National Center for Toxicological Research

Science Advisory Board Meeting

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Agenda Item: FDA Center Perspectives

DR. LEIN: Good morning everybody. I'd like to convene this morning's session. So we'll have presentations from the product centers today, and our first presentation will be from the Center for Biologics Evaluation and Research.

Agenda Item: Center for Biologics Evaluation and Research

DR. WILSON: Good morning. I'm going to try to give you a quick introduction to an overview of the kinds of products that Center for Biologics regulates, some of the major challenges we face, our strategic goals, and then finish in the second half of the presentation with an overview of the types of projects where we have active collaborations with NCTR and drill down on a few specific projects that are of critical importance to the center right now. So this is our template disclaimer, my comments are an informal communication representing my own judgment, and do not bind or obligate FDA.

So for those of you who aren't familiar with the center, we regulate a wide variety of products that are mostly derived from biological materials, hence the term biologics. Allergenics, the first on this list actually

represents over 1300 different allergenic extracts, and they're used both to treat and diagnose allergic disease. And so this is actually a very challenging area for us to regulate. We also regulate blood, blood products, devices related to biologics, gene therapies, and as some of you may know we actually licensed our first gene therapies this year, which we're very excited about.

Human tissues, cellular products, and vaccines both preventive and therapeutic, and xenotransplantation products. So with regard to vaccines, of course as many of you know this is probably one of the most important 20th century impacts on public health. And this is data that shows the burden of disease in the 1900s, before we had vaccines for these major killers, and our current burden of disease as of 2013.

And as you can see we've had a tremendous impact on the public health with regard to these. The Pertussis has had a bump in part because there was a change from a whole cell vaccine to an acellular vaccine in the 80s, which was in part because of adverse effects from the wholesale vaccine. But it turns out that acellular is perhaps slightly less effective, and we've been doing research and developed a baboon animal model to address this, and we're making great progress at trying to figure

out how to improve and come up with a third generation vaccine that will hopefully bring these numbers down a bit.

And then our challenges here, and you'll hear more about this, you got a little bit of a glimmer yesterday, probiotic therapeutics, which includes things like phage therapies, fecal transplantations and so on, as well as probiotics when they're claiming an actual clinical effect, then it's considered a medicine. And then vaccines for infectious diseases of global importance, and of course merging infectious disease are a continuing challenge.

The second major area is keeping the blood supply safe. And again as you can see our rates of potential contamination have come down to miniscule risk in terms of the three major pathogens that were of concern going back to the 80s.

And we're excited because we now have approved for platelet use a pathogen reduction technology which helps to essentially sterilize these products. The challenge there is to be able to apply it to other blood cell products like whole blood and red blood cells, because we do continue to see low rates of bacterial contamination in those products.

Another area is agents of transmissible spongiform encephalopathies. We still don't have a good screening assay, but again work that's going on in our center is getting closer to developing a fairly rapid and very sensitive assay that could replace the current two year bioassay that's the gold standard, which obviously can't be used to screen blood.

And then as you can imagine here the emerging infectious diseases continue to play a major challenge in keeping the blood supply safe. We also have new challenges from things like *Babesia microti* where we see incidences in certain regions like New England, and so we've been working with the blood industry to develop better assays to implement in certain regions, as well as malaria.

And then the advanced therapies is a very exciting area, and as you can imagine the ex vivo or in vivo gene editing that is coming to treat a variety of conditions, again we heard briefly about that yesterday, it's very exciting but it also poses challenges in terms of regulating that. But in the meantime, we're excited that we have now two gene therapies based on CAR-T cell therapy to treat various types of leukemia and lymphoma. Challenges here are how do we prepare for these new and evolving technologies, and manufacturing scale-up.

There's now a large government investment by DOD and NIST to figure out how can we do cell and gene therapy at a large scale that's cost effective while maintaining the appropriate quality control that we need to. Stem cell derived products raise a variety of challenges as well. And then we also now are starting to see in the area of regenerative medicine more combination products or cells that combine with devices and particular 3D printed scaffolds and how to regulate those products.

So we have four major research goals in the center, and those are around the idea of advancing the scientific basis for regulation of biologics, human tissues, and blood. And the first is really relating to CMC, how do we characterize the products. The second is relating to developing and assessing non-clinical models and methods. The third is for improving clinical evaluation pre- and post-licensure. And the fourth is preparing for future regulatory and public health challenges.

With regard to NCTR collaborations that are supporting these research goals, we have a few that are in the area of CMC, and I'll talk about one of those in particular in a few minutes. And then most of them as you would imagine given the expertise and the area of focus

here at NCTR are really relating to go to support non-clinical evaluation. And I'll talk about the first three in more detail in a minute, I won't mention those now.

The PK and bio-distribution of novel adjuvants has been a very productive collaboration where we've gotten a lot of useful information to allow us to evaluate how these adjuvants are working in the context of flu vaccines, and then we're also supporting developing of an animal model to support norovirus vaccine development by collaborating on looking at newly identified strains of canine viruses that may allow us to use those in certain animal models. So we also have a couple of collaborations where the impetus has really come from NCTR, but CBER has the scientific expertise to support the NCTR interest in these.

So the first is a study looking at mechanisms of norovirus and salmonella co-infection. CBER scientists are developing an in vivo enteroid model, and as I mentioned they're trying to get an animal model. This is a huge need for norovirus vaccine development, and they may also be useful tools for looking at this co-infection model.

And then the other area is some work that was done by NCTR to develop an SDAR approach to identify candidate molecules, and in this case they're looking at

antitrypanosomal molecules, and our scientists who work in this area on T cruzi have assays in place to do functional screening of those candidate molecules. But I won't go into those projects any further. What I'll do is I'll spend the last few minutes just giving you some updates on existing and a couple of new collaborations that started in the last year.

So we heard a lot about Fecal Microbiota Transplantation or FMT yesterday. And to just give you the broader context from our perspective in terms of the regulatory challenges, the big challenges are what should we test for, obviously we don't want to do more harm than good, and if there are pathogens in these materials we don't want to introduce pathogens. The challenge is do we have assays that are actually sensitive enough to detect pathogens in this particular sample.

Most of our microbiological screen that are used in the clinical setting are detecting high levels of bacteria by the time somebody presents with an illness and they're going to a clinical center to be tested, and the samples are typically serum or something that's not a fecal sample.

So this is a very important area, and we're working with NCTR to look at this. The other is how does

the manufacturing process alter efficacy. We know that almost all of these have a level of oxygen exposure, we know anaerobes are very important for efficacy, lyophilization and freeze/thaw, we don't know the impact of these additional processes.

And then how do we characterize for potency, efficacy, and manufacturing consistency, especially when you have individual human donors, and these are pooled, but is one pool equivalent to the other and how do you know that. And then we also are challenged because we're starting to see this being applied in a variety of different clinical conditions. And as was mentioned yesterday there's a fairly good database now with treatment of c. diff, but we don't know whether or how this is going to work for these other areas.

So the first project that we have been working on with NCTR as I mentioned is to evaluate assays typically used to screen clinical samples for their relative sensitivity in screening FMT products. And we are doing this with NCTR because of their experience with bioreactors that produce stool cultures by inoculating a base medium of human stool under controlled growth conditions.

And by doing this with various levels of

pathogen alone or in the context of FMT plating and using NGS methods that they'll be able to determine whether or not the pathogen can colonize and the ability to detect them, initially in vitro but we'll also expand that in a mouse model that we've developed in CBER to look at the efficacy of FMT transplants.

The protocol has been approved, testing has been initiated, and we're very excited because this could have a very important impact on helping us understand the assay applicability in this context. The other major project that's been ongoing is to look at the interaction between commensal bacteria and host dendritic cell responses in the context of a c difficile infection, and that's again because this is being applied in many cases to treat antibiotic resistant c. diff.

And so CBER developed a co-culture system with epithelial cells, and NCTR has implemented this and is now expanding it to work on dendritic cells. We think this is going to be important to provide insights in how to also protect against c. diff with a vaccine because it will provide insights into immune responses.

I'll finish with a couple of new projects. The first is looking at off-target mutations in genome editing technologies, and Bob Heflich mentioned this a little bit

yesterday as well. And as you know there's a lot of excitement, but the safety profile of CRISPR mediated or other gene editing technologies still needs to be determined.

And there are methods in place that have been developed by various groups, but not all of them have the kind of sensitivity that we as regulators would find ideal. So NCTR has extensive experience with NGS, so their expertise in applying this, and as you heard about yesterday from Bob they have this interesting new paradigm for being able to look for changes over time.

And so they'll be applying that and then comparing it to other published approaches to determine the relative sensitivity of their method to others. And this obviously has importance to us because it will provide a potentially new method to do this that might be of greater sensitivity than existing methods.

The second new project is in the area of ribosome profiling. So as you probably know for recombinant therapeutic proteins and monoclonal antibodies, a lot of manufacturers do a process called codon optimization in order to increase the efficiency of protein production depending on the cell system that you're using. And what we've come to understand, actually

Chava Kimchi-Sarfaty in our center has been a pioneer in this, is that the so-called silent mutations which are changing codons in a manner that don't change the amino acid actually still have an impact.

And what we think is that they're changing how the transcript interacts with the ribosome, and changing the movement across the ribosome is impacting translation kinetics and protein confirmation, because she can actually identify changes in specific activity of proteins that have been produced through codon optimization with so-called silent mutations. And so the method that she's been exploring to really get a better handle mechanistically on this is something called ribosome profiling. And again, NCTR scientists have experience with doing the data analysis from this.

And so, this has just been getting started, CBER does the experimentation and NCTR is doing the analysis, but we're excited about the potential output of this collaboration and in terms of providing us a lot more mechanistic information, and also potentially an assay that sponsors could use to screen these proteins that have been engineered this way and ensure that they're not being negatively impacted.

So I'll finish with thanks to my colleagues who

helped provide information about ongoing collaborations, Dr. Tegenge from OBE, Paul Carlson you heard a lot about yesterday, he's been doing FMT. Gabriel Parra who is involved in the norovirus collaborations. Alain Debrabant with the T cruzi, and Chava with the ribosome profiling, and Dr. Ye is involved in the gene editing collaboration. I'll stop there and be happy to answer any questions.

DR. LEIN: Thank you very much. You actually got us back on schedule. So what I would recommend is we would have time for maybe one or two questions. But while Carolyn is dealing with questions the next presenter can get setup, and the next presentation will be from the Center on Drug Evaluation and Research. So are there any questions or comments?

DR. LANZA: Ribosome, is that affecting things like insulin and growth hormones and things like that? What's being affected by that?

DR. WILSON: So we regulate in CBER the recombinant proteins that were typically blood derivative, so factor eight, factor nine, factor seven, things like that. So we're looking at it particularly in those products, and we're seeing changes in things like Von Willebrand factor and factor eight and factor nine. So we haven't looked at the smaller molecules like insulin

because we don't regulate that, but I know that we do interact a lot with our CDER colleagues, they're certainly aware of this and there's joint guidance from both centers around this topic.

DR. PILLAI: About norovirus vaccine, is that bad because a high priority item vaccine against norovirus?

DR. WILSON: I don't know if it's on anybody's official list. I think there's a lot of activity and interest in developing a vaccine. Obviously, all the cruise ships, it's starting to have more and more of a major health impact. And so we think it's an important area to invest in. We actually just recently recruited Dr. Parra to the center about two years ago, and it's a very challenging area to work in, both because of the diversity of the virus and the lack of cell culture and animal models.

So he's making a lot of interesting progress and looking in genetic diversity and being able to group them into clades that may be able to identify conserved sequences as targets for a vaccine, because obviously with that kind of variability that's a challenge, and then developing models that would allow assessment of the vaccine. So we're excited that maybe we'll make some inroads there.

Agenda Item: Center for Drug Evaluation and Research

DR. DORSAM: Good morning. My name is Bob Dorsam, I'm Associate Director of Pharm/Tox within the Office of Generic Drugs in CDER, and today it is my pleasure to talk to you about some of the work that we're doing. I'll talk specifically mainly within the Office of Generic Drugs, so I'll tell you about some of our challenges there, as well as some of the research opportunities that I think exist.

So today I'm going to begin by talking very broadly about Pharm/Tox within CDER. I'll lay a basic foundation and discuss the risk/benefit equation that we use when we're considering whether or not to approve a drug product. I'll provide some perspective that exists within the office of new drugs, and within the office of generic drugs, so there are some similarities in that risk benefit, but I'm also going to present where there are some differences in that risk benefit calculus, and how that difference presents some areas of opportunity for research. So that's one of the things that I'm going to leave you with here today.

I will discuss some of the challenges within generic drugs that present research opportunities, and I'll also discuss the pharm tox team within generic drugs.

This is a period of growth for us, and a period of outreach, so we'd like to let you know the sort of work that we're doing and build as many bridges as we can with you.

So to start very broadly CDER has the pharm/tox discipline, we're mainly a review discipline. A large share of pharm/tox exists within the Office of New Drugs, about 175 or so folks are within the Office of New Drugs. Pharm/Tox is also within the Office of Generic Drugs, we're about 15 right now and steadily growing. Pharm/Tox also exists in the Office of Compliance as well as within the Office of Translational Science. And then other super offices as well as sub offices that do pharm tox work will work with us on a consult basis.

So CDER pharm/tox assesses the risk of several aspects of drug formulation, and does so for a specific patient population. So a drug formulation of course has many components and active pharmaceutical ingredients, the excipients, but it also has drug product impurity, there are residual solvents that are hanging around from the process of either synthesis or manufacturing.

There are also things that may leach from the container closure system and get into the drug product, and then there may be elemental impurities in there as

well, and pharm/tox is assessing the safety of each of those elements of the formulation, and that's true both for the Office of New Drugs as well as the Office of Generic Drugs.

Now we're not just reviewing the safety of an excipient, we have to review the safety in a particular context, and that context includes the dose, the route, and the duration for which we're going to be having that used in a particular patient population.

