoD testing consisted of an initial screening phase and a confirmatory phase.

Table 4. LoD Results

Species	Strain 1		Strain 2		Final LoD CFU/mL
	# Positive/Total (%)	CFU/mL	# Positive/Total (%)	CFU/mL	
<i>C. albicans</i>	19/20 (95)	1	21/21 (100)	2	2
<i>C. tropicalis</i>	20/20 (100)	1	21/21 (100)	1	1
<i>C. parapsilosis</i>	20/20 (100)	2	20/20 (100)	3	3
<i>C. glabrata</i>	20/20 (100)	2	20/20 (100)	2	2
<i>C. krusei</i>	19/20 (95)	1	19/20 (95)	1	1

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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.

T2 Biosystems – FDA Decision Summary

f. Analytical Sensitivity:

Fifteen human strains of each target species were tested the T2Candida Panel and T2Dx[®] Instrument. The identification of all isolates was confirmed by sequence analysis of the ITS2 region of the ribosomal operon. Isolates were tested in triplicate at 2-3X LoD; testing was repeated for strains which were not detected. Results of the analytical sensitivity study are shown in Table 5 below.

Table 5. Analytical Sensitivity Results

Species	No. strains tested/no. positive (%)
<i>C. albicans</i>	15/15 (100%)
<i>C. tropicalis</i>	14/15 (93.3%)*
<i>C. krusei</i>	15/15 (100%)
<i>C. glabrata</i>	15/15 (100%)
<i>C. parapsilosis</i>	15/15 (100%)

*Repeat testing of 20 replicates of the *C. tropicalis* isolate that was not detected gave positive results in all replicates.

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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.

T2 Biosystems – FDA Decision Summary

g. *Co-infection Studies:*

A competitive inhibition study was performed to evaluate the sensitivity of the T2Candida Panel and T2Dx[®] Instrument to detect *Candida* present at a concentration of 1-2X LoD in the presence of other clinically relevant organisms that may be present in a co-infection.

Table 6. Results of Competitive Inhibition Studies

Organism combinations	Concentration	No. Pairs Tested	Total No. of Tests (4 Replicates Per Organism Combination)	No. of Positive Tests/Total No. of Tests (%)	95% CI
<i>Candida</i> sp./ <i>Candida</i> sp.	Both at 1 - 2X LoD	31	124	118/124 (95.2%)	89.8 – 97.8
	1-2X LoD/100 CFU/mL	63	252	244/252 (96.8%)	93.8 – 98.4
<i>Candida</i> sp./other genus	1-2X LoD/100 CFU/mL	50	200	189/200 (94.5%)	90.4 – 96.9

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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*.

T2 Biosystems – FDA Decision Summary

f. Analytical Specificity:

A cross reactivity study was performed using 80 non-target, clinically relevant or environmental organisms including 21 yeast species, nine viruses, 25 fungi and 25 species of bacteria. Isolates were initially tested in triplicate at a concentration of 10^6 CFU/mL for yeast, molds and bacteria, and viruses were tested at a concentration of 10^5 PFU/mL. Any strain which showed cross reactivity or gave an invalid result was further evaluated at lower, more clinically relevant concentrations of organisms in blood (100, 33 and 10 CFU/mL).

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.

T2 Biosystems – FDA Decision Summary

Table 7. Species Providing Valid IC Values and No Cross Reactivity

Bacteria	
<i>Acinetobacter baumannii</i>	<i>Staphylococcus aureus</i> MRSA
<i>Bacteroides fragilis</i>	<i>Staphylococcus auricularis</i>
<i>Clostridium perfringens</i>	<i>Staphylococcus epidermidis</i>
<i>Enterobacter cloacae</i>	<i>Staphylococcus haemolyticus</i>
<i>Klebsiella oxytoca</i>	<i>Staphylococcus hominis</i>
<i>Klebsiella pneumoniae</i>	<i>Staphylococcus intermedius</i>
<i>Morganella morganii</i>	<i>Staphylococcus saprophyticus</i>
<i>Pseudomonas aeruginosa</i>	<i>Staphylococcus warneri</i>
<i>Serratia marcescens</i>	<i>Streptococcus mutans</i>
<i>Enterococcus faecalis</i>	<i>Streptococcus pneumoniae</i>
<i>Staphylococcus aureus</i>	<i>Streptococcus pyogenes</i>
Fungi	
Viruses	
<i>Acromonium kiliense</i>	Adenovirus
<i>Malassezia furfur</i>	Cytomegalovirus
<i>Malassezia pachydermatis</i>	Enterovirus
<i>Mucor oblongiellipticus</i>	Epstein-Barr Virus
<i>Phialophora richardsiae</i>	Hepatitis A
<i>Rhizomucor microsporous</i>	Hepatitis B
<i>Rhizopus pusillus</i>	Herpes simplex Virus 1
<i>Rhizopus oryzae</i>	Herpes simplex Virus 2
<i>Scedosporium prolificans</i>	Varicella zoster Virus
<i>Candida haemulonii</i>	

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

T2 Biosystems – FDA Decision Summary

Table 8. Species Providing an Invalid IC or Positive *Candida* Results When Tested at 10⁶ CFU/mL but Not When Tested at Clinically Relevant Concentrations; Not Considered to be Cross Reactive

