National Center for Toxicological Research (NCTR)
Science Advisory Board (SAB)

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TABLE OF CONTENTS

P R O C E E D I N G S

Agenda Item: FDA Center Perspectives

DR. PHILBERT: Good morning. Our first presentation in a series from our colleagues at FDA is from Carolyn, Center for Biologics Evaluation and Research.

DR. WILSON: Good morning. Thank you. I am going to start with an overview of the products we regulate just to orient some of you who may be new on the advisory board. Then I will go into the priorities for our scientific research program, as well as some examples of ongoing and potential future collaborations with NCTR.

We regulate what are called complex biologic products, so things like monoclonal antibodies and most recombinant proteins are regulated in the Center for Drugs. But we regulate things like blood, blood components and derivatives, vaccines both preventative and therapeutic, the novel areas like cell and gene therapies, including stem cells, and that does include things like CRISPR modification of cells. Certain human tissues, live biotherapeutics and, yes, that includes fetal transplantation, allergenic products which actually, although that is a single line, represents over 1200 different extracts that are used both for diagnosis

and treatment of allergies, and then certain related devices, as well.

This year, we stood up a new governance process and revisited our strategic regulatory science and research goals, and developed the following four new goals. One is to advance a scientific basis for regulation of biologics, tissues, blood to enhance safety effectiveness, quality and consistency through development and evaluation of new concepts, methods, models and reagents. The second is to develop and assess non-clinical models and methods with improved predictive value, and implement the three Rs, reduce, refine or replace the use of animals for evaluation of safety and effectiveness.

The third is to improve clinical evaluation of our products through use of new biomarkers, large scientific and health care datasets and innovative design and analysis of clinical studies by applying statistical, epidemiological and mathematical approaches, while also considering patient input to inform benefit risk assessment. Finally, but very importantly, is to prepare for future regulatory and public health challenges through investments and emerging science and technology.

I want to now shift and talk a little bit about

some current collaborations. There was a study that is now completed, although there may be some follow on studies. The issue here was in the case of vaccine adjuvants are very important to help augment and enhance an immune response that will be protective in the case of a vaccine.

There are some adjuvants that we are very familiar with, like alum that has been for decades. But there is a great deal of interest in starting to use and develop new approaches to adjuvants. One of the ones that is being used is squalene oil-in-water emulsion. This has been associated with certain adverse events.

What was requested here was for NCTR to develop a well-designed study to address the pharmacokinetics in order to inform development of a PKPD model. We chose to do this as acollaboration with NCTR because of their extensive experience doing pharmacokinetic studies, their ability to do in vivo imaging and quantification techniques. The results of study were published this year. What they were able to do was show the pharmacokinetics and bio distribution within and without, in this case, a pandemic flu strain 5N1 vaccine.

What they showed was a rapid clearance from the site of administration, minimal systemic exposure, expect

a little bit in the liver. From this, now we have been able to develop a data-driven in silico model for IM administration, which we can apply to other classes of adjuvants to better inform our benefit risk assessment. In the future, we envision that we are going to continue to analyze these data, look at the model predictions and try to apply this to newer generations of emulsions.

A second area, and this is mention by Steve Foley, is work that we are doing in collaboration with the Division of Microbiology around Clostridium difficile. As he mentioned, this is a really important public health pathogen, particularly after antibiotic treatment. It can be life-threatening.

Fecal microbiota transplantation right now has been the treatment of choice to address this. What we are trying to understand is how commensal bacteria and different populations form the commensal bacteria may impact the host immune response, in particular, dendritic cells. With input from our expert on C. difficile, Paul Carlson, NCTR is establishing a co-culture system. We are hopeful that this will help improve our understanding of how microbiota impacts the immune response and may help us to have additional insights into how to regulate these novel approaches or potentially develop vaccines

for treating this important infection.

A third area is to engage with the SEQC2 platform. Here we have a group within the Center for Biologics called HIVE, Highly Integrated Virtual Environment, which is a high-performance computing environment that helps to support analysis of large datasets, including NextGen sequencing. We developed a lot of algorithms and pipelines to support how we approach precision medicine.

One of the things that we have done is to start developing quality control metrics to support de-novo assembly validation protocols. We are doing this work through the SEQC2 because NCTR has really engaged a wide variety of stakeholders with their experience from MAQC and the first SEQC. This is really important to develop community consensus standards around these issues.

But HIVE can provide the environment for SEQC to run these large de-novo assembly protocols and apply the protocols that we have developed in-house. The impact is to have these standardized approaches for data assembly to allow for more robust application of NextGen sequencing.

Now, switching to some future potential areas, one of the big challenges in fecal microbiota

transplantation is having appropriate assays to evaluate the safety of these potential stool samples essentially. The issue is that right now, they are being screened with traditionally clinical lab assays. Of course, those are developed to detect pathogens in the event of a full-on infection. It is very different when you are worried about, is there a tiny bit of salmonella in this fecal transplant material that may be at a very different level than what we are used to detecting in the event of true infectious disease.

What NCTR is bringing to this collaboration is experience with bioreactors that produce stool cultures that can be inoculated with base medium and human stool. The approach that will be taken is to test with pathogens specifically spiked at various levels, and then compare to plating and NextGen sequencing detection to be able to determine what type of sensitivity and performance we see with these different approaches.

Then right now, the status of this is that our understanding of the concept paper has been approved. But it is a very important approach for our center to be able again to better be able to regulate these products and know whether or not the current assays that manufacturers are applying to ensuring the safety are, in

fact, sufficient.

Then this one that NCTR has initiated where they want to apply the use of their SDAR model, which also was presented yesterday, to see whether or not certain anti-parasitic drugs, and the case here is Trypanosoma cruzi, whether or not they would have activity. What we are bringing to this is that we have a great deal of experience in working with T. cruzi. We have the culture assays to be able to evaluate candidate drugs for the anti-parasite activity. My understanding is that this is at the concept paper stage.

Then these are more speculative concepts for future collaborations, where we are seeking potential collaborations on the part of NCTR. Some of you may know that HBOCs or hemoglobin-based oxygen carriers were actively being developed. But really, that development was brought to a standstill because of the oxidation-mediated toxicity of these cell-free oxygen carriers. We need to better understand the toxicological consequences of hemoglobin in relevant animal models.

We thought the extensive experience that NCTR brings to evaluating in vivo toxicity, that there might be opportunities here for them to be able to help us get an animal model that would improve our understanding of

the mechanisms of toxicity. Once we understood that better, then we could work with the manufacturers to potentially develop HBOCs with reduced toxicity.

Then the last concept that I am bringing to the table for consideration is another potential new small animal model to understand red blood cell storage lesions. What happens here is that it has been known for a long time that ex vivo stored red blood cells may, over time, develop what we call storage lesions. These are biochemical, morphological or immunological changes that can occur with these red blood cells over time.

The problem is that when these develop, the clinical consequences, as you can see, are quite severe. It can be acute lung injury, multi-organ failure or mortality. But we don't have a really good way to assess candidate markers of these storage lesions.

So for example, CD Atreya in our center has developed and identified certain micro RNAs that seem to correlate with what we think are storage lesions. But we don't really have a way to then evaluate that, other than in a clinical trial, which is obviously an expensive, cumbersome way to do that. We need this intermediate step to be able to evaluate these candidate assays for looking for these.

I just want to finish with acknowledging the CBER colleagues who helped me prepare these slides. Million Tegenge, an OBE who is involved in the squalene emulsion study, Paul Carlson in the fecal transplantation, Alain Debrabant, who is participating in the T. cruzi study if that gets off the ground, and then Abdu Alayash and CD Atreya from Office of Blood, who provided ideas for future concepts that might be of interest to collaborate. I will stop there and happy to answer any questions.

DR. PHILBERT: Questions for Carolyn?

DR. LANZA: I thought the issue with the HBOCs was that a couplet. One was that they don't dissociate from the oxygen, that they bind, so they have high P02. They also sequester their N0, which can lead to basal constriction. As long as you are still talking about even modified hemoglobin, aren't you still dealing with the same problem, unless you get allosteric regulation of hemoglobin as a fundamental part of it?

DR. WILSON: Yes, you are correct. That is one of the issues is that it holds onto the oxygen for too long. I guess my understanding of the N0 piece is this oxidative toxicity is mediated through N0. I am not the expert in this. I don't really want to speak out of turn

on all the details of this.

DR. LANZA: It leads to constriction and increased hypertension. It is sequestering from the vascular wall. That leads to the vessels actually contracting. That is a major problem.

I just was curious because of the direction. You were talking about learning more about the toxicity. But the key issue is really they don't deliver the oxygen. They carry. It is the disassociation and the lack of that is because of it is allosterically regulated by 23DPG. Somehow, they need to overcome that.

DR. WILSON: Right. We are aware of. Actually, Abdu Alayash has an ongoing research program to look at alternatives to what had been. For example, what he is finding is that fecal hemoglobin haptoglobin actually seems to let go of the oxygen a little bit more effectively than the traditional adult alpha beta hemoglobin. But I think that what he is looking for is a better animal model to translate the biochemical findings before going into some kind of facilitating development further.

DR. SURESH: Have there been any adverse reactions of cases of fecal transplant?

DR. WILSON: I am not aware of that, but again,

I am not the expert to know that for certain. It may be that would also be confidential information that we can't disclose. But I don't know.

DR. PHILBERT: To take that a step further, does a broth that is fairly constant reasonably recapitulate the fluctuations that will go in a gut after a meal, after a little bit of starvation?

DR. WILSON: I think that is a very fair question, but we have to start somewhere. I think that the issue is that nobody is really looking carefully at the sensitivity of these clinical assays for this particular application. This is a model where we can at least start to get a handle on some of those questions. But certainly, it is not going to be a perfect model.

PARTICIPANT: Is the intention to go beyond just identification of what is present to looking at vegetative potential?

DR. WILSON: Yes. We actually also have in-house and CBER, Paul Carlson is doing work to look at different populations of the microbiota and how it impacts, for example, treatment of C. difficile infection. So yes, we are looking at that.

DR. LANZA: So in case of C. difficile, is the concept to move fecal transplantation earlier up in the

care line? We use Vanco because of Vanco-resistant lines. So is it, for instance, screened for Vanco-resistance, and then go ahead with fecal transplantation early? Right now, it is done after many --

DR. WILSON: Right. So right now, as was mentioned yesterday, fecal transplantation is not a licensed therapy. It is being used investigationally. As Steve mentioned yesterday, the Center for Biologics has issued guidance that does call for what is called an enforcement discussion, which allows, and again it is a last course treatment, not early course treatment, to use FMT without an investigational new drug exemption filed with the agency.

But we are trying to work with those groups that are doing a lot of work in this area to get them to come in and do these studies under IND. That will be the only way we can really get a handle on how well this works and gather the clinical trial data and be able to move forward with doing something through our regulatory pathways. If you had a licensed product, and you licensed it for an earlier clinical indication, then you could potentially go there in the future.

I think long-term, really the vision with all of this is to more clearly define what aspects of the

fecal microbiota are critical, so that we don't have to use these pools of stool samples and try to have something that is more clearly defined. But I think we are not there yet obviously.

PARTICIPANT: Thank you very much.

DR. MCGOVERN: Thanks and good morning, everyone. So both myself and David Strauss will be speaking. We will be splitting our time to cover different areas within CDER. I am associate director for the pharmacology/toxicology group within the Office of New Drugs in CDER. I will just talk a little bit about the role of our group here.

Just in terms of the organization with the focus on pharm/tox, so we have our center director, the OND director, and then within the OND director's office, there is the associate director for pharm/tox, which is Karen Davis Bruno. There are three ODE associate directors for pharm/tox. I am one of those three.

Then we have pharm/tox supervisory and review staff that are located in each of the drug review divisions. We have five different ODEs or Office of Drug Evaluation, as well as an office for oncological products. There is no direct supervisory chain between the pharm/tox associate directors and the immediate

office of the Office of New Drugs and the pharm/tox staff in the divisions. But we do coordinate through a pharmacology/toxicology coordinating committee. The role of the associate directors is primarily kind of development of guidance and policy, and trying to ensure some consistency across of the review divisions in terms of enactment of pharm/tox policy.

I have mentioned the pharm/tox coordinating committee. That is one area where, in the last year or two, we have increased our interaction with folks from NCTR, Donna Mendrick sits in on that group. We are able to interact in terms of things NCTR can do for CDER and things CDER might be able to do for NCTR.

Then just the general regulatory drug development within CDER. There is the early stage of discovering research, things which the FDA typically does not see much of. Then once we get into phase one through phase three IND development, in the early stages of IND development, you tend to get most of your non-clinical toxicology/pharmacology data, starting with your short-term toxicology gene tox and pharmacology work.

Then as you get later towards development, there is obviously greater reliance on the clinical data. But we will start seeing some of the reproductive

toxicology and carcinogenicity data. Certainly by the time an NDA or a BLA for biologic comes in, in most cases, we will have a complete set of pharm/tox data which I will describe in a few moments.

We are using the pharm/tox data to primarily identify a reasonably safe dose range. That can then be used to explore dosing in clinical trials. The tox data is used to identify clinical monitoring beyond what you would typically use in terms of standard safety assessment, and to identify or predict risks that are not captured in human trials, especially in areas of reproductive toxicology and carcinogenicity.

As we all know, non-clinical models are not perfect in terms of predicting clinical outcomes. But especially early in development, first dosing in humans, we have had a very good record in terms of using this data to avoid any significant adverse findings in clinical trials.

So the intent and use of pharm/tox data in new drug development, and I am stressing new because these are cases where it is a completely new entity, not previously marketed drugs. We are looking for pharmacology data to establish the pharmacologic properties of the compound and to understand the

toxicological profile. Things like target organs, the dose response and, in many cases, reversibility of any toxicity that we see. Based on all of that data, the main question we are asking is, is that data sufficient to conclude that what is being proposed in clinical investigation is reasonably safe to proceed.

And so the scope of complete pharm/tox information includes pharmacology, which is the primary mechanism of action type data, and a combination of safety pharmacology data looking at central nervous system, respiratory, cardiovascular. Pharmacokinetics and toxicokinetics, generally toxicology, typically especially for small molecules in rodent and non-rodent species. And anywhere from short-term administration out to six to nine-month duration of exposure, depending on the type of product being developed.

Then genetic toxicology work is being done, both in vitro and in vivo. Carcinogenicity data is being generated in a product that is being exposed for an extended period of time, and a battery of reproductive toxicology studies. There can also be some product-specific assessments. If you are going into a pediatric population, juvenile animal studies can be conducted and biocapability type studies, depending on the type of

container closure system that the drug may be contained in.

We don't get all of this data right at the start of an IND submission. It comes as the development program proceeds. There are ICH, International Council for Harmonization, which has guidance, so parties from across the globe are involved in negotiating these guidance. They lay out the types of studies and the timing of the studies would be submitted for regulatory review. These include that they address small molecules, biologics and anti-cancer pharmaceuticals.

All the pharm/tox topics are considered to be important for evaluation of safety, depending on where you are in clinical development. Some may weigh more heavily than others. The expectation is that all the non-clinical topics are addressed at the appropriate time to address this scope of the clinical program.