The patient population presents their own context because their disease has some predispositions, and the active ingredient actually may also predispose them to certain toxicity. And so we want to make sure that the other elements of the formulation don't necessarily exacerbate those predispositions. We use all of this information to inform the risk for determining whether that toxicity is moderable, and ultimately making a decision on whether or not this is a benefit to public health.

So we're taking all of that information about the compound, the dose, the route, and the existing safety information, and just making sure that it fits well with that patient population, ultimately informing whether the compound has increased benefit when compared with risk.

And that's true with both the Office of New Drugs and Office of Generic Drugs. So this is very elemental for the folks in this room, I understand that. I'm just going to ask you to hold onto this one sort of risk benefit calculation as a foundation, and then I'm going to introduce a slight twist to that in a few minutes.

So with regard to new drugs and generics, there is different information and different challenges that are presented across the application types. So if we're developing a new molecular entity, that will undergo testing before first in human trials, and as development proceeds with larger nonclinical studies over time from acute tox up to chronic tox over time, with safety pharmacology, genetic toxicology, ultimately maybe carcinogenicity assessments. And ultimately there is a big battery of non-clinical information to make a determination on the safety, the pharmacology, and the toxicology of that new molecular entity.

Now, that's different than a 505B2 application, because that application is really referencing some prior finding of safety, it's referring to some publications out there in the literature, and so all of the information that they're relying on is not necessarily in a number of

study reports conducted by the applicant, so there are some challenges in reviewing that. We can take it one step further and present generics which rely on the safety and efficacy that was established by the RLD, the Reference Listed Drug or the innovator product. And from now on I'll probably the RLD. The aim for the generic drug is bioequivalence, so that's key.

So the new molecular entity is assessed for safety and efficacy for a patient population, and a generic is aiming for bioequivalence. But that said, it still must have the same safety profile as the RLD, and so we ask that they submit information on the impurities, on the excipients. That information is going to allow us to make a determination if the safety of the generic is on par with the reference listed drug.

So if I were to poll this room about who in the last year has taken a generic drug, I suspect that there would be many hands raised. And that's because 90 percent of the prescriptions out there are for generic drugs. Generics present a very big part of our public health system. And for those of you who watch the news may have heard about drug pricing in the last year or two, and certainly generally in those conversations generic drugs are also offered as a partial solution, because with the

increase in access to generic drugs that does in fact increase the competition and reduce price, that increases access to the public for the necessary medications. So generics are important to overall public health.

So for now on I'm going to focus mainly on generics, but I think I should start by saying a generic is a medicine that is referencing a reference listed drug. It has the same active ingredient, the same strength, the same dosage form, it has the same drug label as the reference listed drug. So there are a lot of similarities and expectations of similarity with the generic and the reference listed drug. And really, they just have to establish a bioequivalence to that RLD.

Now it's important to note that a generic may also differ from the RLD in certain ways. For example, the excipients in the generic formulation for an orally delivered generic, it may have different excipients and generic formulations may also be somewhat different in terms of drug product impurities.

And I say that because the RLD is synthesized in a certain way, it's manufactured in a certain way, sometimes it's proprietary, the generic will also synthesize that active ingredient and manufacture it sometimes in a different way, it might result in different

impurities, but they must submit sufficient information for us to determine that it doesn't change the safety profile.

So while we're not doing large-scale clinical safety studies in generics, they still have to provide the sort of information that we need from a pharm/tox perspective, NOGD, to ensure that this generic does not change the safety profile if the prescription is for the generic as compared with the RLD. And how do we assess that safety just at a very high level? We're using FDA guidance, tox principles, ICH guidance just like the Office of New Drugs is. So we're really trying to be consistent in many ways.

So OGD pharm/tox is also assessing the risk of several aspects of a drug formulation to the same patient population as the RLD. And so this slide is going to look very similar to that last slide that I told you to take a mental picture of. We are not assessing the safety of the active pharmaceutical ingredient.

Safety was already established in the RLD. We don't want to see another study with that active ingredient, but we certainly are interested in the safety of all of these other formulation components. And we're using similar contextual elements to assess whether these

formulation components are safe.

So here's the critical element. Instead of saying is the generic just safe or effective we need it to be on par with the reference listed drug. So we need a therapeutic equivalence, and that therapeutic equivalence is sometimes difficult to ascertain. Not all generic drugs are a simple pill with an organic molecule that when you put it into a patient you can measure plasma levels. Certainly, we have plenty of those, but there are also complex formulations, locally administered products that require a lot more than just PK data.

And so making sure that those complex products are therapeutically equivalent to the RLD really requires some in-depth knowledge and research on formulations and patient responses and toxicity. So what I'm here to do is to present to you that this therapeutic equivalence presents some research opportunities in the generic realm, and is something that I'll elaborate on a little bit more in a few slides.

Before I do that I'll take one slide just to talk to you about the Office of Generic Drugs Pharm/Tox Team. We started in 2014. We're now three years in, we have 11 reviewers, three team leads, a few people in the pipeline coming, and we're hoping for more FTEs to staff

up. It is somewhat of a startup atmosphere that we've had, but I do say after three years we have just completed our one thousandth project.

That's not our one thousandth ANDA mind you, but we have to make a single decision on a particular impurity, that's a project. Or advice to an applicant, that's another project. So we've done a thousand of these and we worked very hard to document the experience that we're gaining over time.

For one reason we need to be internally consistent. If there's a new molecular entity out there that's approved, it's been out on the market, and then it's going to come off patent, our challenge is that we may have four applicants coming in that are aiming to be the first generic against that enemy.

so with four on our tables we need to be internally consistent about the impurities, the excipients, what we're telling one applicant and another, so that requires a bit of being smart about it with databases and information management, knowledge management. So we're also aiming to be the same as the reference listed drug, and so we're constantly trying to be students of what was done with the reference listed drug when it was approved so that we can use similar

thresholds.

So we're trying to get out there and let people know about the sort of work that we're doing, how we're doing it. So we have a review article that we've published. We have posters, including one at the ACT meeting which is occurring right now. We also had a continuing education course, they have pharm/tox and generics, and again just to interact and engage with industry and academia on the sort of work that we're doing so that we can get applications in that are quality and allow us to get to approval quicker.

The sort of work that we're doing internally is to understand what applicants are sending in in their submissions, and then identifying successful practices as well as common pitfalls, and then putting that together to identify trends and then publish it out so that people know what are the successful practices and the kind of information that we're looking for. So we're doing that with impurities, we're also doing that with excipients, and so there's various abstracts that we're developing.

So our whole goal is to achieve an internal consistency as well as a consistency with the reference listed drug, and then be transparent about the sort of work that we're doing through knowledge management and

collaboration. We're creating sheets on sheets just to document their experience. When reviewers open up an application the first thing that they have to do is take a look around and see if this has been reviewed before, what have we said on a topic like this.

Certainly, we're doing a lot of training, all of our reviewers are coming from outside and so there's a lot of mentorship that's going on, and a lot of, we're all students in learning in this environment as well as collaboration. I did want to highlight what I see are very useful tools in collaboration. NCTR's FDALabel I have to say is a phenomenal tool for us.

We're always aiming to understand context, and the sort of information that's in a drug label informs a lot of the context that we need so that reviewers can get into FDA label and start to understand that this is a pediatric indication or what excipients are in that formulation, just using that single tool.

That shortens one of the review paths that our reviewers have to take, it gets us to a good decision much more quickly. So I highlight that as a fabulous tool of benefit to our team probably on a daily basis. So thank you for that.

Also, this is in the Office of New Drugs, so

it’s not OGD, but the Pharm/Tox Smart Template, again a fantastic tool, making reviewers come to solid smart decisions quicker, and I couldn’t say enough about how much of a good use that is of effort to get us to a good public health decision in an efficient manner.

So I’m going to focus a little bit now on the research component. GDUFA has funding which supports generic research, research to develop new approaches and resolve complex generic drug development. As I said generics can have complex active ingredients, that’s a mixture of components, and understanding how to be therapeutically equivalent to that requires advanced analytics sometimes.

There’s also complex formulations as well as combination drugs, devices, produces, and to be therapeutically equivalent really requires engineering, chemistry, toxicology, molecular modeling and simulation, and it’s this cross-disciplinary sort of interaction that gets us to understanding exactly how that RLB is working so that we can get a generic to work similarly.

So during GDUFA I they funded over 100 external projects, and each year OGB is hosting a public hearing to see what the interests are, and they have just listed the science priorities for FY 2018, that’s available online.

And I have abbreviated and excerpted some of those priorities, included a link below for the FY2018 priorities.

And I will go very quickly, but just to say the complex active ingredients, formulations, and dosage forms, we need improved advanced analytics in order to characterize chemical compositions, the molecular structures, and distributions in these formulations for these complex active ingredients.

I have to vet my slides through a number of people, Rob Lionberger's office, Director of the Office of Research in Science oversees the money for GDUFA research, and as he looked through the slides he highlighted two things on this, so I will sort of highlight this also. We're aiming to establish predictive in silico, in vitro, and in vivo studies to evaluate the mutagenic risk of formulations, impurities in some generic products.

And routes of delivery present a number of interesting opportunities and challenges. We're looking to improve physiologically based PK, PVPK models. For drug absorption we have these complex routes of delivery, specifically nasal inhalation, dermal, and ophthalmic routes. These are complex and we need advanced understanding of absorption through these methods in order

to create generics.

So we're also looking to expand characterization based bioequivalence methods across the dermatologic and ophthalmic products. There's definitely a component of the formulation matters, and it's not only the chemistry but also the physics, the physicochemistry, various characteristics of the formulation beyond just the ingredients will impact the activity of that formulation for the patient, so we need to know more about that.

We're looking for tools and methodologies for bioequivalence and substitutability evaluation. So we need to have improved quantitative pharmacology and bioequivalent trial simulations to optimize design of BE studies.

So sometimes there are going to be sparse PK sampling, and we need to know through modeling what is the optimal trial design, and also develop methods that are going to allow FDA to leverage large datasets to make various decisions both in the pre-approval as well as post-marketing surveillance of generic drugs with regard to substitution.

And in that dataset we have things like bioequivalence as well as electronic health records that we're interested in, substitution and utilization

patterns. So how can we use all of this to inform best decision making for generic drugs and pre-marketing and post-marketing? So therein lies some opportunities.

I'm just going to take a minute to highlight one grantee's work, and it's Dr. Brian Shoichet's lab out of UCSF. He's looking to take FDA approved excipients and see if they are interacting with any pharmacologic targets through screening. And this is to better inform generic drug manufacturers' formulation as they're designing their formulation that they have information on what they may be running into as they develop their formulation, and that they may sort of step clear of any potential pitfalls through interactions between excipients and known pharmacologic targets.

So it's a multifaceted project, but one thing that Dr. Brian Shoichet's lab has done is they've taken all the excipients that are in approved FDA products, that's publicly facing information, and he's taken that and then matched it together with structure and chemistry information and then provided a lot of basically compiled a lot of information about each excipient so that people making formulation decisions can do so without having to go to disparate places. So it's aggregating information.

He took a lot of input, including the fact that

from my team we said well if somebody is looking up information on an excipient they should know about safety. So there's a link to TOXNET on the excipient so when they click they'll hit the TOXNET link and then up pops that excipient if it's in TOXNET with available safety information.

So this is getting a lot of traffic now. It's available, and it's always sort of in a development stage, but it's actually working and being used by industry as well as FDA on a daily basis.

As I told you he's looking to screen excipients against various targets. There's a prediction of binding. He's actually following that up with in vitro tests to see if it is actually binding. And then going through all of the predictive binding and then following it up with in vitro, and then using that information and putting it into the excipient browser so that folks who are looking up excipients are actually going to be confronted with that information and know that there is a potential binding there.

And then they can either follow that up or steer clear and work with another excipient. But nonetheless informing what are sometimes called inactive ingredients and providing information that says these aren't actually

always inactive, but they are potentially binding and people should know about that when they're choosing to put them in their generic formulation.

So with that I'll thank you, I'll just say that pharm tox is using a risk benefit equation like many of you know. The generics is looking to be similar to the RLD, and in order to truly do that there are research opportunities where we have to understand how complex products can be equivalent through understanding the sort of key quality components of a formulation so that we can be therapeutically equivalent.

As Pharm/Tox we're doing some outreach in order to let people know the sort of work that we're doing. We are certainly open to collaboration if it's going to benefit generic drug safety review, but also I would like to put out there that there's a host of challenging formulation issues that warrant further research. I have the links in this slide, if you have any questions about that please contact me, I can put you in charge with the right people to further those conversations. With that I'd like to thank you and I'm happy to take any questions.

DR. LEIN: We don't have time for questions, we're on a bit of a breakneck pace here to make the next talk before we get the call from the FDA. The next

presentation will be from the Center for Devices and Radiological Health.

Agenda Item: Center for Devices and Radiological Health

DR. MARGERRISON: Good morning everybody. My name is Ed Margerrison, I am the Director of the Office of Science and Engineering Labs at CDRH, which is the Center for Devices and Radiological Health. And what's not in that title is also the in vitro diagnostics that we're responsible for.

I'm going to take a bit of a tack of admitting that we're typically the redhead stepchild of the agency, and I want to describe a little more broadly what we do, because I joined the agency about a year ago, and I am literally like a deer in headlights every day saying, what, we do that as well? So I'd like to give you a little bit of a feel for that.

So for those of you who have been to White Oak, the Commissioner lives at the front as you'd expect. So the Commission's Office is up here, and they keep Devices right at the back, as you can see. That's our main admin building, 66, and then our research is in 62, and part of 64, and we have part of Bob's area, CDER, in part of that as well.

So to put in perspective what we do at CDRH, of the types of devices 175,000 on the market, there's over half a million proprietary single devices. It's quite amazing. We've got 18,000 different manufacturers that we have to make sure are manufacturing to appropriate standards. There's 25,000 facilities they've got all over the world, we have to make sure they're doing the right thing.