Organisms Giving Invalid IC Results at 10⁶ CFU/mL	
<i>Candida albidus</i>	<i>Aspergillus flavus</i>
<i>Candida dubliniensis</i>	<i>Aspergillus fumigatus</i>
<i>Candida gigantensis</i>	<i>Aspergillus niger</i>
<i>Candida guilliermondii</i>	<i>Aspergillus terreus</i>
<i>Candida kefyr</i>	<i>Exophiala xenobiotica</i>
<i>Candida lusitanae</i>	<i>Fusarium proliferatum</i>
<i>Candida lusitanae</i>	<i>Fusarium oxysporum</i>
<i>Candida nivariensis</i>	<i>Fusarium solani</i>
<i>Candida norvegensis</i>	<i>Kluyveromyces delphensis</i>
<i>Candida pelliculosa</i>	<i>Pichia anomala</i>
<i>Candida utilis</i>	<i>Paecilomyces variotii</i>
<i>Candida viswanathii</i>	<i>Scopulariopsis brevicaulis</i>
<i>Cryptococcus neoformans</i>	<i>Trichosporon asahii</i>
<i>Rhodotorula glutinis</i>	<i>Trichosporon inkin</i>
	<i>Trichosporon mucoides</i>
	<i>Trichoderma reesei</i>
Organisms Giving Positive <i>Candida</i> Results at 10⁶ CFU/mL	
<i>Candida rugosa</i>	<i>Acinetobacter lwoffii</i>
<i>Candida sojae</i>	<i>Escherichia coli</i>
	<i>E. faecalis</i>

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.

T2 Biosystems – FDA Decision Summary

g. Interfering Substances

An interfering substances study was performed to determine and characterize the effects of potential endogenous and exogenous interfering substances on the performance of the T2Candida Panel and the T2Dx[®] Instrument. Interference testing was performed using a paired-difference format; the potentially interfering substance was added to a *Candida*-spiked sample at high concentration (to simulate worse case) and the bias relative to a *Candida* spiked control containing no interfering substances was determined.

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.



T2 Biosystems – FDA Decision Summary

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	Exogenous Interferent
EDTA	Caspofungin
Heparin	Lisinopril
Calcium Hypochlorite	Cytarabine
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	

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.

T2 Biosystems – FDA Decision Summary

Table 14. Contrived Specimen Performance by Detection Channel

Detection Channel	PPA	95 %CI	NPA	95%CI
A/T	94/100 (94.0%)	87.5-97.2	200/200 (100.0%)	98.1-100.0
P	47/50 (94.0%)	83.8-97.9	249/250 (99.6%)	97.8-99.9
K/G	88/100 (88.0%)	80.2-93.0	200/200 (100.0%)	98.1-100.0

Abbreviations: PPA, Positive percent agreement; NPA, Negative percent agreement; A/T, *C. albicans/C. tropicalis* channel; P, *C. parapsilosis* channel; K/G, *C. krusei, C. glabrata* channel

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.



T2 Biosystems – FDA Decision Summary

b. Clinical specificity:

The specificity of the T2Candida Panel and T2Dx[®] Instrument was determined by a prospective comparison of the results of the T2Candida Panel with results from blood culture collected from the same draw at the same anatomical site.

Patients. A total of 1501 blood specimens were drawn from adult patients who had been referred for a diagnostic blood culture per routine standard of care. Informed consent was obtained. Forty-eight percent of specimens were obtained from patients determined to have some level of immunocompromise.

Study Sites. Specimens were collected at nine geographically diverse sites; testing was performed at seven sites.

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.

T2 Biosystems – FDA Decision Summary

Table 17. Prospective Specimen Sensitivity and Specificity by Detection Channel

Detection Channel	Sensitivity	95%CI	Specificity	95%CI
A/T	2/4* (50.0%)	15.0 – 85.0	1479/1497 (98.8%)	98.1 – 99.2
P	2/2 (100%)	34.2 – 100.0	1487/1499 (99.2%)	98.6 – 99.5
K/G	1/1 (100%)	20.6 – 100.0	1499/1500 (99.9%)	99.6 – 99.9

* an additional specimen collected at the same time was positive for *C. albicans*

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



CDRH Help

- Division of Industry and Consumer Education (DICE):
 - <http://www.fda.gov/medicaldevices/deviceregulationandguidance/contacts--divisionofindustryandconsumereducation/ucm20041265.htm>
- Device Advice – Comprehensive Regulatory Assistance
 - <http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/default.htm>

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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.



CDRH Device Databases

- Medical Devices Databases:
 - <http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/Databases/default.htm>
 - De Novo
 - Premarket Approvals (PMA)
 - Premarket Notifications (510(k)s)

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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.



CDRH Pre-submission Program

- **Pre-submission and Meetings with FDA Guidance:**
 - Title: Requests for Feedback on Medical Device Submissions: The Pre-Submission Program and Meetings with Food and Drug Administration Staff
 - <http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM311176.pdf>
 - The Pre-Sub Program
 - Informational Meetings

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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](http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM311176.pdf) 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.

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

thank you!



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

Transition to Q&A

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>> **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.

Are there any unique precautions that have to be considered when labeling a nanotechnology in vitro diagnostic device?

>> **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.

***Is the software or user interface
component of an in vitro diagnostic
device regulated by the FDA? And why?***

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.

What are some examples of manufacturing issues that FDA is interested in when evaluates nanotechnology in vitro diagnostic devices?

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.

Can you please provide examples of FDA resources that small businesses could take advantage of when preparing to submit a nanotechnology in vitro diagnostic device for regulatory approval?

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.

***Are there standard lists of organisms or interferences for given tests? Or are they selected on a case-by-case basis?
Who selects these?***

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/interferences 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 interferences. 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 interferences 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.

How are charges for testing and approval handled?

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.

For pre-submissions and similar requests, how long does a response typically take?

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>

If a device is approved and later modified, what level of modification would require a re-approval?

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.