Before I move on to the next slide, so that is for new drug development. The key challenge, when we are talking about certainly the pharm/tox group within IND and interaction with NCTR is that all of the data we get is generally being provided by the drug sponsor. If there are gaps in the types of data that we have, typically the review revisions are going to go back to

the sponsor and ask them to generate that data.

So in those cases, there is generally not a role for NCTR tox staff to step and in and conduct those studies where it is really the responsibility of the drug sponsor. But it is in cases where older drugs that have been around for a while that are off patent. We don't have regulatory discretion in terms of asking a sponsor to conduct studies. But we still feel it would be useful to have that data generated. That is when we tend to see that interaction between NCTR and the Office of New Drugs in terms of are there things NCTR can do to fill those gaps.

Some examples of those, and these came up yesterday, is in our division of non-prescription drug products, work has been done in terms of oxybenzone reprotox and carcinogenic assessment of triclosan. And then the assessment of pediatric anesthetics for the Division of Anesthetic and Analgesia in addition products.

The last I saw, there are approximately 70 current CDER NCTR collaborations. Not all of them are with the Office of New Drugs, but a good number of them are. Some current collaborations include addressing critical gaps in safety assessment of widely used and/or

widely available drug substances. One thing, and again this came up yesterday, a collaboration with our Division of Non-Prescription Drug Productions in terms of reviewing monographs. There is a very significant backlog in that work. NCTR has been stepping up to help out with that review work.

In addition, many Office of New Drug staff serve as co=PIs on various projects including research on drug-induced cardiotoxicity and genetic toxicology. In addition, the proposals will also be submitted around the Office of New Drugs for staff that have particular experience to provide comment in terms of where do those programs fit into the regulatory context.

In addition, we did have the opportunity to send one of our pharm/tox reviewers down to NCTR this past summer for a two-week period to do some training in neurotoxicity methodology. That was very useful. It would be great to be able to coordinate some activities like that in the future.

A couple of other things, not on my side, but we also have had the opportunity, especially with Donna's help, in terms of identifying researchers at NCTR to provide either webinars or in-person lectures to review staff in areas that the reviewers would find useful and

fits into the context of things they are working on in their review work. That has been very useful in terms of educational training type activities.

Potential collaborations on nonclinical programs for new drug approvals, so new entities, and some of these issues came up yesterday. How do we better extrapolate the relevance of non-clinical toxicology findings to humans and translate those findings to human risk, especially in areas selling genetic toxicology, carcinogenicity, and reproduction and development? There was some conversation going on yesterday in terms of we are conducting carcinogenicity studies often on rats and mice. The big question is how relevant is that data in terms of human risk. Oftentimes, it is not considered to be directly relevant. Certainly, there are areas for improvement in that arena. There are efforts going on within ICH right now to address that, as well.

How do we better identify and evaluate alternative testings or refinements to current testing strategies to improve prediction of human risk? There are efforts going on within ICH in terms of the reproductive testing battery to potentially include alternative assays under certain scenarios. Things like zebra fish, which were discussed yesterday, and

microphysiological approaches such as human tissues or human on chip. There are a great deal of efforts going on in that area. It remains to be seen where we will go with that type of technology.

That is the end of my presentation. I will now turn it over to David.

DR. STRAUSS: Thanks for the opportunity to talk to you this morning. I am the acting director of the Division of Applied Regulatory Science and the senior advisor for Translation and Experimental Medicine in the Office of Clinical Pharmacology and Office of Translational Sciences.

So what do we do? We promote innovation and drug regulatory review, assure the validity of clinical trial design and analysis. We develop and apply quantitative approaches, promote scientific collaboration, and ensure alignment of CDER research with CDER goals.

Within the Office of Clinical Pharmacology, we evaluate PK and PD, understand inter-patient variability, optimize dose and dose regimen to balance benefit and risk, and conduct research to advance clinical pharmacology and better evaluate benefit and risk.

The Division of Applied Regulatory Science

started a few years ago after reorganization and has the vision to move new science into the CDER review process and close the gap between scientific innovation and product review. We perform mission-critical applied research to develop and evaluate tools, standards and approaches to assess the safety, efficacy, quality and performance of drugs. We also perform expert regulatory review consultations for immediate regulatory needs, such as mechanistic evaluation and biological plausibility of new safety signals that may emerge in the post market setting.

We are prioritizing the translational research and review. We have collaboration throughout CDER and with other offices and centers, along with external to the agency. We seek to implement new regulatory review methods and programs. We have a very broad multidisciplinary staff, probably 20 different backgrounds, pharmacologists, toxicologists, clinicians including physicians, veterinarians, pharmacists, other types of biologists, chemists, and computational and quantitative background folks. We have approximately 60 staff which half are FTE government staff, and half are ORISE fellows with a couple of contractors.

I am going to briefly go over some projects in

our division, some of which are collaborations with NCTR. We seek to modernize toxicology and safety pharmacology with humanized assays and genomics. We perform research and review with bio analytical, pharmacokinetics and drug-drug interactions. And use informatics tools for mechanistic safety and regulatory review consults. The sub bullets I am going to go through on the next slides.

Probably our biggest effort in the division that I am very involved with is called the CiPA initiative, Comprehensive In Vitro Proarrhythmia assay. The goal here is to actually completely change how proarrhythmic assessment is done for new drugs in developing new in vitro and in silico paradigm for cardiac safety evaluation that will provide a more accurate and comprehensive mechanistic-based assessment of proarrhythmic potential.

There are four different components to this. The high throughput assessment of effects on multiple ionic currents is in contrast to the current paradigm that only looks at one, the hERG or IKr current. To integrate all this information together in an in silico model of the human ventricular cardiomyocyte and output a proarrhythmic score.

The third component is in vitro effects on

human stem cell-derived cardiomyocytes. This is to check that nothing major was missed from the first two components. Finally, instead of through QT studies, two perform an ECG assessment in early phase one studies to make sure again nothing major was missed, such as a human-specific metabolite or inappropriate predication of protein binding.

In collaboration with the large international consortium, partially coordinated by HESI and some other non-profits, we have all the major global regulatory agencies involved. We are contributing to all of these different components. There is ongoing validation studies, including over 20 labs around the world.

This is one recent publication, Toxicological Sciences, that was a, I will say, pilot, but it was a very large study for the stem cell derived cardiomyocyte component. We did have some collaborators from NCTR. Li Pang did some experimental work here. We did a lot of work at White Oak and CDER and DCRH.

The goal is that standardized mechanistic-based studies can be applied early in drug development to aid and compound selection. Drugs that may have been dropped from development under the current paradigm could have a clearer path to advance. Drugs on the market, QT-

prolonging drugs that are not proarrhythmic could have labeling updated to reflect this. This could be a model for mechanistic-based approaches to be applied in other drug safety areas. We have been interacting with the ICH group and hope to complete all the validation qualification studies by the end of 2017, with the goal of revising or replacing the two relevant ICH guidance.

Other areas, we have a program with humanized mouse models that either have a human immune system, a human liver or both. These models serve to better understand safety concerns for both small and large molecule drug products, especially relevant for immunotherapies. They are being assessed for bio similar versus originator biologics, toxicity, hypersensitivity, drug metabolism and drug-induced liver injury.

We have also done work with micro RNA biomarkers. We focused on drug-induced pancreatic injury, where current biomarkers are not ideal. As most of you are likely aware, these are non-coding RNA molecules that bind to target mRNA causing gene silencing. They can be released from specific tissues. They are stable in bio fluids. We performed a series of studies in mice, rats and dogs looking at microRNAs for drug-induced pancreatic injury.

We have a very active chemical informatics program that creates chemical structure-linked toxicological and clinical effect databases, develops rules for quantifying in vitro, animal and human endpoint data, and develops prediction models through collaborations with multiple companies. We have ongoing research projects to develop (Q)SAR models for bacterial mutation compliance with the ICH M7 guidance and (Q)SAR models for carcinogenicity and ICH S2 genetic toxicity endpoints. One of our emerging areas is using (Q)SAR models for speeding the development of drugs with severely debilitating and life-threatening diseases.

We have a bioinformatics program. As we know, clinical trials do not identify many serious adverse events that lead to safety label changes. We perform research to advance and validate methods and biomedical informatics to enhance pharmacovigilance and inform drug labeling. We are evaluating the performance of software that generates target adverse event profiles. I have a schematic here where this is the set of adverse events associated with a pharmacological target that could go across multiple drugs.

Our chemical informatics program is most active in terms of regulatory review consults. This has

increased dramatically in recent years with new ICH guidance and specifically the ICH M7 guidance. We also have additional non-clinical and clinical (Q)SAR models that I have listed here on this slide.

Our consults here are approximately 20 percent for new drug products and 80 percent for generics, which is driven by this ICH M7 guidance. We also perform additional consults, 25 to 30 a year, that are more in-depth and start with review of existing data and literature. We will often incorporate the biomedical and chemical informatics analysis, and sometimes extend to targeted laboratory investigations.

So moving forward, we want to modernize pharmacology and toxicology to advance drug development. We want to move new science into the regulatory review process. We can incubate new tools or approaches in our division at times. I think there are a lot of opportunities for advancing the CDER NCTR collaborations. To collaborate on research with experimental or computational work occurring both at NCTR and CDER, tackling complementary aspects of a project. We have done some of that with a stem cell-derived cardiomyocyte.

I think it is key to further engage CDER scientists and again to validate and translate laboratory

and computational models into the CDER review process. So thank you very much. Tim, if you want to come back up if there are any questions.

DR. PHILBERT: Thank you. That is a lot of information.

DR. LANZA: One of the things that I work in, and it is a problem, is that we are seeing more and more expensive drugs, personalized drugs. But the contrast agents we have available to us are really legacy.

We know that we have the ability, as the field has moved on now, over 20 years, to actually sub stratify patients, so they wouldn't necessarily get a drug that may have harmful effects, but not have very much likelihood of positive effect on there. The risk benefit is shifted.

Sometimes you can consider doing that with a nuclear tracing. But if you looked across the field of nuclear tracers, really there hasn't been a lot of change in terms of the risk benefit. I work on nuclear. They tend to bind to a receptor that might be used for many different cell types or used on many cell types, not specific to a pathology. But many of these other contrast agents, particularly for MR or something non-invasive, are.

But the field itself has died. It has died because the barriers to translation, both from the standpoint of treating it like a drug and also the need maybe for zero risk, and also the reimbursement cost, which isn't your problem, but for having done that, what the chances are that they will ever get the money back. It essentially killed the field. Yet, we are using more and more personalized medicine.

I wondered if your agency is actually looking at this problem to see what could be done. Is this the right way to do it? Are we just going to exclude these types of technologies from now to forever? As the cost of development gets higher and higher, the will to development gets lower and lower.

DR. MCGOVERN: I don't work directly in that area, so I am not aware of any specific programs going on to address that particular issue. There could be some that just don't run by my desk.

DR. STRAUSS: So you are specifically talking about contrast agents? Yes. I mean, in general, the center has pushed forward a lot of new innovative approaches to speed development in certain areas. But I am not extremely familiar with the contrast agent development. I have some familiarity with MR and the

contrast agents there. But in terms of the pathway for new contrast agents, something we could look into.

DR. LANZA: It is the same as a drug. The other thing I will put out to this, there is a contention between the pharmaceutical industry and imaging. The fundamental contention is we don't want to have an imaging gateway. I will give you breast cancer. We want to treat all the patients with breast cancer with our drug. We don't want to limit our market by having an imaging or a sub stratifying gateway.

I would argue that given the cost and risks of some of these drugs, it would be useful to have a gateway, if it could be done with a blood assay, fine. But if it can't, it really needs to be done with imaging. Imaging is actually in the patient on the tissue-level.

The other side of that is, is it really the goal of us as you, as regulators, to allow drugs to be used widely because you have no evidence to sub stratify, even when they only may work on 20 percent of the patients.

PARTICIPANT: Those are clinical questions. I don't get into that.

PARTICIPANT: I would just say if there are specific issues in that area, it is not uncommon that a

group from industry may approach a given division and seek some form of interaction to communicate on issues like that.

DR. SLIKKER: As you are well aware, the use of imaging not only for the clinical situation, but for preclinical studies, is really advanced. Actually, HESI and other groups have orchestrated large numbers of clinicians, fundamental researchers and regulators to bring them together from academic centers to try to understand how we can better use preclinical imaging to help the review process move faster and quicker and develop translational biomarkers that really are already currently being used in the human population.

I think this area is developing. It has been slower than we wanted. I have been working on it for 12 years now. It has moved a little bit. But the problem is that we need standards that we can use in preclinical imaging assessments, so that they can be easily translated between laboratories and between laboratories up to FDA for regulatory purposes.

We are making progress. We need to make more. But there are projects right now going on. Meryl Paule talked about one of them. He might want to bring that one up again, that we are doing with the clinical staff

within CDER to really understand more about these contrast agents. Meryl, do you want to say something more about that, that you did yesterday?

DR. PAULE: This is Meryl Paule, NCTR. There is clearly an interest and concern about the contrast agents being used. We are trying to move that forward by studying those in terms of the pharmacodynamics and look at the toxicity and the possible downsides of the use of those agents.

DR.STRAUSS: I just had a couple of extra comments. Many people may be familiar. We have a biomarker qualification process in CDER. Also recently, CDER published all the biomarkers that have been used in drug approval in the past for NDAs. They are sort of legacy biomarkers that have been accepted.

We also have a new program started a couple of years ago. It is called the Critical Path Innovation Meeting, CPIM. For instance, if you had a group or some kind of consortia of academia industry that was interested in this problem related to developing new contrast agents, you can come in for a sort of formal/informal meeting. We don’t discuss a specific product, but it is broader questions. This might be an appropriate area for something like that. If you want

more information, I could send that to you, or you could look up the Critical Path Innovation Meetings for CDER.

PARTICIPANT: Underlying some of those questions is a principle that I don't think we have come to grips with. We are getting better on the efficacy side with doing precision medicine and adaptive clinical trials. We are getting there. We are doing a lot of data mining to look for better outcomes.

Is there anyone doing work on what precision medicine means for toxicology and safety? We would exhaust the world's supply of rodents if we tried to do it agent by agent. I don't think we have anywhere near enough information on the structure activity relationships, even within a class, to predict the toxicity. Is anyone at the agency thinking about how you go after safety as we get down to Ns of one?

DR. STRAUSS: I think the biggest application is with the human-induced pluripotent stem cell-derived cell types. There is a lot of interest in academia and lots of publications about using patient-specific stem cell-derived and cardio myocytes for instance.

There are different groups developing libraries of IPS-derived cell types from patients with different diseases. I think there is some more work to be done in

terms of standardization of those assays. That is where I see as the most promising area in the sort of precision medicine for safety pharmacology and toxicology. We do have some areas, some active work in that area, at CDER.

DR. PHILBERT: In collaboration with NCTR?

DR. STRAUSS: We do have some in the stem-cell derived cardiomyocyte space. Actually, we sponsored a small clinical trial related to the new ECG methods to differentiate effects on repolarization and proarrhytmic risk. We then consented all the subjects to have human stem cell-derived cardiomyocytes developed. Most of that work is going on at White Oak at FDA.