Every year we get 22,000 premarket lumps of paperwork let's call them, and nearly one and a half million reports on something going right or wrong with the devices. And we have 1700 people. That's just a number, I was trying to describe to my center director what that actually means. It's about a third of what Caesar's Palace employs. So I joke with him that we literally couldn't even run their kitchens, and yet we're responsible for all that stuff.

As many of you know I used to be in industry, and 10-15 years ago the relationship between CDRH and industry was as Jeff my boss calls it adversarial. It's totally different these days, and I am absolutely proud to be part of CDRH and the agency, I think we do amazing things. One of the reasons that we're different now is that part of our mission is as it says to facilitate

medical device innovation. We're no longer there to sit there and say no you can't, we have an enormous number of collaborations with industry, with academia, and at the last count we had over 800 active agreements in place just at CDRH.

So when we had all the agreements of my colleagues as well, you can see what an amazingly collaborative place the agency is these days. So we do a lot of work, we publish with industry, we've published with academia, we have people in and out all day every day. It's a very dynamic and exciting place.

My office, commonly called OSEL, I joke a little bit because we all spend a lot of time talking about what's regulatory science and trying to define it. In my book it's very simple, it is unacceptable for the rest of the center to say I don't know. If a sponsor or manufacturer comes in with a new device or a new technology and we say well we don't know what questions to ask you, then that really is not helping US patients, because we want to be asking the right questions at the right time, and getting that technology or device onto the market as soon as we can.

Bob talked about risk/benefit. One of the things that has been hammered into me the last year is we call it

benefit/risk for some reason, but it's the same concept. And one of the things that we're now acutely aware of across the agency is that there is also risk in not letting new therapies on the market, because a lot of our therapies and devices are lifesaving therapies and devices, so it's just no longer acceptable to say no, we're not sure about the safety of that, let's stop, we've got to get it going. And in fact, this is now enshrined in law. Last December the previous president signed into law the 21st Century Cures Act.

And one of the provisions in there which relates very much to CDRH and all our colleagues is what's called least burdensome. That's always been there, but now it is enshrined in law. We've reissued guidance on that. We actually have specific timelines that we have to meet through our user fee agreement, MDUFA, and we're legally bound to take the least burdensome approach.

Now, that's great for everybody, because it's good for industry because they have an easier pathway or a quicker pathway or a less burdensome pathway. But it's great for our poor reviewers as well, and I'm sure it's the same with my colleagues, the reviewers are rather like commodities traders, they can do it for three years and they're burned out. There's not that many of them, and we

have 22,000 premarket applications per year before we even start worrying about post market.

So the specific things that we do within OSEL, we have a crystal ball. We're actually looking, like everybody does across the agency, at what's coming up. And a great example of where we did that was about six or seven years ago. We knew that additive manufacturing or 3D printing was going to become more important. It had been around for a couple of decades, but there was nothing in the medical area really that had come to pass.

So this is a great example for us. We started a research project, and we're actually now leading the way across the world for how to regulate 3D printed devices. But it's not just the device, it can be things like cutting guides, et cetera, et cetera. And that sort of technology has a major impact on medical practice, which of course we don't regulate.

But what we're going to find with 3D printing or additive manufacturing is that the manufacturing facility is not going to be a manufacturing facility, it's going to be a desktop somewhere in a hospital, someone is going to have a 3D printer. And that's great. We are going to move to that way. We've got to do it in a responsible way, and that's one of the reasons we're intimately involved in all

those sorts of things.

We have a lot of work that we do on standards, guidances and things like that. We have a fundamental role to play in just providing information to the public, and that's something that we're taking a lot more seriously now. I think we've done it in way too much of a secretive way. We publish papers and we think well that's great, and actually it isn't necessarily. We've got to digest that information and put it out to the public in a form that they can actually access and understand and therefore use.

One of our major functions which separates my office from NIH and other places is that we do what we call regulatory consults. So when things come into the center and the reviewers, who are sometimes less experienced than the people in my office, if they get something that's a little out of their area they come to us, we do a consult on it, and we keep the clock ticking quickly to get that decision made very rapidly, because that's our job. We do about 2500 of those a year.

So I'm not going to go through, there is no test at the end of this, you don't need to memorize this. But just to give you an idea of the sort of areas we work in, I come from the orthopedics and sports medicine industry, where biology, chemistry, and material science were the

whole world. That's it. That's all just in one division in my area. We do a lot of applied mechanics which includes fluid mechanics as well as solid mechanics.

We also have a large effort underway there in ultrasound, because high intensity therapeutic ultrasound is an enormously interesting technology for the future. That's another one that really is beginning to get going. It's used for ablation of tissue for cancer treatment. It can also temporarily open up the blood brain barrier. So that has some very interesting possibilities as well.

We do a lot on imaging, because we're also responsible for all the big expensive machines and all those areas. We recently actually cleared the first 70 MRI for clinical use about two weeks ago, one of the Siemens devices. We do a lot on software reliability. This is a fascinating area for us because we're beginning now to get into the realms of machine learning and adaptive algorithms. So we think one day we know what a machine or an algorithm is doing, tomorrow it could be different.

So we're starting now again, this is a research area that we're looking at to say what questions do we need to ask, how do we regulate it, if the software changes overnight based on its own learning do we have to revalidate that before it can go to use? And the

complexity in this is actually mind boggling, it really is.

Our largest single technical division is actually in biomedical physics, where one of the things we look at as an example is the interaction between different devices. So many of these things now give out an electromagnetic signal, a lot more are on Wi-Fi, and they interact with each other. We're actually one of the very few places that the TSA allows its scanners to be tested, we do all that for them.

And the interaction with those scanners and say a pacemaker is pretty important, as you can imagine. Another very similar area is the theft prevention devices that you see on the exit of stores. They're actually much more prevalent than you think. That's the only place we see them. They can also interact with pacemakers and all the other active devices now that are going into people.

So I'm going to give you some examples of some of the more process things that we're looking at at CDRH. But I wanted to throw out a couple of things that I think are ready for some serious collaboration across NCTR and NTP and beyond. The first is computer modeling and simulation. I genuinely believe that's going to change a lot of regulatory paradigms. One area we're working in for

example is that we're now able to do in silico clinical trials.

One of our partner companies were looking at a new breast screening device, it's a new generation of digital breast tomosynthesis machine, a great advance in technology. So they got their statisticians involved, and it was going to predict the potential for the onset of the tumor in a healthy population. They were going to need 160,000 patients for ten years. Nobody can do that.

So what we've done is we've actually modeled a lot of lesions in breast tissue, we've developed a lot of imaging phantoms and things like that. We've now got a huge database, and we're working with the American Radiology Institute, or I probably got the name wrong, but we have a lot of data now that we can start analyzing.

Over the last weekend we actually ran a pilot in silico trial, and we're going to move on to the phase three over the next week or two. I don't know how it's going, they haven't told me yet. But one of the beauties of this is we can do that really quickly on a huge number of patients. Now, what we're not doing, we're not saying that device is good or bad at this stage, we will get there. The question we're asking is do you get to the same place as a reviewer in their pod with all their paperwork.

So can we actually model what the reviewer is doing with the computer, and that is effectively is part of the validation of the whole experience of using computer modeling simulation in the regulatory pathway. Because at the moment it's a bit of an oddity. Everyone is doing it, everyone is interested in it. We know the potential. But it's still really in the research and the science arena, and has not yet broken sufficiently into the regulatory arena. And that's one of the things that we're trying to push through a great deal through my office.

The other area I want to throw out as very ripe for collaboration as we go forward is the whole area of nickel ions, et cetera, et cetera. This is something that's really been cropping up for a while. We know about nickel sensitivity, but we're beginning to see reports coming in of patient complaints, which means they're real, and they are associated they believe with the release of nickel in the body from various devices.

And I will just throw it out there, we don't know what the answers are. We don't even know what all the questions are at this point. So I'm not going to say a lot of great detail about that, I'm going to throw it out there and say this is something that I want to have the

appropriate conversations with. We're currently pulling together what's known about nickel ion release and other ions as well. We know it's an issue, we're going to address it headlong at this point.

Nickel of course is great for a lot of things. I always like to talk about nitinol which a lot of stents are made from, purely because it's a material that was discovered on the White Oak campus. Nitinol actually stands for Nickel Titanium NOL which was the Naval Ordinance Laboratory, which is what used to be White Oak, our campus.

But we've been looking at a lot of this. The processing of nitinol makes a massive difference to the amount of nickel released. This graph here, that's a log scale at the left, and the different colors are different processing conditions. That's the difference you can get with different processing conditions on nitinol. So we're really beginning to start understanding an awful lot of this and trying to apply it, because nitinol is not nitinol is not nitinol, unfortunately.

A project I wanted to highlight as well is something we're doing with the Adventist hospital fairly locally. Endoscopes are a great example of something that causes a lot of people a lot of headaches, because you

can’t re-sterilize them, and yet they’re used in a sterile environment. They typically get scrubbed with solutions and then someone eyeballs it and says no I don’t think that’s quite clean enough, scrub again, and it really is like this.

We’ve actually now developed a solution internally within the office that we’re currently getting some real live data from Adventist hospital to very quickly, and I mean within one minute, assess the amount of protein that’s left on the surface.

So it’s the beginning - we’re now going to gather clinical evidence and clinical data to say what does that actually mean, is it good, is it bad, where is the limit. Because at the moment, for example in our pre-market areas when endoscopes are approved they also have to have some sort of cleaning protocol associated with them, but we really don’t know how good they are. These are going back into people.

The other area I want to do, just because it’s a really nice video as much as anything, is that we do a lot of modeling so that we can actually assess the effect of devices on the body as we move forward. This particular one is a depolarization across a heart. There are a lot of other things that we model. You can actually go online and

look at the virtual population and download it.

We have now 13 or 14 family members in our virtual population, and there's incredibly detailed anatomical models available of all those people, including a lady in three different stages of pregnancy. That's freely available to the public because it's taxpayer funded and we're very proud of it. The bottom panel there is a real heart and you can see how it's slightly out of sync actually. These are actually being used now in cardiac areas around the world, we're pumping out this data left, right, and center.

So very much like CDER has its development tools we have our medical device development tools as well. We are obligated, and it's the right thing to do, to have predictable and efficient pathways for companies. So we are actually now moving from the pilot into the real phase of our MDDTs, and we should have one done very soon. It basically means that if we've got a decent method then our reviewers just look at a summary report and say it's fine, and it will be done quick.

We have an absolutely loony amount of products that we actually regulate as you've said. We do need a crystal ball. We also have what we call the Advanced Characterization Facilities, the sister to the NanoCore

down here. We also have a sister to the high performance computer, and the 3D printing I've mentioned already.

The last thing I'll say is that one of the things that we're changing as well through my office is that we're reaching out to the small companies. The big ones can look after themselves, I'm not worried about them. The small innovative ones are the ones that are of most concern to the medical device industry, because they're the innovative ones. 80 percent of people in medical devices work in companies with less than 50 people.

And so those are the people we've got to keep alive, keep the innovation coming, because that's where the technology for the big companies is coming from. So I'll stop there, and if I've got 10 seconds for a question I'm happy to answer.

DR. LEIN: I think actually, unfortunately, we have to move on, we're expecting a phone call from the FDA Chief Scientist. But thank you very much. I'm going to turn this over to Dr. Slikker to introduce the FDA Chief Scientist.

DR. SLIKKER: So one thing while we're linking up is that I want to carve out a little bit of time after the presentations are completed from all the centers to have a

discussion period, a short discussion period, because I really enjoy the presentations and I would like to have the ability to ask a few questions and interact with you a bit more. So we'll do that, we just have to fit this timing in. So I appreciate your understanding.

RADM HINTON: Hi this is Denise Hinton.

DR. SLIKKER: Hello, this is Bill Slikker, good morning.

RADM HINTON: Good morning. Thank you for calling in.

DR. SLIKKER: Well thank you for agreeing to give us a few comments about the NCTR's Science Advisory Board. I just want to sort of outline that the room for you here, we have individuals from our Science Advisory Board on one side of the room, our esteemed group there, and the other esteemed group on the other side of the layout are representatives from the various centers, plus a lot of audience from the NCTR in the background.

So we are very excited to get some of your views about the FDA and the system of scientific review that we're undergoing currently. But before we do that I want to say that I believe that your new title has changed recently, is that right Denise?

Agenda Item: NCTR Science Advisory Board

RADM HINTON: I'm actually still Acting Deputy Chief Scientist for Office of Chief Scientist. My commission core title has changed, I've just recently been selected as rear admiral.

DR. SLIKKER: Congratulations on that. We just learned that, and I wanted to let the group realize that now you're Rear Admiral Denise Hinton, I really appreciate that ability to see you rise to that level. Congratulations on that.

RADM HINTON: Well thank you, I appreciate that and I appreciate everyone's support.

DR. SLIKKER: You've been in this role since June of this year as an acting chief scientist as well as the permanent deputy chief scientist. But you have a long experience with FDA, and started in 2002 after a career in the Air Force as an officer.

You joined CDER Division of Cardiovascular and Renal Products, and stayed there until 2010, and you then became Director of the Office of Medical Policy Initiatives, and worked in that area for some time, moving up to the Acting Director of that area. So after that of course we were delighted to have you come in as the Acting Chief Scientist, so it's really good that you have a chance to give us a few words today. So thank you very

much for this opportunity.

RADM HINTON: Thank you. I certainly appreciate it. And I have to say that Commissioner Gottlieb regrets not being able to deliver the opening remarks for the Science Advisory Board, but I am pleased that I am able and was afforded the opportunity.

As you know, FDA is a science based regulatory agency, and the work that's being done across the agency is most impressive, especially in supporting the work that leads to the innovative scientific solutions in support of FDA's mission to improve public health. I just want to commend everyone for their work in this area, and especially NCTR in collaborating across the agency and globally for that matter. And as we know when data gaps exist NCTR researchers partner with other FDA centers to provide the necessary research data.