But we have been talking about potentially sending some of those cells for collaboration here. We are going to be bio banking all of those cells actually, so anybody can use them. But I think, yes, it could be an area for future growth and outside of the cardiomyocyte space.

PARTICIPANT: It just might be an area for agency-wide collaboration and thinking about you get one patient on a beautifully tailored biologic. They have an MI. Is it agent dependent, or were they going to have it anyway? I don’t think any one of us knows how to evaluate that.

DR. REISS: I just wanted to comment to sort of say how things are inching in the direction of trying to use risk stratification biomarkers and so on and so forth. Again, as we were talking about yesterday, it is the issue of sort of the translation of what is seen either in vitro or in vivo.

A good recent example of the use of biomarkers is Keytruda and PD1 biomarkers. That actually has been moving in that direction. Another example I think on the safety side, on the toxicological side, an attempt was made. But then once the clinical trials were done, the benefit seemed to be small as the story around Coumadin and what not, using the polymorphisms there. It is inching, but it is difficult. The translation is difficult. It is proof that the studies can be large and costly.

DR. SLIKKER: In addition to the cardiomyocytes, which I know we are doing work in conjunction with your staff, you guys have some great projects in that area that we are hoping to continue to interact with in the area of neural stem cells. There has been a lot of work on again focusing on the anesthetics. Joe Hanig from CDER working with our staff, we worked through organotypic cells. We worked through

rodent stem cells. Now we are moving to human stem cells to be able to more systematically evaluate the impact of these particular anesthetic agents on developing neurons.

I think that there are several different pathways, as has been talked about as far as using stem cells and also using imaging in a more constructive way to try to guide how we might really implement precision medicine. It is going to take cells from you to solve your problem. We don't need 100 rodents. We need your stem cells. Then we can evaluate those and how they are responding to medicines or to pathways of potential toxicity, and get an answer for you, so that then we can use that to correct your issue. I think we need to learn from the rodent species. But we need to really move as quickly as we can to stem cells from the individual to make these individual decisions.

PARTICIPANT: I don't want to get too deep into this because I think we could go all day on how we would build this strategy. I think what we are highlighting is this is an area for discussion. Perhaps even building a framework for what does personalized medicine mean? How is it likely to be implemented in the short-term? What do we need to know in terms of risk stratification? There are autologous platforms, there are heterologous

platforms. There are sort of completely de-novo platforms building molecule by molecule. I don't think we know yet what we ought to be looking for.

DR. SLIKKER: Actually, we are in communication. We try to keep in close communication between the folks in my group and certainly Li Pang and David's group. But we have set up a communication with folks in the Medical College of Wisconsin and at Stanford for getting personalized iPSC cells to develop into cardiomyocytes. So in that sense, there is an ongoing effort to look at this in terms of individualized cells.

I also thought I would throw out a perspective on that, which is that is personalized medicine from the genetic standpoint and doesn't necessarily capture the fact that by the time somebody is having heart disease, their genes are only part of the story. I think when we talk about personalized medicine, it is a truly agency-wide discussion. But it should take into account biomarkers that we can monitor that really kind of assess the phenotypic of the person.

DR. LANZA: I don't mean to beat a dead horse, but the one thing I didn't even want to mention. I was at a ACC meeting with all these people, where they had all the best people basically, including nuclear, all

imaging agents. It had to do with the issue that even for these nuclear tracers, which might be effective preclinical, they can't piggyback on say a statin study.

The investigator is worried about using a probe that is either unapproved or having two unapproved probes. Even when it is the logical bridge from preclinical into say clinical phase one/phase two, particularly phase two. They are trying to figure out another kind of biomarker that might be as useful or substitute for an imaging marker.

If you would give some thought to this. It is not just for pushing contrast, but it is for actually dealing with better risk stratification and bridging from the preclinical work you are doing to how can we carry that into the clinical, even if it is not for an approval? The issue is safety, of course,

DR. WILSON: I just want to put out there that actually several years ago, the agency developed guidance on co-development of drugs and diagnostics. There is a regulatory pathway for building in that kind of stratification methodology into the evaluation of the new drug at the same time.

DR. LANZA: Yes. It is there, but the pharmaceutical companies just won't (off mic).

DR. PHILBERT: In the interest of time, Bill, you get the last word.

DR. SLIKKER: There are examples, though, where this has been moved forward. If you look at the NIDA-supported studies using imaging to identify in humans modifications due to drug-taking behavior, and studies that we have done in non-human primate after methylphenidate treatment, you can see that these approaches can move across species lines. I agree that it is not easy. I agree that you have to really plan in advance. I agree that we have to make sure that the IRBs are going to allow this to occur. It has to be done with the safety of the patient in mind.

DR. PHILBERT: That seems like a good place to end. Thank you both very much. Thank you, Jose.

DR. CENTENO: Good morning, everyone. Thank you for having me back. We had a little bit of technical issues here with my presentation. It was not present. It finally came through.

Before I start, I would like to mention that my comments here are my own comments. They should not be construed as official FDA. With that in mind, I can tell you all what I want.

I am going to give you a brief outline. I am

going to take a little bit of a different route to describe to you our centers, CDRH. I will give you a short introduction about CDRH and the office that I come from, the Office of Science and Engineering Laboratories. Then I would like to basically follow my short presentation based on the regulatory science priorities wishes. Actually, they are the result that we use to drive our research in both throughout CDRH and also through our research offices like ourselves.

I would like to give you a short sample about the case study where the priorities and I think are the historic collaboration with the NCTR has been key. Then I would like to, at the end, make sure a couple of thoughts, my thoughts, about the potential areas for CDRH and CTR research collaboration.

Yesterday from Bill's summary, you noticed that when you looked at this chart, they described the collaborations, the percent of collaboration projects within the FDA. CDRH was about 13 percent. Historically, that has been the case, if you will. I think that there are opportunities now that we can actually enhance or improve those type of interactions. In my mind, those will be mostly based through the implementation of CDRH research science priorities

through both centers. That is what drives our research. I think that is what will drive our collaborations.

Let me just give you a very quick overview of our center first. The CDRH is a center that has over 1600 part-time and full-time employees. It is a center that is actually composed of seven offices. Three of the offices are research offices to some extent or another. For example, the Office of Device Evaluation, the Office of In Vitro Diagnostic and Radiological Health are both review offices. But they have a component of research.

But I would say that the research arm of CDRH is the Office of Science and Engineering Laboratories. This office, in principle, we are fundamentally a research office. About 75 percent of our mission is on a research. About 25 percent is in support of the review of the consult process.

The way in which the center works on the different type of applications that we receive, probably you know most of the applications that we receive for review are based on the 510 K, which are basically the most common applications that we receive. Most of these applications predicate when it is submitted to the agency.

There are also applications that we receive

which are the premarket applications, the PMAs. These applications basically are for devices that are in class 3 devices. They are high-risk devices. For the most part, they require clinical studies.

We have also applications now for humanitarian type of evaluation devices. For example, many of you know about the Zika. The center works with one of the offices, OIR, to quickly clear the test for Zika in that particular case, to be able to address that issue. We have also what is called the de-novo applications. Those de-novo applications are moderate to high-risk type of devices. Then we have also investigational type of devices. Those are the types of applications that we receive in CDRH for clearance and for approval.

Our director is Jeff Shuren. Then we have other offices dealing with compliance. The Office of Communication and Education, the Office of Management Operations and the Office of Surveillance and Biometrics. This might be potentially the last time that you are going to see this slide because there is a movement right now in which we are trying to reorganize the Office of the Device Evaluation. There would be what is called a super office potentially in the future. That would be a little bit of a different type of reorganization that is

coming up. It is still something that is not going to take place this year and maybe not next year. But it will be something the center is looking into.

What we do, the CDRH is responsible for regulating for manufacture, repackage, relabel and import medical devices that are sold in the United States. The main mission of the center is to provide to both the patients and providers with devices that are safe, that are high-quality, efficient devices and that are both medical devices and radiation emission products.

The office that I come from is the Office of Science and Engineering Laboratories. This office is the research arm of the CDRH. The office is composed of five divisions. One division is the administrative division that allows us to operate throughout the whole office. But we have the Division of Biomedical Physics. I believe that NCTR has a couple of projects with the Division of Biomedical Physics on the imaging side, as well.

There is the Division of Applied Mechanics. Then there is also the Division of Imaging Diagnostic and Software Reliability, which kind of fall within the last discussion that we had because there is quite a bit of use of imaging technologies in this division.

Then there is my division, which is the Division of Biology, Chemistry, and Material Sciences. This division used to be two separate divisions. It used to be the Division of Biology and the Division of Chemistry and Material Science. About two years ago, we joined them. Now it is a division that is a cross-cutting division. We have basically scientists in this division. We have a multidisciplinary division with biologists, chemists, toxicologists, risk assessors, immunotoxicologists, biomedical engineers. There is a wide range of disciplines across this division.

We have three laboratories. One is the Laboratory for a Toxicology and Biocompatibility. I am going to address a little bit of that today when I talk to you about the regulatory science priorities of CDRH. The other laboratory that we have is the Laboratory for Microbiology and Infection Control. This is a laboratory that addresses, of course, infection that helps the medical devices.

Then we have the other laboratory that we have in my division is the Laboratory for Material Science and Performance. This is a laboratory that is dedicated to material characterization, dedicated to do quite a bit of work dealing with the polymer chemistry and performance.

Support facilities that kind of cross here to the NCTR, we have three core facilities. One that we collaborate quite a bit with NCTR is the nanocore that we have at White Oak. This nanocore actually is an image, if you will, of the core facilities here at NCTR. We collaborate on training. We develop training for our reviewers. We developed also the methods and to be able to characterize nano materials in this facility.

We also have the core facility for flow cytometry. We have a core facility for NGS, as well. Those are the types of support facilities that we have in our division. In my division, we have a total of about 60 members in the division and something like about 20 or 30 FTEs in our particular division.

Let me just talk a little bit about the regulatory science area. This is what actually drives our research. In CDRH, we defined regulatory science as the science and the service of regulation. This ensures that regulatory decisions were founded and achieved the desired impact on public health by developing and applying tools, standards and methodologies to study the safety effectiveness, quality and performance of medical devices, and radiation emission products under the framework of the total product life cycle.

This also facilitates good decision-making, especially in the areas of premarket, post market surveillance, compliance and communication. In doing this, we embrace a broad range of disciplines, including engineering, medicine, chemistry, toxicology, epidemiology, statistics and social sciences and other disciplines. That is the way that CDRH defines regulatory science.

The rest of my presentation here, what I would like to do is to base the type of collaborations that can develop with NCTR on the regulatory science priorities of our center. Every year, CDRH published the top ten regulatory science priorities. This goes through in a very extensive to determine what the center needs to be working in each year.

This brings together a wide range of new areas. For example, the 2016 regulatory science priorities, but the 2017 which were just published just about a few weeks ago don't differ that much from this one. They just differ a little bit in the way in which they have been written. But the main approaches are the same.

The center is getting more into the use of big data for regulatory science making, leverage evidence from clinical experience and employ evidence synthesis

across multiple domains in regulatory decision making. Improve the quality and effectiveness of reprocessing reusable medical devices. Develop computational modeling technologies to support regulatory decision making. Enhance performance of digital health and medical device cybersecurity. That is one of the very unique areas today.

Incorporate human factors engineering principles into device design. Many of the devices that seem like now have very complicated instructions on how to use those devices. The center is engaged in trying to simplify and incorporate the use of human practice in understanding the design and engineering and use of medical devices.

Modernize biocompatibility/biological risk evaluation of device materials. This is one that I want to discuss with you within the next few slides. Advance methods to predict clinical performance of medical devices and their materials. Advance the use of patient reported outcome measures in regulatory decision making. Collect and use patient experience preference in regulatory decision making.

You can see the ones that I have highlighted here I would like to touch briefly in the next few slides

with you. Those are what I think are the ones that will have the potential for collaborations with NCTR. But the rest of this regulatory science priorities, you can see that they are patient centric. Actually, the CDRH is looking to have a more patient involvement within the center. In fact, CDRH's employer is supposed to have contact activities that are related to patient engagement activities. That is to improve the way in which we include patient preference in regulatory decision making.

One of the areas that I am going to touch just briefly, and it was mentioned yesterday by the microbiology division, is the issue of infection control. The four that I highlighted in red in the previous slide, those are the ones that are directly related first to work that we do in my division and also work that we can develop in collaboration with NCTR.

The infection control is an area that is, I would say, the foundation of the public health because they are so, in terms of medical devices, today we have about maybe around something like that 1700 different classes of devices. Although it is difficult to establish what is the actual percent of the infection that may be associated with devices, the estimate is, based on that number of classes of devices, that we have

about 60 to 90 percent of hospital-associated infections or the outpatient procedures or even homecare infections are associated with or are device-related.

This is a major problem because last year, about 100,000 deaths associated with infections. It cost billions of dollars to the country. We do have actually a very well-established procedure to look at this issue. Still, we have a lot to go in terms of more research needed.

In our division, we have done research in terms of understanding the infection control and death from the processing devices, such as endoscopes, duodenoscopes and most recently dealing with heater cooler units. These heater cooler units are units that are used in surgical rooms. They are used to maintain the body temperature.

But these units have been associated with the release of non-tuberculosis type of micro bacteria. There have been high incidences of morbidity and mortality on the patients who are exposed to this type of unit. We are currently doing a lot of research in that. The FDA, through our process, has published a couple of FDA safety communications to address this issue to the health care community.

But the one that I would like to touch more on

with you is the biocompatibility research side. Biocompatibility is basically the science by which we look at the biological interactions of device or device materials with the human body. This speaks on two areas. One is exposure to determine what is released from the device and also toxicity to determine how those levers may have a risk of developing adverse health effects.

The goal here is to quantify exposure and toxicity of components released from medical device materials. We have three specific projects in which we are addressing the biocompatibility. We are dealing with color additives that are used in medical devices, absorbable polymers and also mentioned here nickel because it is an active research area. But there are many other methods that we are looking at that have to do with this issue.

Modernizing biocompatibility is a key area of research and work at the FDA. One of the goals is to include more of in vitro testing and less of in vivo animal use in the decision making. I believe that this is a very unique opportunity for collaboration with NCTR.

The other area that you saw on the list of the 10 top regulatory science priorities is the development of computational modeling technologies, both from the

point of view of simulation, statistical techniques and other type of approaches that will allow us to provide a less burdensome approach to the approval of medical devices.

This has been traditionally used in the industry settings. I think that there is a knowledge gap or application gap in the regulatory decision. The development of these technologies improved the support of regulatory decision making.

Again, just to emphasize why it is so important to look at biocompatibility and this area, we have seen in the last few years an increased number of studies that have used risk assessment and toxicology endpoints to look at the evolution of medical devices. In my mind, the development of improved tools and methods to assess and predict biological risk factors of devices, as well as integration of chemical characterization, computational or in silico modeling could result in lessening the dependence on animal testing, which is the goal of modernizing biocompatibility.

An example that I would like to give you for where these regulatory science priorities would make a big difference, we are dealing with devices that contain this material, nitinol. We are looking at the how to

develop both in vitro testing to provide real-world type of prevalence on nickel leaching from these devices and the actual clinical relevance of that approach. But we are looking to incorporate this with computational toxicology modeling.