And examples of that certainly include collaborative work with CDER scientists to determine if gadolinium accumulates in the brain and leads to adverse effects, the work performed under the National Toxicology Program to evaluate the toxicity of arsenic to enable CFSAN to make regulatory decisions, leading on to a collaborative study with CBER to examine the pharmacokinetics and biodistribution of squalene

containing adjunct used in vaccines to contribute to their benefit risk analyses.

There's multiple other examples, notably more collaborative studies with CBM to understand the impact of exposure to residual levels of antimicrobials on the human microbiota, and then of course the ongoing work with collaborators at CDER and the like to predict a host cellular response during fecal microbiota transplantation, and to evaluate risk associated with bacterial pathogen contamination of fecal microbiota transplantation samples.

Needless to say, NCTR scientists are continually evaluating and improving new technologies to enable faster, better, and less expensive evaluation of FDA regulatory products. We're appreciative of the work that's been done with the FDA label, which is the integrated software bioinformatic tool NCTR scientists developed with CDER to assist their review of new drug and the recent survey demonstrated a 93 percent satisfaction level with the application of the tool by FDA users. So thank you for that, we're very proud of that work. And then of course the work with NCTR NORA who jointly established the state of the art NanoCore facility at Jefferson Laboratory in collaboration with and support from the National Toxicology Program.

And this was done to conduct research on the detection, identification, characterization, and toxicological assessment of nanomaterials and FDA related products. The facility there supports research projects from regulatory centers across FDA, conducts hands-on training for reviewers, and collaboratively develops consensus standards and stakeholder involvement with stakeholder involvement.

So NCTR scientists provide literature reviews and consultation to support decision making by other FDA centers. CDER has partnered with NCTR in its major revision of the OTC Monograph System, and NCTR scientists are providing in-depth scientific reviews of key OTC products, such as sun screens, antihistamines, decongestants, cough suppressants, laxative, and food handler antiseptic in order for CDER to modernize the monograph system, and to facilitate the ability of industry to introduce new products.

Commissioner Gottlieb and I are both pleased and excited to learn more and see the further development and growth of the proposed FDA Virtual Center of Excellence for Maternal and Perinatal Pharmacology and Toxicology. I think through coordinated efforts across the centers studies are being planned and conducted to address

important regulatory science needs facing FDA today as well as in the future. Broadly speaking the research of this center falls into categories of in vitro, laboratory animals, human and in silico computational modeling studies.

This virtual center will provide the infrastructure to simulate robust research efforts for faster, less expensive, and more predictive approaches and models. It will harness the collective talent and resources of the agency and serve as a hub for research and collaboration internally and externally. The potential for this proposed center of excellence is tangible and realistic given the current knowledge gaps, needs, and rapidly evolving technology, and will serve to lead the way to improving the safety and/or efficacy of FDA regulated products in the susceptible population.

So thank you NCTR, your staff builds partnerships within FDA, with other US government agencies, and with research and regulatory bodies globally to develop expertise, complementary scientific approaches, and resource collaborations.

FDA with leadership from NCTR is part of the growing global coalition for regulatory science research. It’s comprised of countries around the world, including

those in the European Union, Asia, and North and South America. The goal is to explore how research in selected themes can be used more effectively as a tool for advancing regulatory science, food safety, medical technologies, and public health.

And an example is the outcome from the Global Summit on Regulatory Science in 2016, which focused on nanotechnology standards and applications that provided a roadmap to dramatically increase the number of reference standards available for nanomaterial development and safety assessment.

So I really thank you all for your important work in protecting, promoting, and advancing individual and public health through collaborative and innovative efforts, and you all have done a job well done, and I look forward to seeing more of this work in the present and future. Thank you.

DR. SLIKKER: Thank you very much for those comments. Do you have time for a question or two?

RADM HINTON: Certainly.

DR. SLIKKER: Very good. So the floor is open, if anyone would like to ask a question for Rear Admiral Denise Hinton. Well Denise, while people are trying to think of their first question, I'll ask you one about your

new role. So I know that this is something that we've all been looking forward to, you getting this promotion to Read Admiral, but how is that going to change your role within the FDA, or will it have any particular effect except to give you a better position to work from?

RADM HINTON: Actually, it will just give me a better position to work from. However, it does open the door to I guess more collaboration and more visibility. In the role of Rear Admiral, you also have the title of Assistant Surgeon General, so I'll be working directly with the Surgeon General as well as Commissioner Gottlieb and other leadership across the agencies, and trying to further promote and gain support for the programs and activities we have ongoing throughout the agency itself. So it does provide I think a greater platform to be able to do that.

DR. SLIKKER: Well that's outstanding. One of the things over the years is that FDA has been very successful at having individuals of your quality and character in these roles, and I think it has really benefited FDA as you said to build those connections and interactions throughout the entire health complex of the US. So congratulations once again on that outstanding agreement.

RADM HINTON: Well thank you very much, I

certainly appreciate it.

DR. SLIKKER: We have a question from our Chair of the SAB, Pamela LEIN:

DR. LEIN: Good morning, RADM Hinton, this is Dr. Lein. I was wondering what your perspective is in terms of what you see as emerging needs that the NCTR may be uniquely positioned to help the FDA grapple with.

RADM HINTON: I think one of the things that is going to be on the major focus, in that we're very proud of you guys for even taking on the initiative, is the Virtual Center of Excellence for Maternal and Perinatal Pharmacology and Toxicology.

But outside of that is looking at some predictive approaches and models, looking at the in vitro, the in vivo, and the like. Looking at outside of the use of solely using animal models for some of the toxicology studies. So those are the things that we certainly would appreciate and would like for NCTR to continue to be engaged in. And certainly just coming up with continued solutions to meet those needs.

DR. SLIKKER: Thank you very much. I really appreciate you taking time out of your schedule to meet with us and provide your comments. We really appreciate you being with us today.

RADM HINTON: Thank you so very much. I hope to be able to attend in person next year, looking forward to engage with everyone.

DR. SLIKKER: That’s wonderful. Thank you very much. Bye bye now.

RADM HINTON: Bye, thank you.

DR. LEIN: We’re just having a quick confab here, but I think we’ll continue with our next presentation for Center for Food Safety and Applied Nutrition.

Agenda Item: Center for Food Safety and Applied Nutrition

DR. HATWELL: I’m Karen Hatwell, I’m here from CFSAN and I’m very thankful that you invited us to join you, and that I was able to attend. I know that most of you would prefer perhaps Suzy Fitzpatrick our toxicologist, or Mickey Parish our senior scientist, however they both had constraints, and I feel very lucky to be able to join you guys today. The amount of work that NCTR does is truly incredible. The talks yesterday were fascinating, and I’m going to take home that knowledge to our center and hopefully help continue to develop our relationships and collaborations.

It’s always funny to me, coming from CFSAN, to hear about the other centers complaining about red headed

stepchildren. Do you happen to know that we're not even on your campus? We're not even in your county, we're in Prince Georges County in College Park Maryland.

I found it fascinating when I joined the FDA about ten years ago that the F in FDA is not actually with the rest of DA. And when I go to places to talk, as you can imagine I like to talk, and I mention I'm with the FDA, and they go, oh yes, the Federal Drug Agency, I'm like no, it's the food. We actually have a t-shirt that hopefully you don't see too often, maybe at the gym, that says putting the F in FDA, and that's sort of how I feel. So I like to remind you that we regulate food.

And perhaps it's because we are not the only food organization that we are sort of put a little bit aside. My gut is that someday some administration will merge FDA and USDA. That's just my gut, I'm not the FDA representative here on that, and they're keeping us close in alignment.

So next door to us, just a walking distance, is USDA, and they have a childcare center where people send their kids, so we say hi to them, they have food trucks on certain days, it's a lovely campus. But we don't spend a lot of time with them because we are part of you, the FDA. I will give a short talk, because as a chemist and new to

NCTR I didn’t want to bring too much to you, I wanted to learn more about you. So that will hopefully keep us on time.

So I’ll start with the mission. This one I’m familiar with. We work with our field agency, we work a lot with our field on promoting and protecting the public health. And this is all due to the food supply, keeping it safe, sanitary, wholesome, and honestly labeled, very important to us.

And our cosmetic supply, that they’re safe and properly labeled. Safety is a key to this. And when I talk to people about the FDA I bring up the word safe an awful lot, because that is the thing that we think the most about, how to make our public safe in food, colors, cosmetics, nutritional supplements, the things that we regulate, that’s our biggest concern.

Our products are a variety as you can imagine. Even though we’re food we have a lot of things that fall under that guise. We cover all foods which are not regulated by FSIS, which is mostly meats. We cover food additives and packaging. We cover dietary supplements, colors, cosmetics, infant formula, bottled water.

A lot of the things which you ingest that are not drug related, which do not cause a change in your

body, are regulated by us. And what's so difficult for some of those products, like nutritional supplements, dietary supplements, are they claiming an effect or not. This is the big question as to whether they fall under food or drugs. Colors are found both in food, drugs, cosmetics across the board, so we'll see those kind of additive petitions.

Cosmetics, which can claim an effect or not. It becomes very difficult at the FDA in terms of the regulatory body. We place that burden on the submitter to decide whether they are coming to us as a food, a drug, or some other area. We look in terms of safety. We're very interested in food events. We're very interested in the illnesses that are caused by food, we spend a lot of time on that. Of course, we have our research program, which I'll mention.

And we also are interested in how we portray that food to the public. It's an interesting system when you think about it, if you travel to Europe or to other countries and you take a look at the labeling, how it's portrayed to the consumer what's in their package. We regulate everything in that package, from the package to everything within it.

And what information are we giving them? Do they

know what the packaging is composed of? Most of the time they don't care unless it's a hot button issue like BPA, but they don't think about it, and they also don't think about what's inside that. So oftentimes we'll write something as per our regulations, a color additive, a natural additive, but it doesn't drill down to actually what's in there. If you look at European regulations it's very different, just looking at it from a perspective view.

We have a strategic plan. It's about to expire next year. So I will be involved in rewriting that science and research strategic plan with a group at the FDA. So this is one of the reasons why I'm giving a shorter presentation. I think it will be more interesting next year when we come with our new strategic plan to talk to NCTR and our science advisory board in terms of where we can work together for the next five years.

We will expand our plan to a five-year plan. Some of the things that we've talked about for the last five years were comparing to whether we've actually completed them, involves intervention and prevention and control strategies for microbial and chemical hazards.

So as you know we have a lot of foodborne pathogens. We spend our research program in three areas

mostly, microbiology, chemistry, and toxicology. And part of that is knowing what kind of hazards are in our food, a lot of them are microbiome. Those are the most interesting in terms of whole genome sequencing. We spend a lot of time and effort, the last five years wonderful that kind of cutting edge research, and we have made great progress with people in working on that area.

We develop screening methods for the field laboratories to improve detection. Our chemistry laboratory, the thing that's most cutting edge is our multivariant analysis. We can look at 15, 25, 40 chemicals at a time, just incredible work that we can do in a much faster capacity. But bringing those techniques to laboratories across the country, making sure it's a capacity that can be done easily, simply with the technologies that we have, is very important to us. Method development we spend a lot of time on.

We also look at bioinformatics in making our regulatory decisions. We have a lot of data, we talked about data I think yesterday, and we spend a lot of time thinking about how we're going to deal with that data.

We have a lot of toxicology. Our most cutting-edge approaches that Suzy would be lovely to talk about would be the organ on the chip. I am not as conversant on

that, but I'll tell you that the work that we're doing in our organization on that is going to be amazing. We want to spend our time both in the cutting-edge aspect of organ on chip, but also in the daily aspect. If we have a new food additive, what information do we need to know that it's going to be safe? Diet and health research, which we don't do as much of as we should. Considering our center director is a nutritionist we are probably going to be looking forward to bringing in some more nutritional research in the future.

We've done some work with salt which we're very proud of, but in the laboratory base, the movement is not as forceful in that aspect. And of course, we need to work with our COEs and our stakeholders. We have FTEs in a variety of places, in Illinois, at IIT, in the Moffat Institute we do such interesting work with allergens and food packaging. At Dauphin Island, we have some people there with our seafood program. And I feel like I'm missing one there.

With our COEs we have several of them as well, IFISH, JIFSAN, UMIS, the Western Center, and we work with them to continue our research program. Our research, we really consider ourselves a science based organization, that's all of us at FDA, and we try to take our science to

support our regulatory decisions and our research decisions. We use our research to work in modernizing our food system.

And that's through FSMA, very recently, and through every other act that comes to us. Food labeling has been one that's been coming back to us recently, and those are supported by the science. Our research program does a lot in terms of methods, data analysis, and a lot of that has to support the regulations that we provide.

Our research program is -- oh great, there we go, our seven offices and our core centers of excellence. Our research is not throughout these offices. Analytic outreach does a lot of bioinformatic information. ORS is our toxicology center, that's where all of our toxicology is done. Cosmetics does a small amount of research. As you know we have some projects here with NCTR. Dietary substances do not do any in-house research. Regulatory Sciences where microbiology and chemistry is housed. And then food safety does a lot of their research at external centers like IIT and western center.

This is a snapshot, which I think Bill showed a different snapshot yesterday, so I'm not sure if this is one provided from a different time, but I think the numbers are about the same. CFSAN supports about 17

percent of the research done at NCTR, I think that's about right. We have a variety of collaborations which I'll mention in a few minutes. But we don't have the breadth that some of the centers have.

Our current collaborations involve some information on storage pest fragments, this is a particularly interesting one. Food products as you know, sometimes they're stored for long periods of time. And knowing what kind of contamination through pest are involved in there will be very important for keeping products unadulterated and safe.

Detection of microbial contaminants is huge for us. This one is particularly about the tattoo inks that came up just yesterday I believe they gave a great talk about that.

We're working on a database for hepatotoxicity o dietary supplements, also was discussed yesterday. Milk pasteurization equipment will be an interesting one, bioterrorism has come to us as a discussion and we'll continue to look at that, I'm sure we'll see that in our upcoming strategic plan.