There are many types of devices that contain this material nitinol. Nitinol is a very unique material for medical devices. It contains about 50 percent nickel. There are concerns for release of toxicities. For those of you that may not be aware of this, the historical aspect of nitinol, this alloy which is a nickel titanium alloy, actually this alloy was produced or manufactured at White Oak. It was actually made when the campus was part of the Navy. Nitinol, for example, that word means Nickel Titanium Naval Ordinance Lab. It actually came back to us now that it is used by the industry.

What is the interest that we are addressing? In the past, there have been two types of workshops or panels that have been put together by the CDRH to look at the nickel release for nitinol medical devices. One was in 2012 when there were concerns about nickel leaching testing from cardiovascular devices. The most recent one was in 2015, when there was a panel of nickel effects

from contraceptive devices. These are devices that are within what is called Essure panel meeting.

The main thing here was to look at the relevance of in vitro methods used to relate that clinical picture. Now, this is, in my mind, the source of a very successful because from the first panel, we actually collaborated with the NCTR in developing what is one of the biokinetic models for looking at nickel release from medical devices. Using this computation exposure to look at the systemic nickel release. Then we use that to basically estimate the levels of nickel in serum or urine, and using that to evaluate risk of toxicity.

This is a successful story because it is already published. But what I mean by successful story is that this nickel biokinetic model is used today by our reviewers to look at submissions, applications that come with this type of device.

What are the future regulatory and research areas that, in my mind, are areas for unique collaborations with NCTR? The need to develop test methods for evaluate, for example, the immunological response to metal and, in this case, nitinol-containing devices in response of reproductive tract.

There are a couple of projects here that we are working on. I just listed this here such that you can see the situations that are common to our center right now. We are looking to develop an organ on a chip using fallopian cells to examine localized nickel toxicity. We are using a model which is a humanized mouse to examine nickel immuno and reproductive toxicity.

This particular animal model has this tail like receptor that is sensitive particularly to nickel. We can use it in this particular animal model. We can look at nickel hypersensitivity and some other issues that we need to address for this particular area.

We are using flow cytometry to assess nickel hypersensitivity in allergic people. The reason why we are using this is because the typical type of testing that we have available to look at metal-induced hypersensitivity, not only nickel, but the metal-induced hypersensitivity is either the patch test or the MELISA test. The patch test, on this specific test, it lacks the sensitivity. For the most part, it may give false positives to this look at metal-induced hypersensitivity.

ELISA is a good test. But it uses a radioactive element. What we are trying to do is to use new technologies to get away from that type of approach.

Then the other area that I think will be a future regulatory collaboration with NCTR, as I mentioned at the beginning, is the nanotechnologies. We are working very much in two areas. One is looking at devices that have nanoparticles, either silver or titanium or iron nanoparticles. Then the transportability of those particles across different types of organs.

We are looking also at nanosurfaces, immobilized nanosurfaces that are used with different types of devices, particularly with dental devices. That is one area that I believe that we can collaborate with the NCTR.

In conclusion, I give you a quick overview of CDRH. I hope that you got a good understanding of the regulatory science priorities of CDRH. I used the case sample of nitinol just to give you an overview of why this is important for us to look at biocompatibility and the use of different types of in vitro and computational methods. The last one was basically what is in my mind the opportunities for research collaborations with NCTR. With that, thank you so much.

DR. PHILBERT: Questions?

DR. PILLAI: (Off mic) technology embedded into

the device that is probably going on the body or into the body now. A number of companies are going that direction. How do you benchmark sterilization in those instances? That leads into my second question about this reusable medical system. If you think about sterilization, the gold standard has been plate counts. But we know now that once you subject these microbial pathogens exposed to a lot of sterilization technologies, you cannot just use culture method as an index of inactivation.

That comes back to the bigger question. I think this is an area for collaboration with NCTR is defining that in bacterial cells or bacterial spores.

DR. CENTENO: The first question, we have not done that much work in terms of sterilization, when you look at combination products. So I will probably have to research that a little bit more for you. The second question is in our division, we have been looking at different test soils that allow us to improve or even replace those types of culture testing that has been done today.

Unfortunately, right now, the researcher I used to work with in this area, she passed away. Vicki Hitchins, she was one of the most renown scientists

looking at that particular area of different tests to look at the sterilizing. You can find many of our contributions on the FDA safety communications where we publish many of those.

PARTICIPANT: The only reason I say that is because NCTR has a tremendous capability, imaging and all sorts of integrated approaches to look at spores and inactivation.

DR. MATTES: I just thought I would offer the comment that indeed one of the things that has been explored with the assay referred to yesterday, this flow cytometry assay, rapid B, is not just numbers of bacteria, but whether or not they are dead using like a propidium iodide stain. In fact, I think that sort of gets at your question of assessing both total number and live/dead characteristics.

PARTICIPANT: Do propidium iodide pick up spores?

DR. CENTENO: The propidium iodide basis is the integrity of the cell membrane. But we know now that cell membrane integrity is not at all a good index of liability. You can have an intact membrane, which with propidium iodide would appear as live. But culture would appear as dead. Sterilization validation issues can be

significant. I see Steve shaking his head.

DR. PHILBERT: This also has a lot of indication for the food industry and verification of sterility.

DR. STICE: One of the common threads that I am hearing today that I am hearing through a number of talks and yesterday, this whole area of microphysiologic systems or organ on a chip type of things. There is a very organized program at DOD and NIH. I don't know if FDA has a seat at that table, and you are there. I think it is a great opportunity to take advantage of those things. I like the idea of fallopian tube on a dish. I hadn't heard that one yet.

DR. PHILBERT: Are there no other questions or comments? Thank you very much, Jose. Let's move on to the Office of Veterinary Medicine. There is no talk for that one. We just saved a little time. Actually, we used it up for coffee. Then we are on CTP. Dana?

DR. VAN BEMMEL: Good morning. I am Dana Van Bemmel. I am with Office of Science at the Center for Tobacco Products. I just want to thank the group for inviting us here to talk you a little bit about our center. We are going to talk a little bit about our mission, our current strategic priorities and the types

of research that we are funding and we are looking to fund in order to support those strategic priorities. This is a standard disclaimer.

I think many of the folks in the room are aware that in 2009, the Tobacco Control Act was signed. CTP was later created. The Tobacco Control Act, or the TCA, gave FDA the authority to regulate tobacco products as intended for human consumption. That included the regulation of the manufacturing, marketing and distribution of cigarettes, cigarette tobacco, roll-your-own and smokeless.

Some of you may not be as aware that in this last August of 2016, FDA finalized a rule to regulate products that meet the statutory definition of tobacco products. That includes their components or parts, but excludes their accessories. It made these tobacco products now subject the Tobacco Control Act.

These products include electronic nicotine delivery systems, including e-cigarettes, e-cigars, vape pens. It includes all types of cigars, pipe tobacco, nicotine gels, water pipes or hookah, dissolvables that weren't already covered under Tobacco Control Act. Then there is language written in to cover any future tobacco products that may come down the road.

CTP's mission overall is to protect Americans from tobacco-related death and disease by regulating the manufacture, distribution and marketing of tobacco products, and by educating the public, particularly young people, about the tobacco products, the dangers that their use poses to themselves and others. I took that right off our website.

These are our current five strategic priorities as outlined by the center's leadership. We are looking to advance product standards that yield strong standards to improve public health. We are establishing an integrated, FDA-wise policy on nicotine-containing products that is public health based.

We are developing rules and guidance for product review, manufacturing practices and analytical test methods. We are looking at compliance and enforcement activities around inspection, investigation, monitoring and review activities. Then we are clearly interested in educating the public and looking at educating at-risk audiences on tobacco. I won't spend much time talking about it today. But we have a large campaign out called the real-cost campaign. Anyone who has teenagers or preteens has probably seen these ads on television. They are quite engaging and award-winning

actually in some of the advertising domains.

When we think about the public health standard, you will note in our mission and around the strategic priorities, everything is around the public health standard. The Center for Tobacco Products is a little different than the other centers at FDA. We can't use the traditional safe and effective standard that the other centers use when evaluating tobacco products because clearly, I think we can all agree, tobacco is not safe. Not in the same definition that we would look at drugs, devices, biologics.

The Center for Tobacco Products looks at the public health really taking into account the risks and benefits to both the users and the non-users of tobacco products to assess a net-level public health impact around tobacco products used as we review different information that comes in to the center from different products and as we develop our guidance and other activities.

Much like the other centers that have presented earlier today, within the Office of Science, we are a very diverse group. In order to move forward, our strategic priorities, we rely on a number of different disciplines of science. These four columns across the

slide actually represent our four divisions with the Office of Science including the Division of Product Science, Division of Nonclinical Science, the Division of Individual Health Science and then the Division of Population Health Science. As you can see, we have a very diverse group of scientists who come together to develop the guidance and policies that we are working on, and to review the information that comes in from our stakeholders.

I highlighted the five strategic priorities. Given this is a 15 to 20 minute talk, I didn't have time to run through all of them. I thought in order to give some content into what the center does and the types of research that we need and that we are looking collaborate on, I would run through just a couple today.

Another disclaimer, the potential research scenarios shown in the following slides are presented as a means for illustrating types of studies FDA would find useful. These should not be construed as regulatory actions or research under the consideration of FDA at this time. Some of these examples are examples that we have shared with our grantees and other individuals who are looking to participate in our funding opportunity announcement that we will talk about later. They are

really couched around research and regulatory science.

Let’s talk a little bit about product review. When we look at product review with the Center for Tobacco Products, there are a number of pathways in which industry can put forward a review, but not just industry. When we are talking about investigational tobacco products,that could be a researcher, so looking at a tobacco product in a clinical or research setting.

We have the pre-market tobacco applications or PMTAs. We have the substantial equivalence pathway, which is essentially saying this product we believe is substantially equivalent to something that was already on the market or is currently on the market.

We have exemption from substantial equivalence. Then the final pathway is modified risk tobacco products or MRTPs. In all of these cases, the applicant must provide adequate evidence for FDA to make a finding. Then we are really using the scientific research to evaluate the evidence provided by the applicant. In the case of a modified risk tobacco product, the application may come forward to try to prove that their product is less risky than something that is already on the market. That would be a modified risk.

When we think about product review, we consider

all different aspects of the product. We think about the information related to the product, including the materials, the design, the constituents, composition and the marketing around that tobacco product. We also think about the impact that the use of that tobacco product is going to have, including its appeal, its addictiveness or potential addictiveness. How folks are actually using the tobacco products and their use behaviors.

We look at the pharmacokinetics, the toxicity, initiation and cessation all again around use behavior and how the product is actually being used. Then of course we are thinking always around public health, around the morbidity and mortality related to the products used.

I am going to switch gears a little bit to another strategic priority key area around regulation and guidance. Anyone who has heard our center director or our center leadership speak in the last year or so has heard Mitch Sellers say that one of the most powerful tools that the Tobacco Control Act gave the Center for Tobacco Products is this ability to implement product standards. Advancing product standards is something that we are very interested in.

We are looking to advance product standards

that yield strong standards that can improve public health. Again, Mitch and others have been very open about talking about three standards that we are currently exploring around addictiveness, toxicology and appeal.

When we think about product standards, product standards that FDA could consider include nicotine yields, although I think most of you are probably familiar with the fact that we can't remove nicotine completely from tobacco products. We can't reduce it to zero, but we can reduce it.

We can look at the reduction or elimination of other constituents, including those that are in smoke. We can set standards around the construction, ingredients, components, additives or other properties of a tobacco product. We can set provisions for testing or measuring product characteristics.

We could set a standard around restrictions on the sale and distribution. We could also set standards around the form and content of labeling of a tobacco product. So all of these are things, product standards, that FDA could consider.

Hopefully, that quick run-through of our strategic priorities and some of our regulatory activities gives you a sense of the types of activities

that are happening within the Center for Tobacco Products and gives you a hint of the types of research that we need in order to make our regulatory decisions and review our products.

I wanted to take just a few minutes to talk about some of the research that CTP has been funding in collaboration with other federal agencies and through contracts, again to sort of give you a sense of the work that we are doing and work that we hope to do in the future.

CTP has been fortunate, although we are young center, we have been able to fund a number of different research projects. We have a very healthy research budget. It has allowed us to collaborate with a number of different federal partners, including NIH, CDC, NCTR here, along with other funding opportunities, such as contracts with non-HHS organizations. I should say that this slide was put together based on FY15 activities. In FY16, we were able to fund some work with OSEL at CDRH, which isn't represented here. But we are looking to collaborate with our other centers in addition to NCTR. But we have been very active in working with NCTR over the last five years.

To give you a sense of our types of research

and the numbers and who we are collaborating with, you can see that our partnership with NIH is the greatest number of projects from 2010 to 2015. That collaboration is through the tobacco regulatory science program. It is a program in which we collaborate with NIH, who has the expertise in funding opportunity announcements, so from solicitation to managing of grants. We have the research need around tobacco regulatory science. Really, it has been a win-win across the board.

You can also see that we are funding work with contractors, CDC, NCTR and others. But we have grown a lot over the course of the last five years.

On the street right now, is a notice of intent to publish with NIH. This notice of intent to publish states that we intend to reissue or solicit new applications for our tobacco centers of regulatory science. These are P50 center grants currently. In this notice of intent to publish, we highlight that this will be cooperative agreements.

The first round, we funded 14 centers across the United States. We currently have this notice of intent to publish. We outlined these seven research domains that are of interest. I am sharing it with this group today because I would like to break out the

toxicity area. Within the Office of Science and the Center as a whole, we spent a lot of time thinking about what our current research needs are, where our gaps are in our research portfolio, and what we need to perform some of those regulatory activities that I touched on moments ago.

In the notice of intent to publish, this is the toxicity write-up. If any of you are interested in the other six, they are online at the tobacco regulatory science program website at NIH. Under toxicity, though, we have stated that we are looking to understand how tobacco products and changes to tobacco products characteristics affect their potential to cause morbidity and mortality. This includes animal and cell culture models, as well as novel alternative models and approaches to look at the toxicity of tobacco smoke, aerosols and other specific constituents.

Here in this announcement, we break out two other pieces. In the next couple of slides, I hope to get a little more in-depth just again to give you an idea of the types of research that we are looking for and hopefully stimulate a little thinking in ways in which we could continue these collaborations with NCTR, build upon what we are doing and perhaps start some new projects.

Around the toxicology of smoke and combustible products, we are interested in tox studies looking at constituents that are present in and result from combustion. These constituents may include harmful and potentially harmful constituents, which are listed on our FDA website if you are not familiar with them. It could include ingredients, such as flavors and other products, materials and components. In particular, we are looking to focus future research on constituents that have scientific evidence of toxicity, but limited dose response data and potential for high exposure with product use.

Very similarly, we are interested in constituents and what results from use around the newly deemed products. In particular, we are looking to focus our understanding on the potential toxicity associated with chronic use of electronic nicotine delivery systems. I noted those earlier. Along with ENDS, we are looking to fund more research and get involved in more research around cigars. Both of these, because we have a real lack of data around the toxicity of these products. Priority constituents include the components of e-liquids, other ingredients and product material components that may have potential for high scientific

evidence of toxicity.

Then finally, within that toxicity bullet, we would like to think and do more work around computational modeling and looking at developing computational modeling tools that can inform tobacco regulatory science efforts. Effective tools for integrating diverse dose response and mechanistic data in order to more accurately predict human risk. Those could include in vitro to in vivo extrapolation approaches, as well.

Currently in this FY17 fiscal year, we are funding a number of research projects with NCTR. These are just examples. This is not exhaustive. You can see I have broken it out by our key priority areas, our strategic priority areas. We are working on projects here at NCTR around product standards, informing the nicotine policy and looking at pre ad post-market review. We are trying to cover a number of different activities.

I think Meryl mentioned yesterday, too, we are looking at a concept right now around self-administration in a rodent model that would complement this non-human primate model. That is exciting. I am looking forward to that coming around in the next quarter or so.

With that, I know I have given a real quick overview of CTP and our research. We do a lot of

research of NCTR, and none of it would be possible without our collaborators. In addition to the research scientists who make the research happen at the lab and at CTP, we work closely with Brad Schnackenberg and Charlotte Ashcraft and her team here at NCTR, along with our support group at CTP. With that, I would be happy to answer any questions.

DR. PILLAI: Does CTP have its own lab in Washington, DC area?

DR. VAN BEMMEL: We don’t have our own labs, no. All of our research is through collaborative efforts.

DR. PHILBERT: It is clear that you regulate more than just tobacco. Nicotine is an ingredient, not tobacco, per se. Are you addressing at all the way that kids use these vaping machines by supplementing with carbinol and some even using opiates?

DR. VAN BEMMEL: Right. The way that the Tobacco Control Act is written, we regulate products by which nicotine is derived from tobacco. So any tobacco product that is derived from tobacco. In most cases, when you are looking at those electronic devices, the nicotine has been derived from tobacco. It does fall within our regulatory authority, as long as there is not

a therapeutic claim, which punts it over to CDER.

With respect to how they are using the product, we can only regulate the product based on its intended use. Although we appreciate that there are use behaviors that are happening particularly around electronic devices and marijuana use, it is not just there. It is with blunt use, as well. We are funding some research to try to understand how that dual use is happening and how that impacts their overall use. But we can't regulate those products clearly.

DR. PHILBERT: But you aren't prohibited from doing research in that area?

DR. VAN BEMMEL: We are not. I moved through rather quickly, but within the PATH study, the Population Assessment of Tobacco and Health, that is a collaborative cohort study with NIH. It is a NIDA contract that we fund. That is a longitudinal cohort study. It is going into is fourth year in the field. We are able to ask about other substance use. We do ask about marijuana use. We ask about alcohol use and tobacco behaviors. We are able to ask those questions and do research around that, as long as it informs our overall understanding of the tobacco product use and how people are using that tobacco product.

DR. PHILBERT: Questions, comments?

DR.REISS: I just sort of have a question about your relationship with NCTR. It sounds like, at least the way you presented it, that a lot of your sort of scientific agenda is done through a competitive process. You can correct me if I am wrong. But is it the same thing with your relationship with NCTR? Do you have more of a sort of direct relationship, collaborative relationship, rather than part of the competitive environment?

DR. VAN BEMMEL: You are right in that because most of our research dollars are going through NIH, it is a competitive peer review process. With NCTR, it is not equitable in that competitive process. We are encouraging our scientists from both sides at NCTR and CTP to be talking and working together when they identify opportunities for collaboration to develop concepts.

The hope is that collaboratively our scientists on both sides are working to develop those concepts that then have to run through approval both at NCTR and Office of Science at CTP. Then from those approved concepts would come proposals. It is a little competitive in the sense that, just like any other center or institution for that matter, you have to look at your overall research

dollars and prioritize. It is not as easily aligned in a peer review process as you would have with NIH.

DR. YEAGER: I just wanted to add that when Dana said she talks about the collaborations that we have with NCTR, a lot of those are discussions that are happening on what possibilities may occur and what may happen. But they can be frugal from a small little project that develops a small idea and moves off to the larger things like the inhalation core that is actually an ongoing thing that occurs at NCTR. You can run the gamut with the type of projects that are covered.

DR. VAN BEMMEL: I know their centers work with Donna to help identify where there could potentially be expertise when there is a need that arises. I must admit I tend to go straight to Brad as our liaison to CTP. Nothing personal, Donna, but I go right to Brad. We are communicating all the time. I think that is key to making a successful collaboration is just constant communication. There might be too much communication. Brad can weigh in on that. He might get tired of hearing from me. We try to keep those doors open.

DR. PILLAI: Does your office control like the potential aerosolization of methyl nanoparticles from these vape pens and e-cigarettes?

DR. VAN BEMMEL: Certainly nanoparticles are something that we are interested in. We are interested in all components that may be present in these aerosols. I think we just don't know enough. But these nanocomponents are being aerosolized in an e-cigarette or an e-cigar, then certainly could be regulating and looking at that. We are funding a lot of research around electronic delivery devices.

DR. YEAGER: (Off mic) that goes in other areas. CTP does rely on some degree of leveraging. In the sense that any questions that come up identifying like what NCTR does all around nanomaterials having an understanding of what is in the literature, what the nanocore is doing in NCTR, what the nanocore is doing in CDRH and having an understanding and moving in that direction. But I think it is not something we operate in isolation. We have to collaborate with others. We need to leverage what others are doing.

DR. PILLAI: There are a lot of these importers from China, not necessarily China, a lot of other countries, who bring in these e-liquids, et cetera. Where does the regulation actually interact with the actual retail of those materials? Is it at the point of sale? Is it the import?

DR. YEAGER: A tobacco product would be regulated as it is used in the product. It is a finished product. If you sell an e-liquid separately, that would be regulated as its own product. If it is with a kit, then the whole kit gets regulated, which includes that e-liquid. But in a sense it is what the final product that goes to the consumer is.

DR. VAN BEMMEL: I think if I understood your question correctly, we regulate it at the point of sale. So we regulate the product manufacture, distribution and marketing of the product. It is not necessarily the import into the country, if that is what I understood.

DR. PILLAI: So all of these retail stores should have some sort of paperwork to know they are approved or to sell these products?

DR. YEAGER: Well, a manufacturer, if something goes to a point of sale, a manufacturer should have an order that they have marketing authorization order.

DR. VAN BEMMEL: But I will say, and there is not time to go through it all now because it is very detailed, but within the deeming rule that was finalized in August of this past year, there is a lot of enforcement. It is outlining the various enforcements. You are talking very specifically about some products

that are just newly regulated. Someone may not have that piece of paper in their pocket yet. It may not necessarily be required. It is very detailed. I would invite you, if you are interested, to go under the website.

DR. YEAGER: There are a lot of nuances to it, too.

DR. PHILBERT: There is a lot of emerging evidence that side stream smoke is dangerous. Are you looking at sort of secondhand vaping?

DR. VAN BEMMEL: So you are talking about the secondhand exposure to aerosols? Yes. We are funding research in that area. We would be interested in looking at that. I think that falls under this whole umbrella of what we don't know around the electronic nicotine license.

DR. PHILBERT: There are no other questions?

DR. MATTES: One question that came up when you were talking about the law sort of allowing you to or mandating, whatever, to set product standards. The question that comes to mind is that I understand that there can be additives and components of tobacco or cigarettes or e-cigarettes that are addictive above and in addition to nicotine. So could there be a standard

set for addictiveness that would allow, let's say, circumvent any effort to increase or maintain addictiveness, while reducing nicotine?

DR. VAN BEMMEL: Right. So really, any constituent within the tobacco product is something that we can regulate. As I showed, we are definitely looking at product standards, and we are interested in exploring product standards around addictiveness. I think it is fair to say that can include a number of constituents within a product.

DR. PHILBERT: Thank you very much, Dana. John will lead us through the Center for Veterinary Medicine.

DR. GRAHAM: Okay, thank you. I will try not to keep us too long and get us back on schedule.

DR. PHILBERT: We are doing fine because we are vetting a great deal of discussion in each one. Please take your time.

DR. GRAHAM: So for the benefit of the new members of the advisory board, I am going to give a very brief overview of CVM. Our acting director right now is Tracy Forfa. Dunham left last spring. We are actively looking for a new permanent director.

There are five offices underneath. The center director as you see. Primary offices are the Office of

New Animal Drug Evaluation, where new animal drug applications are submitted. The Office of Surveillance and Compliance, which are our post-marketing efforts. The Office of Research, where we conduct research in support of regulatory decision making both at the Office of New Animal Drug Evaluation and for OSC.

We also have an Office of Minor Use and Minor Species that don't cover the major animals that you would think of, cats, dogs, horses, cows, pigs, chickens, and turkeys, I believe. There are seven major species. Everything else in veterinary medicine is considered minor.

At the Office of Research, which is located in Laurel, Maryland, away from White Oak by about 20 minutes where the majority of the FDA sits in the DC area, we have got three research divisions and two special programs that I am going to briefly go through. Our division of residue chemistry is led by Dr. Phil Kijak. We are focused on the things you see up here. We conduct new animal drug application method trials.

If a sponsor has a drug that is to be used in a food animal, the sponsor must develop a method that can detect that particular drug or its metabolites in edible tissues. That method has to get validated in a couple of

labs, a government lab and a non-government lab. We are the government lab that validates that method. Those trials, typically what happens is the sponsor comes in, teaches our staff the method. Then we go on to validate it under good laboratory practices and only if we can successfully show that the method does indeed detect the drug in edible tissues. That becomes part of the evaluation to approve the new animal drug.

We also look at test kits for looking at various drugs in the milk supply in the United States. Right now, test kits that are out there are only testing a limited number of antibiotics. We are looking to expand the number of veterinary drugs that could be detected in milk to protect the milk supply in the United States.

We look for mycotoxins in animal feed. A real hot topic is antibiotics in distiller's grains. I am going to have a little bit more to say about what we are doing in the way of antimicrobial resistance in a few slides.

But in the ethanol industry here, fuel ethanol not the drinking kind of ethanol, antibiotics are used to keep bacterial loads down, so that the product has a higher yield and doesn't get eaten away. Well, if you

think of the grains that are used, especially the corn grains primarily in corn ethanol, you can think of them like little English muffins with all these nooks and crannies that the antibiotics get into. Well, we have been able to show through research that those very low levels of antibiotics are enough to select for antibiotic resistance.

This is kind of a political issue because if you try to pull the use of antibiotics off, the ethanol industry gets mad at us for trying to curb their profit by limiting their yield. The farmers or the producers of large animals that use those grains for feed get irritated that a large supply of nutrients has been removed. I stay out of the political part of that. But the science is what helps drive regulatory decision-making. Indications are that there amounts of antibiotics in those distiller's grains that are contributing to the rise in antimicrobial resistance. Finally, we screen for hormones in animal muscle, as well.

Our Division of Applied Veterinary Research, we cover a number of things. We do our milk and meat safety there. Oftentimes, we need to incur a specific drug or chemical in tissues that are then analyzed by others. We

incur those tissues.

We have a large agriculture research facility with all of the major fish species that humans consume. We do some antimicrobial resistance research in those fish. But we also have some disease models that look at efficacy of some of these antibiotics in treating some of these diseases in fish.

We do a significant amount of work in antimicrobial resistance. Again, I am going to talk more about that in another slide or two. We do have a program in biomarker research where we are looking for biomarkers of inflammation. We have been going back and forth with Meryl and the Division of Neurotoxicology here at NCTR to kind of share information on the biomarkers that we are finding.

Of course, animals can’t tell you, on a scale of one to ten, how much pain are you in? That also makes it difficult for judging the efficacy of drugs. So we are trying to create a model that sponsors could use, so that when they submit data, they can show to us that indeed the anti-inflammatories for these animals are indeed efficacious.

We have a very active program in genetically-engineered animals, which are considered drugs, not

animals. They are regulated just like drugs are. You have heard in the news the term, frankenfish. These are salmon that grow very large very quickly. Whenever there is a genetically-engineered animal that a company wants to put on the market, they have to have a validated method that can detect the DNA of that specific genetically-engineered animal. The fear being that, at least as far as the salmon is concerned, they don't want the salmon getting out into the wild and transferring that DNA to other fish. We have to make sure that doesn't happen.

There are other genetically-engineered animals. There are some genetically-engineered pigs that are being used for harvesting tissue for use in human transplantation that have been modified in such a way that reduces the likelihood of rejection. There are GE chickens that we have been working on. That is kind of a hot up and coming issue. More and more, we are seeing genetically-engineered animals.

Of course, this, too, has a political backlash because any time you say the words, genetically engineered, the general public goes into a panic. Although, if you look at the ingredients on many of the foods you eat, especially those that are plant-based,

people are eating genetically-modified stuff all the time, every single day. They are safe. It is just the perception issue.

We are also starting to do a lot of work in stem cells. This is another area of potential collaboration with NCTR because you have been doing the stem cell work longer than we have. Now, our stem cells are primarily derived from horses and dogs because those are the veterinary products that are being proposed for use in veterinary medicine.

Our Division of Animal and Food Microbiology is led by Maureen Davidson. This is where we look at antimicrobial resistance mechanisms and evolution. We have been working closely with Steve Foley in the Division of Microbiology here, where he talked to you yesterday about some of the studies that his division has been working on to help support our efforts here. They have been critical in helping us with looking at virulence factors, for instance. Besides working closely with the Office of Research, he also works with personnel in ONAID who are helping to review some antibiotic drugs that are coming through.

We do routine testing for NARMS. I will talk about NARMS in a minute. Plasmid sequencing, we look for

biological contamination and antimicrobial resistance in animal feeds. Of course, we are doing whole genome sequencing, which leads to the whole issue of large quantities of data and infrastructure that is needed. I kind of complained about that last year, and nothing has really changed to improve the situation. I am sure next year when I am standing here, I will be repeating what I am just saying now. It is a challenge for all of us.

I did like the talk about the liquid biopsies that we heard yesterday, where they were referring to use of cloud computing. I think he was using Google Cloud. It is unclear to me whether or not the FDA is pursuing a similar type of thing.

Of course, you need specialists to be able to analyze all this information via bioinformatics. This is another area that I think would be right for us to get further assistance from at NCTR for their Division of Biostatistics and Bioinformatics.

So NARMS, quite quickly, monitors trends in antimicrobial resistance amongst foodborne bacteria from three sources, humans, retail meats and animals. We look at it from a farm-to-fork continuum. We try to disseminate timely information on what we found and conduct research to better understand who antimicrobial

resistance emerges, persists and spreads.

NARMS is basically a combination of the CDC, the FDA and the USDA looking isolates that come from either humans, retail meats or on the farm or at slaughterhouses from animals. That data now all gets integrated. We can actually trace how antimicrobial resistance can move from the farm to you, as a human, through the food chain.

Our Veterinary Laboratory Investigation and Response Network, shortened as Vet-LIRN, is a network of 38 laboratories across the United States and one at the University of Wealth in Canada. We are looking for trends in illnesses or deaths in animals. So either an individual pet owner can directly report to the FDA a problem that they have had with their pet. I fed Fifi a new food, and then Fifi immediately started vomiting. All the other cats in the house started dying.

Or veterinary services could also notice some sort of trend and get it reported to us. This network that is set up allows us to send biological samples and potential necropsies to different labs across the United States to get evaluated to try to track down exactly what the problem is.