Looking at a toxicant through whole genome sequencing in dried food. Also vary under needs or necessities. And finally, one on particle size and

composition for nanoparticles. We don't do nanoparticle research at our center directly, but we spend a lot of time at IAT and here I think making use of the nano facilities. There are probably some more.

There are a couple of things that I'd like to mention but which I don't have slides for. When we talk about our research program we use a system called CARTS, which is a tracking system. What we ask our researchers to do is to put in an abstract, a timeline, goals for the project, and at the end of the project if there should have been a paper submitted we connect back to that. It's a way for us to keep track of the research.

And one of the benefits for using this system is it has allowed us when we've asked about how we spend our money and our research plan and to defend our organization, we can say this is everything we've done, the system has tracked it nicely. Unfortunately, we haven't been able to get our COEs and our collaborators to necessarily buy into using our CART system.

I think we feel strongly in the future that we would like all collaborators who are using CFSAN money to be part of that CART system so that we can track he research that's done there. This is not a meddling system, this is just for us to support and defend our research

program and how we spend our money. So one of the things I encourage NCTR is when you have a collaborator at CFSAN to please be talking about using that system.

As I mentioned before we have a strategic plan realignment that's coming up next year. I'm sure we'll be back to NCTR and our other COEs to talk to them about how they will connect in with our goals and objectives. I was looking at your strategic plan, which is nicely outlined in our binder, I've been looking at everybody's strategic plans lately to see how we go about doing it.

It's been interesting to think about how strategic plans are run. I've been thinking about our current one and seeing how we've fulfilled those goals and objectives, and I find that it's difficult to see if we've fulfilled those goals and objectives, because it's not that there was no implementation, but there was no comparison, there's no data at the end, what's the metric for fulfilling the goal or objective.

So I think one of the things I'd like to talk about as we do this yearlong process for a new strategic plan, is how will we prove that we have done what we hope to do. Such a weird way to think as a scientist. But I'm looking forward to that, I think it will help us be able to define our research program, will this be something

that will help us.

One last thing, when I was coming to give this talk I sat down with Mickey and Suzy and I said I want to make sure that I cover what you find important as well as what I find important, because I'm the one here. What is it that I should bring to NCTR, what can I look in their eyes and say that CFSAN wants you to know. And the thing that they both said is they want you to know that we consider NCTR a partner.

We consider you a supporter, a collaborator, a coworker, a friend, a partner in the research that we do. We don't think of NCTR as someone doing our work, we think of us doing work with you together. And we hope that that continues, that partnership continues in the future. So if there's time I will happily answer questions, if there isn't I will happily step off the stage.

DR. LEIN: There is time for a question or two. Greg.

DR. LANZA: That was great. Could you address this business of nutraceuticals and whether that's in your world and particularly in cardiology beets, nitric oxide in beets.

DR. HATEWELL: As a nutritional supplement?

DR. LANZA: Is there any kind of regulation, or

any kind of anything over all these beet supplements that are for NO and improves energy, because our patients are coming in with them, and some of them of course we've got them on nitrates and other things. So I'm trying to figure out where do they nutraceuticals come.

DR. HATWELL: I think this is one of the most difficult places in food and probably drug regulation is this cutout of dietary supplements. I guess the way we look at it is if they're coming as a food which doesn't have an effect on the body, that's how we treat it. But if they're coming with an effect on the body, please step in, then I imagine that CDER looks at it in that direction. It's so difficult. And we try to talk back and forth in it. And we feel your pain because we're the consumer too, we eat the food, our friends and family are taking the dietary supplements.

And if I were to have the ear of Congress I would say please clarify this regulation, how do you want us to deal with it. But we do the best we can with it, whether we're looking at an effect which would be a drug, or a nutritional which would be a food. But we do try to spend a lot of time analyzing the product itself in terms of its labeling and its clarity.

So for instance UMIS just gave a wonderful talk

on their work on chamomile, I know you're not asking about chamomile. But chamomile can be multiple plants, and it's not always labeled as which plant it is, and each plant has a different effect, and what is the level of the chamomile in the body. So that's a perspective we are. Are we at least giving the consumer the correct information of the product on the container, and can they know at least that they can depend on that. So that's the perspective we take. I wish I could give you more.

DR. LANZA: I don't want to harp on it, but they're selling them as beet concentrates and kids and a lot of other people are using them before they go running races and a whole variety of stuff, and of course we always have other problems with young kids who have undisclosed cardiomyopathies and things. I just wondered who is looking at this. Because it's one thing if you're eating beets out of a jar, but these are like liquid energy supplements.

DR. LANIYONU: Just a quick response. These, actually I'm not from CFSAN so I'm actually talking like a member of the public. This is actually an area where if you take a poll most Americans don't want regulations on really. Usually most people say don't touch my dietary supplement, don't touch my (indiscernible comments). Fuzzy

area for regulation.

DR. LANZA: My biggest issue is, it's not the same as the batch and potency and see or anything like that. I have no trouble with what it is, it's just that you don't know if what they're getting this time is four times higher than what they've been using before or not at all. That's I think the issue for me, not whether they should be able to eat beats or grind up beats.

DR. PILLAI: (Off mic)

DR. HATWELL: I don't think so. Not for Center of Excellence, COE, yes. That is, I think there is probably an official definition which I'll be happy if somebody else can give. But I believe it is considered a collaboration where there are no FDA employees located. Is there a memorandum of understanding in terms of collaboratory research is -- Is not an FDA center. Two differences. Sometimes it's difficult, for instance at Illinois Institute of Technology there is an FDA center within it, and then there is also the COE around it. So we have a few FTEs there on site, and then the non FTEs who are work for ITE as part of our COE. Confusing, huh?

DR. LEIN: Thank you very much. I think we'll move on to our next presentation, and we'll take a break after the next presentation. So we'll hear from the Center

for Tobacco Products. Take it away.

Agenda Item: Center for Tobacco Products

DR. BACKINGER: Now for something totally different, tobacco. And I know Ed mentioned he feels the CDRH is the redheaded stepchild, but I really think it's tobacco. But we won't argue. SO just briefly, I know some of you have heard this before, so I'm just going to go through it very quickly. We're the newest center at FDA, we didn't exist until September 2009, so FY2010, because it wasn't until June of 2009 that FDA was given authority to regulate tobacco products. And at that time we were given authority just to regulate only cigarettes, cigarette tobacco, roll your own tobacco, and smokeless tobacco.

And then just about a year ago, in August of 2016 we finalized a rule that we call the deeming rule, because we deemed all other tobacco products that meet the definition of a tobacco product to be under our regulatory authority. So that includes, and I won't read this, but everything that you can imagine, as long as it's derived from tobacco. So nicotine is derived from tobacco. Hookah, nicotine gels, dissolvables, and so it covers everything including future tobacco products.

So the reason I say we're the red headed

stepchild, because I know all the other centers and Karen was just talking about this, talking about safety. And FDA, the other centers evaluate products based on safety and efficacy standard, and we don't. Because we can't. Tobacco is inherently harmful, it is not safe.

So we don't approve products, we authorize them for marketing because we're not approving them so that people don't get the idea that they're actually safe or effective. I guess one could argue that they are effective because they actually kill half of all users. That's a joke. And this is outlined in the statute in the 2009 Tobacco Control Act. We use a public health standard, we have to take into account both the benefits and risks to both the users of the tobacco products and the non-users.

So we have to assess the net population effect when we look at evaluating a tobacco product for marketing. So I think hopefully everybody knows this, but I wanted to focus a few minutes on our commissioner Dr. Gottlieb on the 20th of July made an announcement, a public announcement, and he said nicotine is astonishingly addictive.

And when nicotine is attached to cigarette smoke particles it's not only highly addictive, but an addictive chemical mix of death and disease. So what he outlined on

July 28 is a comprehensive regulatory plan around nicotine and tobacco. So just kind of getting at a goal, we envision a world where cigarettes no longer create or sustain addiction, and adults who need nicotine can get it from a less harmful source.

And so we're doing this because we really see the need to move people away from the most harmful tobacco product to least harmful products. And this also includes looking at working with some of our sister centers around innovations and medicinal nicotine and other therapeutic cessation products.

So what does that mean? We want to put nicotine in the middle of the discussion. And I'll only talk about this for a minute, because this obviously is very relevant for NCTR, which is the harmful constituents, but it's nicotine is really the issue of the central issue of addiction.

And we are acknowledging that while nicotine is highly addictive, that it's delivered in a range, a continuum of risk, from the most harmful products, which are combusted products, cigarettes, and other combusted products, to less harmful, because it's the act of burning the tobacco that creates the harmful and potentially harmful constituents, nitrosamines, and other cancer

causing agents and lung and cardiovascular endpoints.

So we're trying to strike a balance between how are we going to regulate these tobacco products moving forward. As I mentioned we only had the jurisdiction to regulate all these other tobacco products for about a year. And obviously everything that we do is based on a sound scientific foundation.

So how are we going to do that? So we're going to publish some product standards. We want to focus on reducing both addictiveness but also toxicity and the appeal of products so that we can prevent addiction, harness people not moving into initiating tobacco products, and encouraging cessation. We also want to encourage and innovative less harmful products so that people can still get the nicotine that they want, and then address the role of therapeutic products.

So what are we going to do? I think, and this was also part of Dr. Gottlieb's July 28th announcement, he said that we are going to issue an advance notice of proposed rulemaking to look at lowering nicotine in combusted cigarettes. So we're going to put out this ANPRM to ask questions, like how would manufacturers comply with this, what would be the unintended consequences, and then implementation and enforcement.

So the notion is if you put nicotine at a threshold that's non-addicting, that people may try them, but they're not going to get the nicotine to move on to addiction, and current smokers won't get the nicotine satisfaction so that they will quit. So we're going to put out an ANPRM hopefully in the near future, I don't have any timelines for that, but I know that Dr. Gottlieb announced that in July. We're also going to put out some other ANPRMs, getting back to some of the issues around flavors.

So looking at flavors, including menthol, how is that attracting youth, how is that helping smokers switch to potentially harmful products. In the rea of flavors we want to look at appeal but also toxicity of different flavors. And again, this one is across the spectrum of tobacco products, so it wouldn't include not only electronic cigarettes but also other products, hookah that have flavors in them.

And then as I think some people know that we put out proposed rulemaking a while ago to reduce the harms in smokeless tobacco in order to reduce levels of NNN. And so we still are in the process of reviewing those comments, but that's still in the mix of potential regulatory action. So we're trying to have a broad comprehensive

program to get at all the products to really again to prevent initiation and help people quit smoking so that we can reduce the burden of death and disease.

So here's our research program in a nutshell. This has been presented previously, but we have a very robust research program. We work with other federal agencies, we do a fair amount of grant funding through NIH. We work with NIH very closely. We have research contracts. We work with other partners in the government such as CDC, we work with census, and obviously we work with NCTR. So these are the areas that we have outlined, and I wouldn't call it a strategic plan per say, but we have topic areas that we're interested in research.

And again, because we're kind of like the new kid on the block, we still have quite a bit to learn. I mean I go to parties, and someone asks what do I do, and I tell them what I do, I oversee research programs in tobacco. And they're like research, don't we know everything we need to know?

We know it's bad. What are you doing? It's like oh there's all these questions that we still have, and so here it's just outlining questions around addiction, chemistry and engineering, understanding knowledge, attitudes, and behaviors on some of the products, toxicity

and carcinogenicity, health consequences, communication, marketing, and economics and policies.

And this is just to show you that within the Office of Science at CTP we have all of these scientific disciplines represented, because again trying to understand the net population impact and looking at that public health standard is really important. So we have to bring it all together, it's not just one scientific discipline, it's all of them combined.

So I'm not going to go over this, because I think all of the division directors yesterday went over projects that were working already with CTP, but primarily we're working with NCTR in three areas. We're working with NCTR in the areas of addiction, we're working with NCTR in the area of toxicity, and then modeling that Weida Tong was talking about yesterday, working with understanding how to bring all this information together and find things that we need to know. So I won't belabor that.

Just lastly, with my last few slides, these have been publicly posted I'm not going to read all of this, but this is kind of the areas that we are focusing on in toxicity. So when you think about gosh the plethora of tobacco products that are on the market, most of the research that has been done for decades has been done on

cigarettes. And then there's been a fair amount of research on smokeless tobacco.

But for a lot of these products, even though some of it makes intuitive sense like cigars because it's combusted, would it have the same toxicity profile as cigarettes, some of these products have not been studied as well, and if we're going to work on putting out a specific rule or product standard, we need to have information about those products and those product classes. So around toxicology, we need to understand how different characteristics and changes in those characteristics affect constituent exposure and toxicity. We need to look at comparing toxicity assays across and within different products to understand the relative potential risk and harm. When we get to addiction we really need to understand the characteristics in those tobacco products and how they impact addiction and abuse liability, and that includes flavors, looking at low nicotine content cigarettes which I mentioned previously.

And electronic cigarettes is still an area, these products are relatively new and you've probably seen a boom both in advertising and how many are on the market and places where you can mix your own flavors, and really understanding the toxicological issues around some of the

flavors and interaction with the device will be important moving forward.

So with that I just wanted to say thank you to both our NCTR colleagues who make this happen, as well at the CTP colleagues that help oversee the interactions between CTP and NCTR on this research component. I wanted to briefly just mention Dana van Bemmel, she's been here in previous years, some of you know her. There was a call from HHS to have people volunteer to be deployed by FEMA for hurricane relief, and Dana was volunteered, even though she has twin boys who are age 13 and obviously still at home, and a husband, and I don't even know how many pets.

But she was gone and worked in Jacksonville Florida for six weeks, and yesterday was her first day back in the office, so that's why I'm here, because I couldn't ask her to come to NCTR. She's been away from her family for six weeks. And with that, thank you, and I'll answer any questions if there is time. Thanks.

DR. LEIN: We do have time for a question.

DR.PILLAI Cathy, I enjoyed your talk. A question is, maybe I missed it, you didn't say anything about THC. Most of your slides are about nicotine. Some of it is now coming up as vape juice and being used on all of those

types of devices. So your office is not involved in any of that activity?

DR. BACKINGER: We are not, because we do not have the authority to study that. With the Tobacco Control Act, our whole center is funded through user fees, through tobacco product manufacturers, and it's very clear within the tobacco control act what we can use our funds for, and it can only be for tobacco products and tobacco regulation. So anything that we do has to be related to tobacco. So we can't study that per say.

Now obviously we do include some questions around marijuana use when we have studies, because we have to understand if you're asking kids for example if they're using e-cigarettes, we have to understand if they're using them for marijuana. But we can't really study the marijuana aspects of it.

DR. LEIN: Any other questions or comments around the table? Okay, so then we're going to take a break. We can reassemble at 10:15, and we'll finish with the last two product center presentations, and a reminder of Donna's request that those of us that preordered box lunches to pay for them at the cafeteria.

(Break)

DR. LEIN: Let's start the rest of the morning.

Everyone please take your seats. Okay, thank you. We would like to resume. Donna has a quick comment.

DR. MENDRICK: For those of you at the table, if you want these books mailed to you, the last page is a mailing address. Just put in your name, and we will mail them to you.

DR. LEIN: Okay. So just to remind everybody that we didn't have a chance for questions after some of the presentations this morning. There will be a general discussion period after the centers have completed their presentations.

So we are moving now onto the presentation by the Center for Veterinary Medicine. Thank you.

Agenda Item: Center for Veterinary Medicine

DR. GRAHAM: Good morning. We will get right into it. Both the Center for Veterinary Medicine and CFSAN are actually underneath at the FDA, the Office of Foods and Veterinary Medicine. CVM's specific mission to protect both and animal health. A term that you will hear more and more frequently now is one health because the health of animals will affect the health of humans and vice versa.

OR's mission, as part of CVM's mission, is to protect animal human health by providing research to

support the regulatory decision-making about food, feed and drugs. So every year, CVM looks at its key initiatives, which are part of actually OFEM's strategic plan, which is readily available on the web. We have six of them that we are currently working. The first is implementing the Food Safety Modernization Act, which was signed by Barack Obama in 2011. It is a law that gives the FDA additional authority it never had before, such as immediate recall authorities. So FSMA gives the FDA the ability to oversee the processes of growing, harvesting and processing food products.

Another large key initiative that we have was the issue of antimicrobial resistance strategies. That would include some of our guidance for industries that we have released to limit the use of medically important antibiotics in food animals that went into effect this past January.

We also have concerns on unapproved and compounded animal drugs. There are still a number of unapproved animal drugs that are out there. The Food, Drug and Cosmetic Act did not initially include drugs that are geared towards veterinary use. That was relatively late in the game. So there is still a lot of products out there that are not licensed, but they are still used. We

are making attempts to identify those with the highest risk to get them to either become licensed or pull them from the market. And compounded drugs also pose a challenge for us.

We have, of course, pre-market animal drug review, part of which involves emerging technologies. More and more veterinary products are being developed using stem cells, specifically or mostly for both canine and equine therapeutic purposes. We are trying to wrap our arms around how we can look at the manufacturer products to make sure they are not only efficacious, but we don't have any batch-to-batch variations. It is a very challenging thing, I think both on the human side, as well as the veterinary side.

Another emerging technology that we are in is genetically engineered animals. And genetically engineered animals, whether they are meant as a food source, such as the AquaBounty salmon that you hear about in the news, or those that are meant to be biofarm animals, to produce some sort of product that will be used to treat humans. The animal itself is still processed like it was a drug, as far as approval is concerned. If it is for food, it stays within CVM. If it also is used as a bio pharm product, well, whatever it is producing,

CBER would have a role in that as a biologic that gets produced. But we still produce the genetically-engineered animals and approve those for marketing.

And then of course, we have got post-market drug safety effectiveness and quality efforts that are ongoing. We have got quite a large surveillance and compliance effort in animal drugs and other animal products because unlike the human side, we do not conduct extensive clinical tests the way you have in humans. So many of the side effects are actually found after the products have already been released, and there is a large population of animals that have been given these particular drugs.

Our center director is Steve Solomon, under which he has got five offices. The two offices that I deal with mostly are the Office of New Animal Drug Evaluation led by Steve Vaughn. This particular office is where drug applications come in for either pioneer or generic drugs for use in animals.

Then of course, the Office of Surveillance and Compliance, which works closely with the Office of Regulatory Affairs if we need some sort of inspections made. And we also assist with writing letters to pull products.

And then there is the Office of Minor Use and

Minor Species. Unless you are a major species, it is very difficult or challenging, I should say, to convince industry to propose drugs for minor species. There is just no market in it. Money drives things. There are things that that particular office does try to encourage that, for instance, extending patent protection, delinquent patent protection, and waiving some application fees, things like that.

So within the Office of Research, I have got three research divisions. I will talk about each of those. The Division of Residue Chemistry led by Phil Kijak, the Division of Applied Veterinary Research led by Raoul Gonzales, the Division of Animal and Food Microbiology led by Maureen Davidson. Then we have got two surveillance programs, NARMS led by Pat McDermott and Heather Tate, and Vet-LIRN led by Renate Reimschuessel. I am going to briefly review those surveillance programs for you now.

I am going to start off with Vet-LIRN. Vet-LIRN stands for Veterinary Laboratory Investigation and Response Network. So its function is to promote human and animal health by collaborating with veterinary diagnostic laboratories across the United States to provide scientific information, build lab capacity and train

scientists. And investigate CVM-regulated products, mostly animal feeds and animal drugs.

Vet-LIRN came about in 2010 as a formally funded program after the 2007 melamine incidents, where it became apparent that things were happening to dogs across the country. We couldn't, at that time, figure out what was going on and what was the cause. So really Vet-LIRN will do investigators into cases that have been reported either by individual pet owners or by their veterinarians and will look for patterns.

Most of the time, when people have submitted something or a veterinarian has submitted something, they think that it could be related to the food the animal is eating, not so much a drug that was given, but the food that I was given.

I would say more times than not, by the time the investigation gets done, it turns out it is not the food. There is something else going on with the animal that we end up figuring out this is what caused the illness or the death of the animal or groups of animals. But every now and then, something happens. We find, yes, indeed, there has been typically bacterial contamination in a food product that ends up getting recalled, saving more illness. So we currently have 39 labs across the United

States, with one of those labs actually at the University of Guelph in Canada.

NARMS stands for the National Antimicrobial Resistance Monitoring System, which looks for extent and temporal trends in antimicrobial resistance in enteric bacteria. It is a collaboration amongst the FDA, the CDC and the USDA. It helps CVM in promoting antimicrobial stewardship and supporting the agency's mission.

So NARMS itself specifically monitors trends and antimicrobial resistance among foodborne bacteria that come from humans, retail meats and animals. We disseminate timely information to promote interventions that reduce resistance amongst foodborne bacteria. And these interventions aren't just limited to trying to limit antimicrobial use in animals. It could be other agricultural farm practices that can help reduce the buildup of antimicrobial resistance.

We also conduct laboratory research to better understand the emergence, persistence and spread of antimicrobial resistance. We do much of that in one of our research divisions. We also collaborate closely with the Division of Microbiology here at NCTR to address these issues.

So toward the end of my presentation, you are

going to see a list of actual projects that we are working on. Most of them fall under Carl and Steve's area. And then we assist the FDA in making decisions related to the approval of safe and effective antimicrobial drugs for use in animals.

So here is a quick structure. You can see more about NARMS by hitting that link that is up there. But the CDC will collect isolates from human infections. The USDA will collect samples, typically at slaughter time. Some of the samples are environmental samples or HACCP isolates. Others are cecal samples taken from the ceca of animals. And the FDA conducts research or looks at antimicrobial trends in isolates collected from the main retail meats. You can see the four organisms down there that we concentrate on.

Now recently, NARMS was reviewed by an FDA Science Board Subcommittee. That was about two weeks ago. There were several recommendations that had been made. Those can be found online, as well. But a couple of the recommendations are to expand this testing into seafood, specifically shrimp because we import a lot of shrimp. So I have directed Pat McDermott to contact CFSAN because they were already working on issues with shrimp themselves and shrimp imports, and also look for other pathogens

beside the four that are listed here.

So the Division of Animal and Food Microbiology is where we study antimicrobial resistance mechanisms and evolution. NARMS itself does not have a laboratory. So anything they need done is done in DAFM. So we do routine NARMS testing of the isolates, although we are moving away from the standard tests that have been used in the past, such as PFGE and antimicrobial susceptibility testing and moving to whole genome sequencing, which can give us all those answers in a timely manner.

We look at plasmid sequencing, contamination and AMR found in animal feeds. And doing more and more work with metagenomics. CVM, as you know, had asked NCTR to look into the human microbiome. Carl mentioned that project when he was discussing it yesterday.

We have also done work in house in pigs on the meta genome. The effect on the meta genome, when the animal is given low levels of antibiotics over time, that research has been completed. It is in the process of being written up now.

Division of Residue Chemistry, we conduct method trials for new animal drugs, where the drug is expected to be used in a food animal. The sponsor then must have a method to detect that drug in edible tissues of animals.

We are one of the labs that validates that.

We also look at test kits that detect antibiotics in milk, to make sure that the mil supply in this country is safe. We look for mycotoxins in animal feeds, antibiotics in distillers grains is another big kind of issue. It can become a political issue. The ethanol producers use antibiotics of human importance to cut down on bacteria eating into their product.

But those small levels of antibiotics make it into the distiller grans. The distiller grains become part of the feed that goes into animals. We have shown through research that those low levels of antibiotics found in distillers grains are enough to select for antimicrobial resistance. And then of course, we look at hormones in animal muscle.

And finally, our Division of Applied Veterinary Research is where we incur residues in tissues for further research. We do biomarker research to look for biomarkers of pain and inflammation in animals. I already mentioned work in stem cells. Right now, we are concentrating on canine stem cells. We do work, as I mentioned before, on GE animals.

So the method trials we run in GE animals are similar to what we do with drugs. Only instead of looking

for drug residue, we are looking for the DNA construct has been altered. And then we encourage it in fish and poultry and porcine for antimicrobial resistance.

So I am going to quickly just go through this list. This is the list of the current areas we are working with. This was the one I had mentioned before and Carl had mentioned yesterday on the human intestinal biota. We also have Steve Foley looking at the role of plasmid-encoded factors in *Salmonella enterica* virulence.

And what you see here, the ones in red are people from CVM who are actively working on this project. This isn't like a project that we have thrown across the fence and asked NCR to do some work, and we get the results thrown on the other side. It represents a true collaboration where our scientists at both ends are actually working with each other on this.

FDA-regulated products using high throughput and high content quantitative approaches to cultured human cells, in genotoxicity. *Salmonella enterica* virulence and plasmid characterization databases and analysis tool. Using metabolically competent human cell lines to perform high throughput genotoxicity testing. Multi-drug efflux pump mechanisms in AMR.

This is my last slide. Potential areas of

future collaboration besides continuing to help us work on antimicrobial resistance, which again I said is one of our key internationals. It has to do with how we address compounded and unapproved drugs. One of the areas I think NCTR could help us with is looking at ADME of these particular drugs.

In the past, all we have really done with compounded drugs is to look at what is the active ingredient. We have been able to show the active ingredient might be the same, but the salt is different. We haven't been able to take any action on it because we haven't done any work to say, well, because the salt is different, the bioavailability is likely different. Therefore, it is not as efficacious. We need to look more into these compounded drugs. That is really something on our radar screens. So with that, hopefully I am on time.

Agenda Item: FDA Center Perspectives Office of Regulatory Affairs

DR. LEIN: Excellent job. Actually, I would ask you to sit down and we will have the next one. We will open it up for general questions afterwards. The last presentation this morning will be from the FDA Center Perspectives Office of Regulatory Affairs.

DR. LINDER: Good morning. Thank you for the

opportunity to discuss a little bit within what has been going within the Office of Regulatory Affairs. I think the last couple of times I have had the opportunity to talk in front of this audience, I briefly mentioned that ORA was undergoing a big reorganization effort due to program alignment.

I am happy to say that was executed on the May the 15th. So now I am going to really try to steer us in the direction of what impact did that have on our science and more specifically, as I drill down our instructional structure, the introduction of a new office, that's sole function is research, which I think will allow us to have a better integration and collaboration with the centers and NCTR.

So in 2013, Commissioner Hamburg really put a charge to the agency as a whole for what we call program alignment. One of the goals of that was to modernize and strengthen the FDA workforce to improve public health. Well, you can think about that, we did from a regulatory affairs perspective. For us, that really meant aligning by commodity, much like the centers had.

I know that Dr. Graham mentioned earlier that CVM and CFSAN are under OFVM. Well, that is also analogous to the medical products center, as well. They

have a super office. So we really thought about how do we structure our office to pair up nicely with the way the product centers are paired up such that they had dedicated resources, both from an investigative standpoint and from a regulatory science standpoint.

If you just look at our old model, I guess this is prior to May 15th, it was a little bit scattered. The blue box indicates really where the boots met the ground part of function of ORA was. And that was through these regional components.

We had five regions. Within each of those regions, you had district offices, resident posts and laboratories that really function on a geographic level. An import comes in. You take it to the local lab, and they analyze it. Well, that is all great, except for if the lab doesn't have specialized expertise in whatever the commodity that was picked up and analyzed for.

So it led to some inefficiencies that we thought, by program aligning, we could gain. And so, as of May 15th, we introduced our new operational and organization structure, where it really aligns nicely with the center perspectives. And it also does two really nice things. If you think about prior to May 15th, a week or a month or a year in the life of an investigator who goes

out and performs these functions at different firms and import areas, they were charged with understanding and being able to audit all types of commodities. And I think the challenges within something like a food manufacturing facility at a medical products facility are not the same.