More times than not, the problem is not related

to the food that the animal has gotten. There is some sort of underlying disease process going on that nobody really knew about. But every now and then, we do find the problem did come from food, and there are pet food recalls. Listeria seems to be on the rise in pet food. We end up noticing these things early and then FDA taking regulatory action to get these products pulled from the market.

This Vet-LIRN actually started in 2010 really as a result of the melamine cyanuric acid issue that started cropping up in 2007. We are still actively involved with NCTR on research in melamine and cyanuric acid. There are ongoing studies.

Some of the things that we are finding in the pet cases that are coming through indicate Fanconi Syndrome, which is an effect on the proximal tubules in the kidney. We see that with cyanuric acid and melamine. We are not sure what is causing the current issue. So a lot of things are happening related to jerky pet treats. We haven’t nailed down exactly what is causing that problem.

I want to take you on a quick tour of an example of a study or a series of studies that was done that had definitive regulatory impact that we conducted.

This deals with arsenic-based compounds. This also helps further bolster why Fred Beland is working looking at arsenic and why arsenic is still so important to public health.

There have been organic-based arsenical compounds used in chickens since 1944 when the drug, 3-Nitro was approved. The active ingredient in it is a chemical called roxarsone. There are also some organic arsenicals that are used in chickens for growth promotion, feed efficiency and improved pigmentation. You see them listed there, nitarsone, arsanilic acid and carbarsone.

These organic arsenicals, especially roxarsone, were approved to be used either standalone or in combination with other drugs to also prevent coccidiosis, which is a parasitic disease that infects the intestinal tracks of chickens and can wipe out a whole colony relatively quickly.

When roxarsone and the other organic arsenicals were approved, it was assumed that organic arsenic and not inorganic arsenic would be excreted from the chickens. Of course, the organic compounds are much less toxic that the inorganic compounds, which are known to be human carcinogens.

The inorganic exists in two forms, arsenic three and arsenic five. There were concerns that we were finding inorganic arsenic in the meat of the chickens that were fed roxarsone. In 2009 and 2011, we conducted studies to answer the question, can an approved organic arsenical like roxarsone, when it is incorporated into chicken feed and fed to chickens according to the approved label directions, result in the presence of inorganic arsenic in edible tissues. We were able to develop and validate an analytical method that could pick up organic and inorganic forms of arsenic in chicken meat.

What were the results? Well, the livers of chickens given feed that contained 3-Nitro had concentrations of inorganic arsenic that were higher than inorganic arsenic concentrations in the livers of chickens which were given non-medicated feed. We presented this to the sponsor of the drug, trying to get them to pull the drug off the market. They said, well, we don’t like your science. We have some questions.

There were four questions that they identified. Is the homogeneity and stability of roxarsone okay in medicated feed? In other words, they were worried. Did we mix it in a barrel and have the stuff float down to

the bottom of the barrel, so that when we tapped feed at the bottom of the barrel to feed to the animals, they were getting an increased dose of roxarsone.

Could the inorganic arsenic found in the livers of those birds come from a source other than the medicated feed? We used alkaline tetramethylammonium hydroxide, or TMAH, as a solvent to detect arsenic species. Their question was, well, could that particular method degrade some arsenic species into inorganic species. The fact that we stored these tissues at minus 80 degrees for a period of time and then thawed them out to do analysis later. Did that freezing thawing have any effect on the arsenic species that were found?

We ended up in 2012 starting another round of tests. The first thing we did was look for the stability of roxarsone in medicated feed. Here you see one of the 55-gallon plastic drums that we stored the feed in. The feed were in 50-pound batches. You see the top of the can here has a bunch of different holes drilled in it. We used these very long cars in order to take samples of feed from the top, middle and bottom of each batch, and look at the stability of the roxarsone and the arsenic species in that feed over time, from the time the feed was mixed, day zero, to two months later, which covered

the period of the in vivo studies.

What conclusions did we find? Roxarsone type A medicated article can be homogenously incorporated into feed and is stable in feed over the two months. We answered the sponsor's question, no. The medicated feed remained homogenous. We did not have some chickens getting more or less drug than other chickens.

We also analyzed the water that the chickens drink and found that the water was not the source of inorganic arsenic that are observed in the livers of the poultry given in that earlier study. We next generated incurred tissue, looking for arsenic in different species in poultry liver. Poultry were fed either non-medicated feed or roxarsone-medicated feed. We did again analyze the water that the birds were drinking and verified that there was no arsenic in the water.

We added roxarsone at the highest approved concentration. The species was assessed both in the feed at the start and at the end of the study. The birds were on the study for 42 days. On day 42, they were euthanized, and their livers were collected for analysis.

What was the impact of the extraction solution? I mentioned before that TMAH had been used initially in the initial study. We came up with a water-based

extraction method to eliminate the possibility that it was the TMAH that was causing the organic arsenic to turn into inorganic arsenic.

We found that the water extraction works well with feed and fortified tissue samples, but not with incurred samples. We ran the water extraction procedure with the feed and our fortified tissue samples, but stayed with the TMAH for the incurred samples. But we ran those two procedures in parallel, and we did not see any differences. It was not the extraction procedure that was causing an increase in organic.

So what is the stability of roxarsone and arsenic species stored for long periods of time? We detected the following arsenic species. It is the ones that you see in red here that had sufficient precision accuracy and an established level of quantitation that we were able to find. We did find these breakdown products. We did find inorganic arsenic-5. DMA, dimethylacetamide acid, was detectable in all tissue samples. Its concentration did not change with freezing over the period of time.

We detected arsenic 3 and 5 in most, but not everyone, of the liver samples. We found that storage does not change the concentration of these organic

arsenic species over time. The roxarsone was not stable in TMAH extracts. However, it does not break down into inorganic. It would break down under other things, but not inorganic.

Freezing and thawing does not appreciably impact the concentration of the various arsenic species. We did find, though, that we did have to freeze it because arsenic species are not stable when stored under normal refrigeration.

So what were the conclusions of these particular studies? There is no appreciable inorganic arsenic in our drinking water, which supports the 2009 study findings. Roxarsone medicated feed was stable for the duration of the study. There were detectable levels of total arsenic in livers of birds given medicated feed. Long-term storage of incurred livers does not impact the concentration of arsenic species. That only happens if we were to just refrigerate it and let it sit in a refrigerator, which we did not do.

Roxarsone was homogenous in the medicated feed with no evidence of settling of roxarsone. The overall conclusions that we took back to the company was that the results from the current set of studies supports and extends the findings of the 2009 study. It also

addressed key issues that the sponsor had raised. If you are interested in finding out more about these particular studies, I have a link here where the final reports have been made publicly available.

What is the regulatory impact? Well, in February 2014, the sponsor, Zoetis, after seeing our data voluntarily withdrew their new animal drug applications for 3-Nitro, as well as two of the three others that were still on the market, arsanilic acid and carbarsone. However, they kept Histostat or nitarsone on the market. Why? Because it is the only drug out there that can prevent histomoniasis or blackhead disease in turkeys and chickens.

We did consult with experts in the field, including folks at NCTR on the chemistry of arsenic and wrote a position paper that we felt that the chemistry being observed in 3-Nitro would be similar to that in nitarsone. So we were pushing to have nitarsone, even though we did not do any research on nitarsone, we were pushing the company to pull nitarsone off the market.

Indeed, the pressure was successful because on April 1st, 2015, they announced that they were pulling it off the market. Of course, this has posed a challenge for people who raise chickens because now there is no

drug out there that can address histomoniasis. But it is not a problem that really creeps up across all the United States. It typically occurs down in the south in very warm and humid temperatures. It could be some agricultural changes could help address those issues, as well.

This is my last slide to talk about some key initiatives that CVM has. We are spending a lot of our effort on the Food Safety Modernization Act. Again, antimicrobial resistance strategy is another big key initiative we are working on. We are already getting assistance from the Division of Microbiology here at NCTR and helping address those issues. Those issues aren't going to go away any time soon.

Another big thing that we are looking at is unapproved and compounded animal drugs. Just as there are compounding of drugs used in human medicine, there is a lot of compounding going on in veterinary medicine. Those drugs have not been proven to be safe and effective.

We had one instance in the past year, and I won't tell you what the particular drug was, that was being compounded. However, when we did a chemical analysis on it at OR, we found that while the active

ingredient was in the new compounded drug, it was with a different salt. When you put it with a different salt, the question is raised, is it bioavailable, yes or no? That could speak towards efficacy. That is a problem.

Approval of veterinary drugs came on board late compared to approval of human drugs, as far as the history of the FDA is concerned. There are still a lot of drugs being used out there that are not approved for veterinary use. We are trying to figure out what to do with it and how to get them through a route of approval.

Emerging technologies, the big one I mentioned already was genetically-engineered animals, how do we handle those. What kind of guidance do we give for industry on that, as well as stem cells. So that is my overview of CVM. I am open to any questions you might have.

DR. PHILBERT: Questions?

DR. LANZA: Isn't it possible to make the progenies sterile so they can't breed? In other words, in the crossbred animals, the hybrid animal, couldn't that animal be made sterile, so it can't breed to the wild type? Just like you can do that in plants?

DR. GRAHAM: I don't believe that has been done in animals. That is why we are looking at these

procedures because of the very fear. Now, let's take the salmon, for instance. They are actually being raised in a lake high in the Andes in South America. The chances of them getting out and into the Atlantic or the Pacific Ocean aren't that high. But if they were to get out, they could breed. That DNA could get passed on.

They have not been engineered to not reproduce because the whole point for the company is to let them reproduce themselves, so that we can get a lot of animals. But I am not aware of anything in their genetic makeup that would prevent that particular gene that has been changed from being passed onto a wild animal.

DR. LANZA: That may be an area to consider. In the two parental lines, you could bring them down. Then in the crossbred progeny line that you are carrying, that progeny line could be made either to have poor reproductive (indiscernible)I guess is the right word, or not. It may require making one of the parent lines genetically-modified in that way.

But then when you make that crossbred line, which provides a hybrid vigor, then you will have a dud animal. I am just wondering if that isn't something that you might want to consider. I think GEMS are going to become greater and greater, not fewer and fewer.

DR. GRAHAM: That is a good point. I will bring it up with the folks in ONADE who are overseeing this and ask them that question. I just don't believe that.

PARTICIPANT: That is the strategy of the plant is to make the seeds so you don't have seeds. Otherwise, they would grow one crop, take the seeds and never buy the product again.

DR. GRAHAM: This, though, is not so much an FDA issue as it is an economic issue for the company who is trying to sell it to the public. If you think about the FDA's position, they are looking at a new animal drug application. All we have to do is take a look at whether or not we can discover their DNA in other animals.

It is actually not our job to prevent that DNA from escaping. That is a public issue, public perception issue that the company would have to address. I don't think that we at the Center for Veterinary Medicine could say, we are not going to approve your product unless you also genetically modify it to do this, that and the other thing.

PARTICIPANT: I appreciate that. But the other side of it is that the public is looking to you, whether it is justified or not, and I don't think it is

necessarily justified in terms of safety, but they are looking to you for the confidence. That creates a burden for you in many different ways.

DR. GRAHAM: There is no doubt about that. This whole thing with genetic engineering in general, not just about these salmon, it is a big public issue. There was this big issue over the past year about labeling products. Are they genetically engineered, yes or no? The label, I believe, doesn't have anything to say about specifically what was engineered and what were the genes. But it is to let the public know whether or not there is genetically engineered material in it. Of course, different states wanted to regulate labels their own way, and that was cut down, so there is going to be some sort of uniform labeling about what is in there.

Now, as far as assuring the public when they look to us for confidence, they can be confident that we have validated the method that can detect this DNA and that this method is being used when samples that are being imported are being analyzed by ORA. Most of the fish that is consumed in the United States is imported. The only fish that really isn't imported too much is catfish. We have got a lot of catfish, especially being raised in the Mississippi Delta area. But most of our

fish is actually imported.

It is testing at those import points that helps, just like with any other food product that is coming into the market. The Office of Regulatory Affairs can sample those things and put import alerts where they find stuff coming in that shouldn't be coming in. The public has to have confidence in the surveillance systems that the FDA has put in place for products that are coming into the market.

DR. PHILBERT: I think going forward, it will be important for this committee to sort of separate the science from the enforcement, the regulatory authority. That is funded under a separate line item. I think we all know that the amount of food crossing the US border, let alone produced within it, is bewildering. The FSIS has been systematically defunded, both at true true and related to some degree. We have got good science. We have got inspection regimens. But they are not working as efficiency as we might hope.

PARTICIPANT: A follow-up question on that. Is there any ongoing effort on public education as to the safety of GE animals, especially the salmon in particular?

DR. GRAHAM: Yes. Part of the FSMA that I was

talking about had to do with educating the public. That is one of our key initiatives. There is documentation being written up to help educate the public about not only GE animals, but other types of issues. It is certainly a huge concern that the public understand why we are doing the science we are doing and what it means to them.

DR. SLIKKER: Going back to the stem work, and I was thinking that a few months ago, it was announced that there were some 600 plus clinical shops across the US that provided stem cells to humans. But I sort of have this feeling that the number of shops that provide stem cells for animals is probably even greater than that.

I am wondering, part of the idea there is that stem cells have to be a certain type at a certain stage of maturation and a certain characteristic in order for them to be useful in their proposed purpose. I was just thinking that certainly that is something that NCTR is really interested in looking into and is already starting to develop approaches to characterize stem cells, understand their stage of development and their functional status before we use them and evaluate them and use them as model systems. Maybe that could be

another target area that we could work with.

DR. GRAHAM: So a couple of things that we are working on now have to do with how do we know the product that is being given to the patient is what it says it is? A lot of that has to do with the media in which the cells are being raised.

Fetal calf serum, which typically has been used, has a lot of proteins in it. We don't know what that is doing. Dr. Lax Devireddy, who is our stem cell expert at OR, has worked on a formulation for media that does not include fetal calf serum. He is in the process. That is intellectual property. I can't tell you what is in it right now. But he is in the process of getting that intellectual property protected. When people heard about this, there is significant interest in learning what is in there.

Now, that being said, it is not a one for all media, meaning the media is going to be different for horses, humans and dogs. Right now, he has worked it out for dogs. We need to know any product that comes in from a sponsor, if they want to legally bring it onto the market, we have to be assured that it is being manufactured in a uniform way. That is the parameters that you mentioned is the stage of maturity right,

functionally is it right.

We are also looking at biomechanical properties and sizes of these cells. Right now, products that you find out there that are being used by individual veterinarians, yes, it is just mom and pop operations. Who knows what is going into it. It is certainly not uniform. But if it is going to be approved by the FDA, we need to tell the industry, this is what we expect to see when we are evaluating these products.

DR. SLIKKER: Well, we would like to work with you on that because we do have five different laboratories at NCTR working with different kinds of stem cells. One of the goals there is to really understand how to characterize them, so we can compare outcome.

DR. GRAHAM: I agree that is an area that you could help us with.

DR. STICE: I think the FDA has basically shut down what the new guidance is, a lot of the non-mom and pop operations. The University of Georgia, the veterinary school used to do client-based animals. But the minimally manipulated new guidance has shut them down. There are fewer of those instances out there these days in the veterinary field. But it is certainly an area of interest.