In order to strengthen our workforce, all of our investigational compliance components were then aligned, so that they can focus on one commodity area. Hopefully then, increase their specialization and increase our efficiencies in the investigational component of our work. It doesn't look like a lot on this, but ORA as a whole is roughly 5000 FTEs. That is before you factor in contractors or special government employees, et cetera, these other mechanisms to get support. It really is quite a large office.

From the laboratory size standpoint, when we were in the regional model, each region had its own labs. Those were administered through what is known as a Regional Food and Drug director. Well, that led to a variety of different policies, procedures, processes for how science was conducted in the laboratories. Our goal was, through program alignment and reorganization, to create an Office of Regulatory Science, which included all the laboratory components within ORA, as well as our

headquarter components, which integrate with the centers and their priorities.

It is important to recognize that our work comes to us form the product centers. So they set the strategic guidelines. They set the compliance guidelines. They set the regulatory framework. And then they ask us to go out and do the enforcement type of activities against their framework and what their priorities are.

So within the Office of Regulatory Science, you notice I am going to drill down further and further as we go through this. We now have 16 laboratories. And those are product or commodity aligned, very similar and analogous to what the FDA product centers are. We have our food and feed laboratories. That is their primary focus. We have our medical products specialty laboratory components, as well.

And I think the most important of this, in the upper left-hand corner, where I am going with this is the establishment of a new office, the Office of Research Coordination Evaluation, as we like to refer to it as ORCE because, of course, as government employees, we have to have lots of acronyms. It doesn’t seem like a lot again, when you look at it here. Our laboratory, Office of Regulatory Science, once it was reorganized, is about 1000

employees. Again, before we get to contractors, support staff, et cetera, just 100 government FTEs.

We do tens of thousands of samples a year in all types of commodities, food, drugs, medical devices. We have tobacco work. Just about every product center, we do some work for in different types of areas.

Our office is led by Paul Norris. He couldn't be here today. That is why I am here. This is also important to point out. We stood up for the first time ever. I told you ORA was about 5000 employees. We did not have a centralized safety office. We occupy roughly 215 fixed locations. When you think about ports of entry, you think about district offices, you think about international mail facilities.

We have international offices in China, India and other parts of the globe. We didn't have a centralized safety office. And so, that now resides within the Office of Regulatory Science. It is a huge improvement for us to be able to coordinate that on a national level. And then also integrate with the new Office of Lab Safety and Science and the Office of Commissioner.

So just to give you kind of a geographical picture of where our laboratories are at and how they are

commodity-aligned now, we do have a pretty good footprint across the United States. A lot of these points of entry had historically been there for many years based on the amount of work that came in.

I would like to highlight kind of a new entity for us as the Port Everglades Screening Station first of its kind, where we are actually screening products coming directly into us in the Fort Lauderdale area coming into the port with rapid screening technologies there. Hopefully to turn around products.

You think about imports, perishable imports, you don't want them sitting on the dock very long because then they become worthless at some point. So kind of a pilot program to stand that up and hopefully get products in and out of the country quicker.

A few of the key names within our office, again, this is kind of our leadership roster for about a thousand laboratories. I am going to drill down a little bit farther into the Office of Research Coordination and Evaluation. That is led by Selen Stromgren. Those of you that have been around ORA science for a while might recognize her. She has been around in various areas within the medical products and food arena, has a nice background and is on board to lead that office for us now.

I am going to come back to that one. So what is the mission of this Office of Research Coordination and Evaluation? I mean, what is it really intended to do. What it is intended to do is bring ORA science to a single focal point. If you think about all the different commodities that we help regulate, and all the different testing paradigms, it is quite a large inventory of science.

We needed that key entry point, not only for our laboratories to come in and bring projects in or proposals in for new methods or new technologies, but also for our center colleagues to come in and say, hey, look, we want to go in a new direction. They didn't have that single focal point before. They may have had to go to the lab. They may have went to the regional food and drug director. Or they may have went into what was our previous office, the Division of Field Science. It is a focal point for bringing our science and leading it forward.

The research group, so ORAN, unlike a lot of the other centers, we don't have a very large dedicated research group. Really what our research involves is analysts at the bench who have identified perhaps efficiencies that could be gained or new technologies that could help us improve efficiency, improve scopes of

testing, things like that. So instead of having these dedicated PI mechanisms, we really have a lot of diverse analysts who do little components of research.

We do have a very small contingent. I would say 10 to 15 dedicated researchers within our laboratory component who do serve as PIs. But it is again a pretty small percentage. And then also quality, all of our laboratories are ISO 17025 accredited. That is a lot of work, but it also helps increase confidence for our stakeholders and the public to know that the work that comes out of our laboratories is sound and of high degree of certainty as we take regulatory action or make regulatory decisions.

So under the Office of Research Coordination and Evaluation, our quality component is now stationed there in hope that it can integrate again with the Office of Laboratory Science and Safety, with the office commissioner who is also standing up some quality components for the product centers, as well as the ISO 9000 component of our districts. So all of our investigators are also ISO accredited under 9000, where our labs are 17025.

And so, how are we going to do some of these things? What does it really look like? Those were the

missions. But I mean, practicality, where were the gaps, and how are we going to fill them?

When you think about the fractured structure into these isolated regions, as I mentioned earlier, with these different policies and procedures, we didn't have an overarching document for something as simple as what are we going to publish and how are we going to review it? That is a big thing for regulatory agencies and research communities is to publish whether it is peer-reviewed journal articles, whether it is laboratory information bulletins, which ORA generates a lot of.

Those go out to state partner labs, those go out to academic institutions. They are a rapid way to dissemination scientific methodology that could be used for public health. But we didn't have any document. We didn't have an overarching guidance on how we were going to do that and how we were going to review it.

So something as simple as creating these standard operating procedures to harmonize processes, whether it is peer review, whether it is publications that are coming in, whether it is external presentations at conferences or at sister agency symposia. Whether it is just the research proposals that come in from the lab as a whole or get submitted through intermural grants program

within the agency. We didn't have those processes delineated and documented. So that is one of our kind of first past projects that we have been working on the last few months is to generate those SOPs, so that we have some harmonization across our laboratory and science network.

One of the other things, and I mentioned this earlier, is net technologies. I mean, we get ideas all the time from laboratories, from the centers, from various workgroups within the agency of directions that people want to go with science. Those are typically involved investments, either human capital investments, instrumentation investments. We needed a single repository for someone to look at that scientifically with the centers and say, is this the right direction to go.

So this new office is going to do that. Hopefully, that will lead to a better use of our dollars towards new technologies and new directions. And also, factoring in that we need to have some component of our science forward thinking. We are always constantly behind it seems like. So hopefully this office is going to take that role.

The other component of this is that we really expect the office to engage with the centers more directly on research interests. We have a couple of different

mechanisms to do that now through the Office of Foods and Veterinary Medicine. It is not quite as overarching on the medical products side, but we want a better engagement. What are the directions? What are your strategic priorities? What technologies can we collaborate on for something like multi-lab validation studies, which is a key component to all the regulatory analysis and methods that we use.

And then finally, the quality component that I discussed earlier, really about how can we improve the confidence in our findings. ISO accreditation is one thing. It is a great big document management system. You have a third-party accreditor come in and look at your document system and do some type of investigational audits on a periodic basis. But that oftentimes doesn’t get you to the level of technical audit that you need to have to really improve to take it to that next degree.

So we have instituted some policies and some processes in which we are now sending in technical experts in technologies or in programmatic areas within our laboratories to look for opportunities for improvement. This has just happened in the last year or so. It has really benefited us because we have sent these staff members in prior to the ISO audits.

And what we have found is that by instituting that type of process, when the ISO auditor gets in there, we have very few audit findings, if any. I want to say two or three of our labs went through ISO 17025 accreditation audits this year. Out of that, I believe we had at least two that had no audit findings. It has really, I think, increased our quality and our confidence in our laboratory findings and our laboratories as a whole.

This is just kind of an overview of our program-aligned research landscape. At the top, you see the different research areas. Again, I mentioned that the majority of our research efforts are in regulatory methods development, refinement, improvement, process improvements. You see that the top row obviously has the most populated cells.

And then as you go down into other key component areas, we have more specialization, where there may be one lab working on, as an example, counterfeit drugs or tobacco products or things like that. It is quite a diverse landscape when you consider what we have, the produce centers that we work with and the oversight of science that we have to deal with on a daily basis. With that, I will close.

DR. LEIN: I think if it is okay with the people who made the presentations for the product centers, that we just open this up to a general discussion. Awesome. All right, so any questions or comments from the scientific advisory board?

DR. PILLAI: Sean, just a specific question to you. I was kind of interested when you said that you were setting up protocols for framework, for harmonized criteria for generation of scientific publications. Will the guidelines that you generated in your office trickle down to NCTR saying that they can only publish paper that fit the criteria? Isn't that a lot of top-down control of publications that is coming organically from the center?

DR. LINDER: So it is not so much, most of the centers already have some type of guideline for publication or review of publications. I can't speak to NCTR, but I know several of the product centers have a very elaborate review process for something like a peer-reviewed publication.

What we are trying to do is really take that and model it towards ORA science, to stand up what many of the other centers and the review processes that they have already outlined. We just haven't had that because we didn't have that single science.

DR. PILLAI: Oh, so that is just for your office.

DR. LINDER: Correct.

DR. PILLAI: Okay, so it is not coming down from that office down to all the centers.

DR. LINDER: That is correct. Most of the other centers, I don't want to speak for them, but I believe each one has their own individual process or standard operating procedure for reviewing publications or presentations. We are just standing that up in the Office of Regulatory Affairs because it didn't exist prior to this.

DR. PILLAI: Just one last comment. You said that you are benchmarking for your lab protocol. There is no ISO audit red flags. ISO audit and the research lab, sometimes they have conflicts. My only comment, just a thought, is would you rely so heavily on an ISO audit red flag compared to deep science being pursued?

A lot of times in a research laboratory, it is not amenable to ISO type auditing. Not necessarily am I saying that you should not have good lab practices or anything. That is not at all what I am saying. An ISO auditor, generally he or she looks at issues that are not really conductive to a research product flow through.

DR. LINDER: That is a good point. I should have been clearer on that. When we set up our laboratories with the ISO audits, we get to choose the scope of what the accreditation is going to be. In our laboratories, we really focus on the regulatory science, the regulatory analyses, and not so much the research. I can't think of any of our laboratories in which we have strictly the research components under the scope of accreditation. So the ISO auditors aren't actually looking at that.

DR. JAIN: This is a question for Dr. Graham. What were the illnesses which are transmitted through the wild animals, like Lyme disease through the deer or possible rabies through the raccoon or coyotes, are they under the purview of veterinary division? Or who is watching them or monitoring them or doing anything about them?

DR. GRAHAM: CVM is not.

DR. JAIN: I mean, is there any agency or any other organization? Some of them are assuming epidemic proportion.

DR. GRAHAM: I mean, certainly if you are talking about humans being affected by animals, any kind of human disease is overseen by the CDC. They would have

knowledge of those kinds of incidents or outbreaks occurring. And we would be consulted if there was a veterinary question. But we don't do any active research on transmission of zoonotic diseases at this time.

I also wanted to follow up with a comment to something that Suresh said about how publications are handled. I can speak towards how NCTR and CVM deal with that. If we have a collaborative manuscript, it undergoes review on both sides.

But there are incidences when NCTR PIs will write manuscripts themselves without names of anybody from CVM. But nonetheless, NCTR submits those to us for internal review to make sure that things that are being said aren't contrary to existing policies. So I think that is working really well. And therefore, they are not saying something that one arm of FDA contradicts another arm of the FDA, as far as that. I think that is working quite well from my perspective. I don't know how the other centers feel about that.

DR. LANZA : I have a couple of quick questions. The first one is very simple. Dr. Dorsam. When you had generic equals RLD, what is the tolerance? Like it has to be within 90 percent of the reference drug, 90 with some level of power? I didn't understand how close you could

be and still be generic. Seventy?

DR. DORSAM: That is a good question. I think that, in part, might depend upon the endpoint and the sensitivity. Typically, we would think of between 85 percent to 115 as the range for the main endpoints for bioequivalence.

DR. LANZA : Okay, thank you. Dr. Linder, I listened very interesting to your presentation. I definitely appreciate the process stuff, getting accredited. But I didn’t quite get if you could pull out like the top one or two unmet needs relative to public safety that your branch is pursuing as their main goals. There were so many different things. I didn’t get what is number one and two on your list.

DR. LINDER: It is interesting. We do have a few initiatives that I think obviously have been discussed by many of the other centers, the Opioid Initiative, and we are taking an active role in that as many of the other centers are.

We have staff at the International Mail Facilities. I think there are nine of those in the United States. They handle millions of parcels a day. There have been incidences of APIs or misbranded drugs, different things like that coming through those. We

actively, with colleagues at different federal agencies, monitor those things coming in. I think that is one of our big activities right now is time to ramp up that. It has been a priority of the commissioner and the president to work towards that. I think that is the one that probably has the most visibility right now.

Since our whole organization really restructured, I think right now, we are still trying to hash out where our biggest gaps from a laboratory side and from an investigative side. We have had a lot of challenges as the other centers have mentioned with budgetary constraints and hiring constraints. You completely reorganize in a period in which you have a hiring freeze and uncertain budgets. It has been very challenging for us.

I think right now, we are really trying to refine down across all of our structures of what are our most critical needs just to fill out. I inadvertently skipped over the one slide that showed the Office of Research Coordination Evaluation. But that model, I think, had about 10 FTE on it to really stand this office up. I think we have the director and I believe we have three others. We are like at 30 percent of our ten FTE. It is tough to stand a new office up and do all these

great things we want to do with the challenges right now.

DR. STICE: I was struck by the, I guess, commonality between the human and the animal in the sense that they are both interested in cell therapies. That is a big area for both of you. I guess maybe it goes without saying, you are working together. But I guess where is NCTR in that field.