There is another person at FDA, Steve Bauer, that is very much involved in characterization of MSCs.

DR. GRAHAM: We are working with Steve Bauer. He is one of the co-investigators on a chief scientist grant that Dr. Devireddy is working on. In fact, when he first got to OR about two years ago, we didn't have a lab for him. He was actually working out of Steve's lab. The two of them are working together on that particular grant.

DR. PILLAI: Does your office deal with irradiation of animal feed? Or is that a different office?

DR. GRAHAM: We are looking for the effects of irradiation through Vet-LIRN. In other words, some of the laboratories in Vet-LIRN have the ability to look at that particular parameter in feed. It is not something that is routinely done.

If there are signs or symptoms going on that might indicate there is an issue with that, then the samples could get evaluated. But we don't have any ongoing research specifically into looking at effects of radiation of animal feeds.

DR. PILLAI: The reason I ask is because NCTR, this tremendous genomic and transcriptomic resource, and

one of the challenges that animal feed irradiation is that in the US, there is an upper limit of 50. I am not pointing fingers at any country or region of the world. But a lot of the animal feed, a good amount coming to the United States, is imported. There is no way you can currently say that a country or manufacturer is irradiating twice that amount.

One method of actually detecting above a certain limit is potentially looking for molecular scars or signatures in the genomes (off mic).

DR. GRAHAM: I think I can have Dr. Renate Reimschussel, who is the lead of Vet-LIRN, talk with NCTR about that. She is already involved in the melamine cyanuric acid studies going on down here. She is already a collaborator, so she is quite familiar.

DR. PHILBERT: No more questions, then we will move on. Thank you very much.

DR. LINDER: My name is Sean Linder. I am a senior science advisor within the Office of Regulatory Science. I would like to kind of take a step back. We have had a lot of interesting discussions this morning about in-depth research and just kind of frame my talk that is a little bit different. That is that ORA has a very small research component to it.

Our main mission is to carry out, and I am going to discuss this in future slides, but to carry out the routine regulatory enforcement activities that are developed from product centers themselves. If you think of it as a regulatory cycle, all of the product centers that you have heard from this morning develop the framework. In many instances, they turn that framework over to ORA to carry out the day-to-day activities.

So what are our roles and responsibilities within the Office of Regulatory Affairs? We perform the majority of the inspections on firms that produce FDA-regulated devices, both domestically and internationally. We also do the majority of the investigations for consumer complaints. If you have an illness associated with a product that FDA regulates, and you phone that into the agency, we typically send out an investigator to discuss that with you and perhaps collect product, if there is any left, that you consumed.

We also do a great amount of work with emergencies, outbreaks and criminal activity. I think that we all recognize that our commodity changes are more global in nature now, and that we have a lot of purchasing over the internet, some of which is authentic and some of which may not be authentic. We have the only

criminal activity component within the agency, and that is the Office of Criminal Investigations.

We do, as I mentioned before, the majority of the enforcement activities in collaboration with the product centers, depending on which commodity potentially is outside of the regulatory framework. Then most of my talk is going to be really focused on our laboratory network, which does the analysis of samples that are collected by investigators. I will go over that in a couple of slides.

We also do all of the line reviews for imported products. Obviously, this was discussed earlier this morning. We import a tremendous amount of products which are regulated by the FDA. Those are all reviewed internally within ORA through various algorithms, some of which are manual, some of which are computer-driven, looking for risk assessment and products which potentially could cause an adverse human health impact.

So a little bit about us. Unlike many of our center components and colleagues, except for NCTR, we don’t have a huge headquarters component in Washington. It is there, but it is a very small percentage of our total workforce. Our total workforce currently right now within ORA is north of 5000 employees. We do have

international offices, which are listed here.

When you think about it, the United States is so geographically diverse that we have to have these offices. Otherwise, you have people on planes, trains and automobiles constantly. We have roughly 200 offices, 13 labs and one border screening station just within the domestic continental constraints of the United States.

I would like to bring to everyone's attention, this is kind of a new thing. We actually have a first of its kind border screening station. We had a charge recently in the last few years to do more point of the import analysis, both for micro and for chemical testing. That was finally stood up and operational about a year ago. That is kind of a new strategy that we are looking towards. As these imported products are coming in, actually screening them as they come through the points of entry as opposed to other types of strategies to screen those.

Our laboratory network, which I will focus on the next two slides, has about 900 total analysts spread across 13 labs. These are the locations of the labs. I thought at first I would put the names of them. But unfortunately, we are going through a reorganization. Some of the names are going to change a little bit, so

that would have been perhaps confusing.

Historically, ORA has been divided into five regions, which are really divided geographically. Each one of those regions had what was referred to as a regional food and drug director who had the managerial oversight of all of the laboratories, investigative compliance type of activities within those geographic regions. Due to an agency initiative called Program Alignment, we are in a reorganization effort to more align to commodity-driven managerial structures, so that our center colleagues who developed these regulatory framework for us have dedicated a specialized resource, both on the investigational front and on the laboratory analysis front.

Just highlighting a few of our laboratories that have some of the small research component, the Arkansas clearly has the interaction with NCTR with our Nano 4 that was developed in the late 2000s, as well as the agency's only surveillance program to look at dioxin and dioxin-like compounds. Additionally, our forensic chemistry in Cincinnati, Ohio, also has a very unique niche to it. They perform all of the criminal investigation type of samples, as well as perform a great deal of method development for emerging public health

issues.

You can think of some of the big ones that have been in the news recently. Melamine, they were a big stakeholder in that. Deepwater Horizon, so these things that we aren't necessarily prepared for that come to us. The Forensic Chemistry Center is a tremendous asset for the agency because of their technology and specialization within that laboratory.

A couple of the other ones that kind of have a unique niche and interest, the one in Kansas has a program with CFSAN called the total diet study in which they look at actual human diets, and then analyze for various organic and inorganic constituents to look at what the exposure levels are. That gets built into a tremendous data package. Then it gets shifted to CFSAN to look at our risk assessment type of strategies based on human consumption.

The last one I will bring up is the one in Winchester, Massachusetts, which is our device laboratory. It is kind of interesting that it is our laboratory that does device testing. We do anything from microwave testing to lasers to condoms to these sterile gowns and looking at leakage rates. That is a very unique niche there, as well.

A little bit about our demographics, we are primarily driven by microbiologists and chemists. That is the majority of our work. We do have 20 engineers. Those are all located at the Winchester facility I just discussed. You can look at the FTE levels there on the right. Our lab in Atlanta is by far the largest. Our lab, I believe, in Philadelphia is our smallest.

There has been a lot of discussion about collaborations and working with the centers. As has been described earlier, all of our work pretty much is generated by our interactions with the centers. They set the framework. They send the assignments. They tell us the work that they want completed. But this is a pie graph to illustrate the majority of our laboratory work that is certainly in the food-testing realm with the other roughly 25 percent coming from medical products and tobacco.

So a little bit about our work, you can read the slide, but we kind of cover the gamut of products that are regulated by FDA across our 13 labs. As I mentioned earlier, every year, the centers come together within their managerial structures and components, and decide what their risk priorities are going to be. What do they want tested? What do they want inspected? What

do they need ORA to do in the field, both domestically and internationally? That is done through a process called work planning.

Every year, we just actually finished this cycle because we just started a new fiscal year. Then we reallocate ORA resources and programs within our lab to try to adapt to whatever the risk strategies are that the centers develop. You can see that again it is quite a diverse set of analyses, both chemical and microbiological, engineering and radio chemistry, as well. Then someone mentioned import alerts as a strategy, as well, that the agency looks at products that are coming in.

If the products are out of compliance, then they get put on import alert. Future attempts to import from that product or from that importer result in a statutory requirement that the products get tested by an independent party. The independent party then generates this huge amount of data, submits it back to the agency to prove compliance. So the ORA labs review the majority of those packages, as well, to look at if a product is now admissible to be entered into commerce.

I mentioned the reorganization. Certainly the larger reorganization is our investigative staff. But

also the laboratories are undergoing a reorganization. Really, one of the key components that I would like to talk about there is standing up the Office of Research Coordination Evaluation.

For many years, this has kind of been a mishmash of bubble-up type of research and methods development activities within our labs because they all had different hierarchal structures and different priorities. This is ORA's attempt, and I think it is a good one, to stand up a single-science component to not only manage its labs, but also manage and direct the research components and method development components within those laboratories, and then can directly engage the centers to make sure that our priorities and their priorities are aligned.

We are hoping to, at least this is the goal, there are various obstacles that you have to go through. But both of these reorganizations were hoping to implement this year. So for the laboratory perspective, what you see, and I mentioned this earlier, is that no longer will the laboratories report to this regional food and drug directorate, but more the Office of Regulatory Science, which is my office.

I will close with a couple of current

collaborations and perhaps some potential for new collaborations. I think that this has been mentioned and reviewed by the science board numerous times. But we have a very strong collaborative relationship in the area of nanotechnology. Anything from developing methodologies, working with centers, in helping each other, understanding the impact that is going to have on the products that we regulate.

It was mentioned yesterday, as well, about this pattern recognition technology about bugs, yes, real live bugs. We do have statuary rules about the amount of bug fragments, hairs, fecal matter, things like that, that are admissible in food products for them to be compliant. You think about someone sitting at a microscope looking at this all day. Could that be further refined and optimized if we could do that with digital pattern recognition? So NCTR has been working with us for a couple of years on that. A lot of great ideas there. The last one is we have had a couple of different collaborations really providing analytical support to the Division of Microbiology with some of the vet drugs with Carl's group.

Potential areas for collaboration, this was mentioned a lot yesterday about bioinformatics. It seems

that there are opportunities there. You think ORA labs and analyzing tens of thousands of samples, microbiological samples every year. We obviously get isolates out of that.

We have whole genome sequencing technology in each one of our microlabs. There is a tremendous amount of data that comes out of those processes. It was mentioned yesterday, I think Carolyn mentioned it, that the IT infrastructure is not what we would ideally like it to be. Where do we store that data? How do we mine that data? How does it get used and transferred to other government components that it could be beneficial to?

Those are the types of questions that I think we are still developing as this technology matures more, as we use it in regulatory trace back type of scenarios more. It seems like NCTR has that expertise. They could perhaps engage us, along with our primary stakeholders in this area, with CVM and CFSAN and Office of Foods and Veterinary Medicine. That is one particular area.

The second area that I would like to mention is ORA is standing up some advanced pharmaceutical testing. This year, we are bringing on NMR technology. It is not a technology that we have traditionally used. But as pharma products become more advanced, we are trying to

keep up with that and bring on technologies with our colleagues at the Center for Drugs to be able to test those for regulatory compliance. We think there are opportunities here to leverage the expertise that we know NCTR has in that area.

The last two are really how does the agency with ORA kind of being the feet on the ground, per se, in a lot of instances, how do we reach out and communicate better the need for expertise for areas in which we don't have that, whether that is toxicological data, whether that is health assessment data, whether that is analytical methodologies.

Until yesterday, there was a lot of issues with botanical and homeopathic type of things. I heard an interesting talk yesterday about aloe vera. We don't necessarily have a method. I am not saying it is a health concern. But if it were, that is an example where NCTR has those type of methodologies readily available. But unless we are in a forum like this, I don't know how we find that.

So there are some strategies going on within the Office of Food and Veterinary Medicine and ORA to look at method portals and tracking research and documenting research through different IT platforms.

Actually, there is a really nice opportunity with research tracking. We have historically used a program called CARTS, which was developed, I think, in CFSAN. CVM and ORA are now using that for research tracking. That is going to be transitioning to a new research tracking platform. At least there are workgroups being formed to discuss that. Perhaps there is an opportunity for NCTR to engage in that, as well. I understand they have their own programs. That is great. But maybe just have some type of component where they could list their projects, so that we could then go back and search that like a database, if there was a need to bring in some additional resources.

With that, I will close and answer any questions.

DR. PHILBERT: Thank you. Questions? You don’t benefit from user fees?

DR. LINDER: We do to some extent. Like your GDUFA, your generic user drug fees, we do have resources that are derived from that. We also have a performance agreement with CTP, which is user-fee driven. We have an analytical lab in Atlanta that does some work with CTP. So yes, we do. But even those resources are then programmed or work planned through the center in which

those fees are derived.

DR. PHILBERT: Where do fines go? You have a criminal investigation. I just noticed today that you gave a letter of warning to a pharmaceutical company in China.

DR. LINDER: Right. Well, warning letters don't typically result in fines. So typically fines and things would go through, I guess, the Department of Justice and end up back at the treasury. They don't come back to the agency as far as I am aware.

DR. PHILBERT: That might be something to work on.

DR. SLIKKER: This idea about communicating who has the expertise, who has the equipment, who has the capabilities that may be shared. I know that the commission has been working very hard on getting this out now. There will be a template that we are using. I suppose that some of your group is using it. I don't know about the other centers. But there is a template that is built off of a NIH kind of base that will allow us to have a nice picture of the researcher, his or her strengths and expertise, as well as some of the ongoing research activities.

Carolyn, is this being also looked at within

CBER and some of the other centers?

DR. WILSON: I have not been directly involved in those conversations at the agency level. CBER is revamping our own external website for that. Then internally in CBER, we have our own research database that tracks people with a pull-down keyword list for expertise, so that we can do those kinds of analyses internally. Certainly people in other centers could contact me if you want to find that.

But there have been conversations in the past about having an FDA database for expertise. Actually, First used to do that, but it was discontinued.

DR. SLIKKER: Right. So we had one, we lost it. But now I think there is one that is trying to be recreated. And you are right, almost every center has their own internal thing that could be shared. But I think the commissioner is trying to work on one now that would be more equally shared. But in any case, that is a good idea. Of course, you could just sort of stop by my office and we can chat, too. That will always be good.

DR. PILLAI: You mentioned a border inspection station. Is it in Texas or California?

DR. LINDER: It is actually in Fort Lauderdale, Florida. There is a big point of entry. Port Everglades

is the name of the port. Apparently, we receive a lot of products there. I have not been there personally, but apparently that is a huge import area for the agency.

DR. PHILBERT: My tongue was only partially in my cheek because we do have a member from FDA Science Board right here on this particular science board. It occurs to me that a number of the initiatives that end up in compliance, in detection of contamination, and adulteration and so on, ought to come back into RND rather than arguing for de-novo money. Or you are going into a CR pretty soon, so arguing for it every quarter. There ought to be some way of keeping up the technology, refreshing it and so on, to the extent that you feel comfortable. That might be something to bring up at the Science Board agency wide.

Are there any other specific questions for Sean? If not, then thank you very much.

Agenda Item: Discussion of NCTR Research

The last 20 minutes or so that we have with our colleagues from the centers, I wanted to open up the discussion to themes on all sides that we heard over the last day and a half, opportunities that you didn’t come into the room thinking about, but that was stimulated by the discussion here. Hopefully at the end of 20 minutes,

which is very short, are there any threads that can be picked up for further development?

DR. PILLAI: One of the threads I heard between what you all need and what NCTR can provide are like training programs. I think I heard some say that they have sent people here for training on certain methodologies, et cetera. I think when NCTR develops a public suite of training programs that is available. Then I think it enhances better collaborations, face-to-face opportunities. I think that becomes more seamless.

DR. SLIKKER: That is a good idea. In fact, over the last 10 or 15 years, we have an exchange program that is available on the website for people to apply to. We have had usually two or three or four or five individuals come to the NCTR and spend either two or three days or a couple of weeks, as you noted in the one example with the recent one with the neuro tox division.

But I think even more importantly we have than the nanocore training facility, which we bring onsite individuals into the Jefferson Labs. They train with Sean and our group that Neal heads up as far as the nanocore. That is onsite, hands-on training. But then, we also have a roadshow that goes to White Oak or CFSAN and talks about it in a more didactic kind of way.

I think it is also important to realize that we send people to White Oak and to CFSAN and to CVM for training, for experience, for understanding what the issues are. We are trying to get more ideas about what a reviewer's life is really like. A lot of times, our leadership and senior staff are going there to try to pick up those gems to be able to figure out really what the issue is that we can help with.

I agree with you that exchange should be done. It is being done. It could be done more. But we do actually have things on the web where people could sign up. That is how we get volunteers.

Now, the key is the person has to have the time and the funding to come to NCTR. Oftentimes, we have funded them to come. In other cases, the home center has funded them to come. But it is definitely possible and something that we have been trying to advertise for people to do that where we can.

The webinars are getting better and better. They are not perfect. But the ones that more recently not only can you see what the person is saying and see the slides, but then you can ask questions afterwards, either by typing it in or actually being live and being able to speak your questions directly to the speaker that

is there at White Oak and vice versa.

We are just creating an upgraded sort of technology center sort of conference room where we are going to have even better capability projecting what is going on at the Jefferson labs to White Oak and CFSAN and vice versa. These are all areas that we are working on, and they are important, I agree.

DR. WATERS: What about some of the folks that are developing the software in the bioinformatics group, particularly the R2R framework? We heard a lot about that last year. I didn't hear anything about that this year. Is there an opportunity for some of those developers to go to White Oak to talk to the reviewers?

DR. SLIKKER: You are absolutely right. We didn't emphasize it, but that activity is continuing. It is actually developing even more than before with actually putting some of those tools on the desk of the reviewers for them to try out and then to give us feedback on how we can improve them, all being orchestrated by the folks at CDER now. But we think that those technologies would be available to other reviewers, as well.

So yes, we definitely have, just in the last couple of months. There was a large group that went

there. Just as importantly is what Carolyn brought up about the conduits and bandwidth of exchange of information. I mean, it is sometimes faster to send somebody there than it is to send the data here through the little measly lines that we are currently using.

It is not just between us and White Oak. It is between White Oak and some of their own groups there, plus CVM and CFSAN. This is an agency-wide issue that has to be fixed. We have got to have better conduits, better bandwidth possibilities. Then we can start to do more of what you are talking about. But there have been specialized subsets of cleansed data that have been sent to us, so that we could say how we could manipulate that to be more useful to the reviewer. And send it back to them and say, is this better? How does this work? Those exchanges are really key. You are absolutely right.

DR. CENTENO: I don't know how much is used here at NCTR, but we have mechanisms. That way, we can actually do some of the enhanced training. We have details, different offices or groups. They can come to work on research or maybe going to the reviewer's office to get acquainted with that type of what they do at the review level. That might be something that could be explored here at the NCTR, as well, and vice versa. Have

some details from White Oak coming here to NCTR.

PARTICIPANT: That seems like a very good idea actually to send some NCTR folks to detail to product center. Have you guys ever done that?

DR. SLIKKER: Oh, yes. In fact, some of our division vectors actually more or less live in DC and spend a lot of time at White Oak and other FDA facilities there because it is so important to be able to make those connections. So every chance that I get to go there, which is frequently, I always try to set up five or six appointments to meet with folks and be able to pick up new ideas and new connections.

And there have been others that have stayed three and four and five and six days or more to really try to absorb what the important issues are. We can always do more of that. But as you are well aware, any time they are not working in your lab in White Oak or leaving things forward there, they are on the road someplace else. We have to balance all of those things against each other.

DR. STRAUSS: If I just may follow up, so I wasn’t referring to short visits, but actual four-month detail where somebody is detailing and actually working as a reviewer for four months. I mean, that is done

between centers. CDRH folks will detail to CDER and vice versa. I was referring more to longer term and not division directors, but the scientists to actually detail to one of the product centers. It might be something to think about.

DR. SLIKKER: What we have done is that some of the commissioner's fellows or other post-doctoral fellows in particular who want to have more opportunity to understand what the reviewer's role is. They have been detailed up there for two and three months at a time. So we have taken advantage of that kind of training opportunity, which I think is important.

But you are right. The idea of trying to walk in the reviewer's shoes to understand what the real issues can be is important to actually get the formulation, which is one of the foundations of how we move things forward. I understand your perspective on that.

DR. PHILBERT: John, did you have something to add to that?

DR. GRAHAM: This was more of a comment for David to qualify a statement that he was looking about more longer term training. Donna is up there and is in pretty routine contact, I guess with the other centers,

but at least me, on various issues about how can we further collaborate. She is also chairing the emerging sciences working group that involved all of us here. I think there has been very good communication that I have seen increased over the past three years since I have been with the FDA with interactions of NCTR staff with the various centers.

DR. LANZA: One of the things that I noticed across all the programs, or many of them, was the role of nanotechnology. Nanotechnology, I have been in it for over 20 years. The situation is that there is more than just chemistry and characterization. There is a complete need for more understanding about the models that are used to test these things because some of them are very promiscuous. It can give you efficacy when it really doesn't translate. There are issues of physical toxicity, it is heavy metal residues. For instance, in some of these things, there are a lot of these really not targeted when they say they are. Many of them are leaching the drug in a way. They are more like an excipient.

The NCTR, you have a spot here that consolidates a lot of that experience that is not something that you might need all the time. But it is

something you might need now and then. That experience can go from chemistry all the way to the final.

I wonder whether there isn't a way to take advantage of the NCTR to help you get up to speed on a lot of applications in that regard in the review process, all the way from IMDs to NDAs.

DR. GRAHAM: Let me address that. At one of the FDA science forums, I guess about a year and a half or two years ago, I met NCTR's nanotoxicologist. His name is escaping me. We have had some investigators within the Center for Veterinary Medicine who wanted to do some work in nanotoxicology. I am concerned when they want to use these things outside of engineering controls. This could be the next asbestos. Asbestos was supposed to be safe, too.

I, at the Office of Research, have said that in order for any concept paper to get my signature on it to go forward has to go through our safety officer who must consult with the experts down here at NCTR on the safety of this. My concern is for the safety of the workforce when it comes to dealing with these particular things. We do have a way of interacting with NCTR as far as their expertise, knowing that we don't have that expertise.

PARTICIPANT: Actually, I just wanted to make

one additional comment, which is there is an agency-wide taskforce on nanotechnology. Actually, Neil who was just mentioned is the chair of that group. That group does look across the agency, what are the needs, and trying to increase coordination, communication and understanding of the research to address those needs.

DR. CENTENO: There is one area that I think is very important here to address. When you look at nanoparticles, nanotechnology collaboration, I think that there is very little that we have done on developing the standards. It is something that needs to be addressed.

Also, I think that there is a need to develop intake values for nanoparticles, specifically when you actually look at different sizes of nanoparticles. Right now, we have one manuscript that is coming out, only on one side, specific one side, 20 nanometers that we actually verified in a cell. It is going to be used as part of potentially for the standards. That is one area of research that there are a lot of gaps in. We should see how we can use this to develop standards and also to develop TIs for different nanoparticles.

PARTICIPANT: I would push a little bit further than that because dose metrics are not understood well at all for any. If you have two components, if you just

have a (indiscernible) at the nanoscale and an API, you need to solve for both simultaneously. We are still not sure what the interaction is from an efficacy point of view or from a safety point of view.

Also, just to expand on what you said, Jose, I know CDRH has done a lot of work on the way that nanomaterials themselves interfere with standard assays. So developing new assays and so on, there is a lot of just sort of basic science to be done that could be in collaboration with NCTR.

MR. REISS: I just want to follow up on a couple of sort of organizational points. John, could you explain a little bit more perhaps about how the emerging sciences working group works? That would be really great. I was just trying to understand how the organization thinks a little bit about this.

Also, the related question is these taskforces that are run across sort of the agency. Who governs them? What is the process to make sure that people are in or not in the loop on that?

PARTICIPANT: Donna, do you want to take that on? Donna is actually the chair of that committee and can speak to the history of it.

PARTICIPANT: We have an emerging sciences

working group with the idea of looking at horizon scanning. Sciences and technologies are going to affect FDA products in five or more years. We are meeting with a lot of other government agencies to learn what their funding, what they know about.

We recently put out a federal registry notice asking the public to submit their knowledge of five things we should be looking at. We are going to create an internal FDA site where FDA people can put in these kind of comments, as well. That is really what we are looking at.

From that information, we can help drive additional science of things we aren't thinking about. It might define additional workgroups under that.

The working groups that are being run out of FDA tend to be under the heading of the Office of Chief Scientists. They are under the senior science council. It really depends on what they are. Some of them might be just one center-specific. A lot of them actually do cross centers. Genomics crosses centers. They tend to be wide open within the FDA.

PARTICIPANT: The issue about the working groups when they are convened as part of the senior science council, there is a charter that goes with them.

Usually it is a request to the centers for who should be the membership. Then it depends on the nature of the work and the discussion in those groups weather they are more open or more closed in terms of membership. If they are really just talking about the science, they tend to be a little more open. If they want to also be talking about how the science should be driving evolution of regulatory policies, then it has to be a little more managed as far as membership.

DR. FELTER: (Off mic) Following up on one of Shawn's last bullet points about the need for a list of available expertise in case of emergencies. I guess my question for the different centers is whether it is second nature to consider, and in the case where something has come up very quickly that needs to be addressed asap. You don't really have time to sit back and develop your protocols in a traditional sense.

Whether outreach to NCTR is part of that thinking process because sometimes, from my experience, Proctor and Gamble, we have a similar challenge where we have a central group that does a lot of research and has a lot of expertise that isn't necessarily as well recognized by our equivalent of our offices, which might be fabric and homecare, baby care, et cetera. It is not

dissimilar in terms of when I think about how often we don’t all know what each other can bring to the table.

I am wondering whether there would be a benefit to having that outreach just as a sort of an automatic thought process as opposed to waiting until there is a list of people with expertise. We also try that. Every year, we get a reminder to update our expertise in the system, so people know who to go to. In all honesty, that is not how they find the people with expertise. It is a great idea, but it doesn’t actually work that way. It is more by who you know and who you talk to. I am just wondering if that is happening now or if that is an opportunity for improving the communication and the opportunities.

I was thinking about like what happened with the melamine cyanuric acid example where NCTR got involved very quickly. Are there other opportunities like that, that aren’t currently being seen in the same way?

DR. SLIKKER: I really appreciate your comment because that is something that we are always looking for. That is one reason we have the NCTR office at White Oak. It is actually right above the cafeteria. So actually, Donna can look down and spy on people and catch them

while they are trying to get lunch in a hurry. We have used that tactic.

But also, what has been really good is that you heard many of the centers, and it has really been nice to see this, has invited Donna into their review groups and/or science groups or groups that meet every month or so. She is sort of a member of those groups, which is really excellent. That gives her direct access.

The idea is that Donna and that office, and it has a couple of little swing spaces, so that when I and other people come to visit, we get a place to stay. You might say we have a computer while we are going out and meeting with folks and people coming in to meet with us. It really does serve some of that role you speak of.

But I think that all of the seminars that we have been talking about, all of the webinars, all the interactions, all of those help, including this meeting here. It only happens once a year. But I hear things from the various centers at this meeting that I don't pick up at other sources.

I would kind of like to question the group that is here. I am so glad that you are from the other centers, whether or not you hear things from not just NCTR, but your other centers that you are sitting next to

that you don't pick up in sort of your day-to-day activities at White Oak, even though you might be a building away. I think here, we kind of distilled down on some of the issues that we think are really important for collaboration. You put them up on the screen, and we get a chance to look at them. I am not sure that you get that in everyday interactions in a White Oak facility. I think it really works in many different ways to bring people together.

DR. PHILBERT: Anybody care to respond? I saw some nodding and some smiling. It might be fatigue. Greg, we are running out of time. Did you have another? Our time is exhausted. Bill has got one quick one.

DR. SLIKKER: The question that is put to us by our illustrious, in-depth group over here of Katrina and Pam about better metrics. They want to see better metrics on how research is moving the ball forward. My question, while you are all sitting here, is do you have ideas about better metrics that FDA and CTR could use to really calibrate how well we are doing in responding to issues and into moving the ball forward as far as FDA-wide issues.

I know you have been asked this question before, but does anyone have good ideas about metrics?

We have heard about guidance documents. We have heard about things as far as withdrawal activities. We have heard about developing new technologies that hopefully will help run through the gamut of the valley of death as we move products through the critical path.

But what sort of parameters, what sort of endpoints would you say are most useful and kind of calibrate this activity?

DR. WILSON: I think that it is not a one-size fits all. That is a really complicated question to ask. We actually do have in internal agency-wide group that is looking at that question. We meet sort of once or twice a year right now, or maybe it is two or three times a year.

What we have been doing is sort of sharing best practices around that question. I think there are short-term and long-term metrics, especially as it translates into the regulatory domain. Some things, like development of new guidance, can take years to translate from scientific discoveries in the lab. I just think that is a really big, complicated topic to address, but very important.

DR. VAN BEMMEL: I just wanted to build on that. You are right. It is a very complicated question.

I am not sure if you are aware, Bill, that within CTP, we are evaluating our own research program. Many of the endpoints that we are looking at are things that you mentioned. Whether or not it gets into it, the research is used to inform regulatory documents, white papers, that kind of thing, but also tracking publications. NCTR is part of that overall portfolio analysis. We would be happy to share with you what we have done. It might help you either think a little bit more outside the box or at least help inform how the work you are doing with CTP is impacting what we are doing.

DR. SLIKKER: That would be helpful.

DR. PHILBERT: I really strongly encourage you to seek advice from experts. There are people who do program evaluation as part of their own academic or business endeavors. There is a set of disciplines.

PARTICIPANT: (Off mic).

DR. CENTENO: I take Katrina's point in another way, as well. This is a very complicated question. When you look at the metrics of success, I also look at this as a way that impacts the immediate public health. It has an immediate public health impact.

One of the things that we used in our office is looking at how our research impact in the public health

through the FDA safety communications. It is not only science that you can publish in Science or Nature, but it is also doing science that actually happened with immediate impact to the public. This is something that we looked very much and use as a metric. For example, during the PMAPS, we used that in our center.

DR. PHILBERT: We are at the end of our time together. I did want to publicly thank Suresh and Katrina. This, along with myself, is our last face-to-face meeting with the board. I want to especially thank the representatives from the centers for engaging with us and helping us understand the connections between NCTR and the rest of the agency, and for your willingness to sort of jump in and correct us and inform us and generally to discuss matters.

With that, I am going to close the public session. We have some folks who have planes to make. I am going to suggest a strict five-minute bio break.

(Whereupon, the meeting was adjourned.)