I understand there are lots of animals that are used in toxicology these days. Can we reduce that for cell therapy through some of the new research that might be going on here? Following cell, I know that you need to follow each cell and where they end up. Imaging is a big part of the center here, too. I am just wondering if there are thoughts for the future in that area.

DR. WILSON: I will just briefly mention that we have a very active collaboration with CVM. In fact, actually the investigator that they recruited to work in that area came and spent some time in our laboratories to learn some of the methodologies that we used to evaluate stem cells.

And then I will mention, and leave it to John to elaborate further if he wants, I think for us, what we are really focusing on in biologics is stem cells as medical products and what are the issues and challenges and

methods that need to be developed to address the system cells as products, which is a very different question than what you point out as NCTR's focus, which is can we develop stem cells as models for preclinical or non-clinical evaluation of a variety of medical products or other potentially toxic agents.

So we also have had interactions with the stem cell group at NCTR and share methods with them, as well. But it is not our primary focus to look at stem cells in that context.

DR. STICE: I guess I was more interested in the safety side, on the imaging side, the expertise that is here in developing better ways on the safety side for a biologic.

DR. WILSON: Actually, it is interesting because Pam and I were just talking about that on the way down this morning. We actually rely heavily on Serguei's expertise on MRI. We have been trying to adapt the use of MRI to track stem cells in vivo. It continues to be somewhat challenging. We are making some inroads there, but there is still a lot of work. But we are grateful to NCPR's expertise in helping us along that road.

DR. GRAHAM: We are much along the same lines as CBER is. But they are actually further ahead than we are,

where they are looking at application. Right now, we seem to be focusing on the manufacturing of these products because they start out as very heterogeneous. And that is problematic because as you go from batch to batch, you have got huge variations.

So before we can put our requirements on industry, we have to define those requirements. So the size of the cells, another thing that we are looking at, biophysical characteristics of the cells. But we spent a lot of time working on stuff that can be used that doesn't include fetal bovine serum. When you include fetal bovine serum in the media, you are bringing a lot of things along with it that just aren't good.

So our scientists who had been working again on a chief scientist grant with one of CBER's scientists, developed a media that was free of fetal bovine serum. That was a huge step. We are working really towards how do we want to make sure that the product is uniform before we even start talking about tracing where it goes in the body and its efficacious in canines and equines. So we are further behind than the human side. But I assume the human side still has the same kinds of challenges with the product. When you get these applications in, how can you tell that one batch is going to be as effective as the

next batch? That is not an easy question to answer.

DR. LEIN: There was another question.

DR. PILLAI: This is primarily I would like to get a collective thought on this. Especially with the genomics technology platform, with NextGen sequencing, the technology is changing rapidly, almost on a month-by-month basis. I am not trying to endorse any company or anything, but just as an example, is the nanopore technology, which is making Agilent and Illumina sequences obsolete in a sense? The price points are dropping.

So how much of discussion takes place among all the centers and NCTR included because there is a tremendous amount of capability in terms of standardization of platforms, et cetera? These are things that a sponsor bringing in a new drug may not use Illumina sequence, probably would use a nano bioport dataset. How agile are FDA centers in dealing with these datasets?

DR. GRAHAM: I think if you look to your left at Donna, Donna might be able to address that issue because she chairs a committee at FDA level to look at emerging technologies and where we should be going.

DR. WILSON: I think that group is actually broader than just sequencing. I wanted to make the group aware that we actually have had for, I don’t know, since

maybe at least five years an FDA-wide group on NextGen sequencing. It is called the Genomics Working Group, where we have representatives from across the agency and ORA, where we have conversations around exactly these kinds of discussions. We also share guidance documents that are under development, policies and that kind of thing.

I think that we have taken, as an agency, a number of approaches. Certainly, CDRH has worked very actively with NIST on the Genome in a Bottle, so that there is physical reference materials that can standardize across different platforms. Our center has been taking a lead in some of the bioinformatics components in terms of data standards.

We had a workshop last spring on something called biocompute objects that can be used to communicate bioinformatics pipelines and a variety of other parameters used in data analysis. We recognize this is a really important area, and that we need to engage with a number of stakeholders to develop appropriate approaches to standardize these methodologies, while not stifling the innovation.

DR. MENDRICK: I will make a comment that John was referring to. I had an FDA-wide emerging sciences and

technology working group. What we are doing is horizon scanning. I want to put a plug in because we have a federal registry notice out and a SharePoint site. If people know of emerging sciences and technologies that might impact FDA products in five or more years, please put your ideas in. It can be confidential. It doesn't have to be confidential. You can choose.

But we are really looking at emerging. So people, for example, say nano. Well, nano is evolving, but we have already approved some nano products. That is, to me, not emerging. So really talking about things we maybe haven't heard of or are not ready for. I will put that plug in. Thanks, John.

DR. LANZA: I wanted to follow up a little bit because the variability applies to some other things. I was just wondering if the NCTR should be exploring this issue of exomes. In our NIH review panel, we are seeing them all the time. For the most part, we are actually not supporting them. And for one reason is they are not defined. We don't really know what they are testing. Their characterization is poor.

But there may be potential. Oftentimes, they show there is some potential. We don't know where to go with it. I wondered as a biological, is this something

that is really translational. Is this something that needs a lot more research? Is this something NCTR should be doing? Because it was just once or twice, but now, there is even a study group looking at these. That is quite a bit of money and quite a bit of effort.

DR. LEIN: I would absolutely second it. It was actually on my list in bold letters here, exosomes. I had not heard anything about exosomes. I totally agree with Greg even in the neuro arena, there is a lot of discussion about exosomes. That is, I think, an emerging area that somebody in FDA is going to be wanting to look at soon.

I also will take this chance as the chair, I have been pretty quiet, to say that, first of all, I want to congratulate everybody within NCTR, Bill and colleagues sitting behind me, as well as all the representatives from the product centers here. I have been sitting on the Scientific Advisory Board now, I think this is my third year. It is remarkable how much you have come forward in terms of integrating your efforts across the various centers.

I think the first chair is here. We kind of looked at each other like, wow, there is a lot going on. They don’t seem to be talking to each other. I think that has definitely made a huge revolution. You should all be

patting yourselves on the back. I am really impressed by what I have seen here today and yesterday in terms of the integration and the working together.

Which does bring me to my big question, which is it is a very complex organization. There is a lot of shared mission. There is a lot of shared technologies. There is a lot of the same problems and issues that you are all facing, resource allocation probably being one of the largest.

So two questions, what sorts of structures do you have in place? I have heard about the working group now for emerging technologies. But in terms of just in general, is there a kind of format for allowing you to seek out what expertise in technologies are already available, so you are not duplicating effort unnecessarily. And then secondly, what are some of the primary barriers that you face as product centers in terms of trying to interact or interface with NCTR?

DR. DR. WILSON: I will take first stab. You raise a lot of very important points. We have several forums for communication. One is, in addition to the Emerging Sciences Working Group, we also have something called the Senior Science Council, where representatives like Ed and I and John, I think, is on it and a variety of

other scientific leads within the agency come together once a month. We discuss a variety of issues relating to the scientific policies and coordination.

We also, through the Senior Science Council, authorize a variety of different working groups. The FDA genomics working group, the emerging sciences working group that you heard about, and then there is about a dozen others in a variety of different technologies. Nano technology is another one and so on to address areas that, as we start to see themes emerging across the agency that are touching more than one center and we think could really benefit from a cross-center conversation, we will authorize these working groups. Then they will report back to us periodically.

As far as technology, we also have a process called the Shared Resources Program, which is also a Subcommittee of the Senior Science Council. And what this group does is we solicit applications on a yearly basis for new shared resources. For large capital equipment typically defined as greater 150,000 on a government scale. But no one center necessarily can easily afford, but also that is likely that more than one center could benefit from. And so, this allows us to be able to apply for essentially end of year fallout money to be able to

support a large capital purchase.

And also, identify those needs where we should be making those kinds of investments, and then standing up a structure and a long-term commitment. We actually have a MOU that is signed by all the center directors each year where the initial investment for the purchase may come from fallout. But then, there is additional cost to operate it and do preventative maintenance. And that is done in a cost-sharing model across the agency where each center director, depending on how important the resource is to them, maybe chip in certain amounts of resources. I feel like there was another part of your question that I forgot. Maybe somebody else can chime in.

DR. LEIN: The second part of the question is really are there barriers to forging cooperative agreements with NCTR and, if so, what are they?

DR. WILSON: I think not generally. I Think the biggest challenge is that there is a geographic barrier. This annual meeting is a great opportunity for us as center representatives to hear about the science, touch base in person with the various scientists here and just be able to continue to foster those interactions and identify potential new areas.

DR. MARGERRISON: As the relative new boy to the

agency, I have a slightly different perspective sometimes. And one of the things that I have noticed is it is a complex organization. There is a lot of very different agendas, and there is a lot of very shared stuff.

What I think does exist is a very good network of people because people do want to cooperate. I think Caroline described beautifully the formal mechanisms. I think there is a really good informal mechanism that works.

So for example, if I once contact CBER, then I don't need to know who that contact is. I will call Caroline. I will find out within 24 hours. That is very active across certainly White Oak. I think with the collaborators and friends and colleagues that we have here, as well. That is something I think can be very easily overlooked. But it is alive and working pretty well, I think.

DR. LANIYONU: My first comment is sometimes, I wonder what it feels like from the NCTR prospect here. I have had occasion to collaborate with NCTR. Sometimes, they will send messages for comments or feedback. But because the primary job at White Oak is review, review, review, the timeline, if I want to be in academics, that is how (indiscernible) someone giving me feedback on this

proposal. They are waiting for it.

My assumption is that it is perhaps frustrating from their end that maybe the timeliness of response might be slow. That is neither here or there. It is simply the hierarchy of things that folks at White Oak needs to work on - reviews, meetings. Probably when they are giving feedback, it is during the weekend or at night when you can take a break. I wonder how that has frustrated them.

The other thing I am not too sure of how to get to is actually a way of allowing many, at the centers actually know more about the capabilities of NCTR. There were issues that the scientists remark on what we are dealing on gadolinium. I am actively involved in that research. When we went for the advisory, they asked us to focus primarily on elderly, neonates and the needs of young children.

I have been thinking of studies that you can naturally do to answer some of the chatter they gives us. I was reading some of the things that the meeting group would do. I never realized that those capabilities actually exist. This is not a question that I should be churning around in my head. This is stuff that perhaps I should just reach out to NCTR and let us know how we can forge that corporation.

This is an excellent facility of standing scientists and the models, the review sites know about the folks (indiscernible) might not be a bad idea. It might not be a bad idea for NCTR to come and do a science day for us. I don't know whether you are a part of it or you could do it on your own, a few scientists coming around. Or going to specific division or centers that are more advanced to the technologies or the platforms that you are looking to advocate for. Those will be ways that we can stop thinking about research that you can do, focus on what we do best and allow you to do what you have in a capacity and capability to do.

DR. LEIN: Thank you. Bill, did you want to respond to those?

DR. SLIKKER: I wanted to. First of all, enter into the conversation about ways in which we currently interact and how to include and expand that. Caroline did a great job of outlining the primary ones.

I think a couple of secondary ones are actually the various kinds of capability we have to attract funds to support research. This is the commissioner's challenge grants. We have OWH grants. We have diversity grants, as well as nano core grants. I think these really bring people together. In order to be competitive, often times

you need to have that idea of having multiple centers involved. That really brings people together to find support and attract attention to those areas.

The other thing is that we have a variety of ways over the years to try to get information about expertise across the various centers of FDA. And one that was a push forward about a year or so plus ago was one to put bio sketches available for everyone to read. And so, the NCTR took that opportunity, and now our bio sketches for our researchers are just about ready to be made available to the public. That means that in there is expertise and training that could be of value.

So if someone else within FDA wanted to know who within FDA could address this particular issue, you could go to those particular bio sketches and search them and find out where that expertise may be. Those are just a couple of additional ways that we have been pushing forward. But I think that certainly, as you noted, the amount of exchange in interaction has dramatically improved. So hopefully, that is sort of helpful as background information.

DR. LEIN: Any other questions or comments around the table from either side of the table? All right. Any last thing you would like to say, Bill?

DR. SLIKKER: Well, first of all, I want to thank, just as Pam did, the members, various representatives form the product line centers and ORA for being here. Also, our SAB board, I think this discussion that we have had over the last day and a half has been excellent. I think we have had more opportunity for exchange of ideas than perhaps ever before.

I also think that it is great to have some new members that are both on our board and new members that are also representing the various centers because that gives us even greater chance of getting to know each other. I am hoping that those that can, can take advantage of any tours that we may have of NCTR, so you can also see the facilities. But you have met a lot of the staff. I think we have been able then to make connections to who you might contact when you have a particular issue in mind.

And I think that sort of familiarity is really key to moving FDA forward is to be able to utilize all the resources that FDA has, including those at NCTR, to move FDA's work forward. I appreciate everyone taking part, including the presenters from NCTR. Also, that the staff that helped make this happen, Donna as the one who is responsible for legal representation of this. And

certainly, behind here is Kim and Jeff who ran a lot of the AV stuff. But also, I want to thank Pam for organizing the session and moving it through so nicely, and coordinating the efforts that we have had over the last several months. She will be, of course, in this role in the next year, as well. We really appreciate that support from all the SAB members and your leadership at the table.

So thank you all very much. It has been a wonderful opportunity. We also get a chance to acknowledge that we have a new Rear Admirable in the midst of FDA, which is really nice for Denise Hinton to come in and give us some comments, as well. I appreciate everyone taking part. Safe travels for those that need to get back home again. Thank you.

DR. LEIN: And with that, unless Donna has one last, nope, she has nothing to say. I will close the session. So the public session is now closed. And those members of the SAB please stay here. We will have a closed session beginning at 11:30.

(Whereupon, the public session was adjourned.)