our role in those. The question is, is there anything else that we should be putting on our list now. We obviously have lots of meetings in the future to help the agency.

Yes, Larry?

DR. SASICH: This is not a particularly well-thought out comment, but just thinking over some of the requirements of FDAAA in terms of providing scientifically accurate and useful information for the public and then what -- I think it was the commissioner or Frank who said about doing a science writers symposium.

Do we, as a Science Board, have any role in trying to advocate for or try to encourage the agency to have a greater role in informing the public about these enormously complex issues that are going on right now? And do we come -- talking to my colleagues from different backgrounds, we come to these meetings and we're sometimes absolutely overwhelmed with new problems, with new issues

that aren't part of our educational background.

And I think the science part of it is -- there must be a component of science that is looking at or should be looking at the communication of useful information and whatever "useful" happens to be -- how you might define that.

So, like I said, this was not really well thought-out, bit it just kind of popped into my mind.

DR. TORTI: So, that's a great idea, Larry. And maybe we should begin by sort of giving you, the Science Board, an overview of our, sort of -- how we communicate and what the content and character of that communication is, so then you can give us feedback as to where additional communication is necessary.

This is an active area of interest of ours, and we have a number of groups that are heavily involved in issues of

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communication to the public, to professional societies, to physicians directly, to -- you name it, there's a program developed to address it. But giving you the totality and the strategy related to that, and to some extent how successful we think we've been there would be a good starting point for looking at other things we could do.

We'd really welcome thoughts about -- I mean, just the issue of how to communicate risk is something that deserves a real discussion. So, we'd be glad to do it.

DR. MCNEIL: That actually raises the potential usefulness of a risk assessor as a member of the Science Board or somebody who think a lot about presenting risks. I don't mean "risk assessment" per se, but -- yes, Rhona?

DR. APPLEBAUM: I'd be more detailed and say a "risk communicator."

DR. MCNEIL: Risk communicator. Better said, correct.

Anything else on this topic? All right. Why don't we move on then. We have a packed hour and three quarters involving salmonella and melamine. And the plan, as you can see from the agenda is to have the presentation -- a two-part presentation on salmonella, then on melamine.

What we'll do is we'll do the salmonella, have questions, do the melamine, have questions, and if there's time left over, we'll have questions from either one. But given the time, we'll probably stop the salmonella discussion at about 11 -- let's see. What time? Halfway. We'll stop at half-way.

Well, it will be halfway through an hour and three quarters.

DR. TORTI: So, it will be just as Dave is coming up and -- I'm sorry.

DR. MCNEIL: Go ahead. No, that's all right.

DR. TORTI: I was just going to say

-- so just to frame this again -- these are two examples of important issues in the agency for which we believe science can make an important contribution. Not every aspect of what you're going to hear relates to a scientific decision, but we want to try and frame this as to where science can actually have an impact.

And as you'll see, two very different kinds of science, in terms of how we're thinking about this. So, with that, I'll turn it over to Dave Acheson.

OVERVIEW OF CURRENT METHODS FOR DETECTION OF CONTAMINANTS IN FDA-REGULATED PRODUCTS: SALMONELLA RAPID DETECTION

DR. ACHESON: Thank you very much to both of you. My role here in the context of the salmonella is to kind of paint the big picture, and to get everybody on the same page, given the diversity of backgrounds. And I apologize that for some of you, this will be Food Safety 101 and for others of you,

hopefully it will be a little educational.

What I'm going to do is to start with a background, and then my colleague Steve Musser from CFSAN -- Carlos, this is not advancing. Here we go, Thank you.

I want to talk initially about some of the detection challenges, then go into what we call the anatomy of an outbreak, which sort of lays out how detection technology would apply in the context of a food borne illness outbreak, what our role is from the FDA perspective, and then the importance of rapid detection tools.

And I want to emphasize that when we're dealing with this, essentially it is beginning at the local and state health departments, Centers for Disease Control, FDA, USDA, FSIS -- all have a part to play in the context of the importance of rapid detection technology.

So, with apologies to my colleague Lonnie King from CDC, I am going to talk a

little bit about CDC's area simply because if I don't, it isn't going to fit together properly.

In terms of the challenges, what are we thinking about when we want detection technology? And I know that the focus, ultimately, is salmonella detection, which is something that came out as a lesson learned from the salmonella Saintpaul outbreak. We need to do these things faster and rapid detection technology is a part of that.

In that context, in an outbreak situation, you need technology that's going to work for human samples. You need technology that's going to work for food samples, and environmental samples, in terms of soil and water and so on, and then ultimately, sometimes animal samples as well.

In routine situations, you want to be able to sample during inspections, which could be domestic or it could be imports. That's going to be exclusively foods.

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Other challenges -- they need to be fast. We can detect salmonella, E.coli, very adequately right now, but as you'll hear from Steve, we need to try to do this faster. So, speed is critical because the goal here -- why do we want rapid detection technology? It is to shut down an outbreak. It's to find a problem earlier. The sooner we find it, the sooner we protect public health, the sooner we can communicate to consumers. And you'll see in the context of my example of the anatomy of an outbreak how that plays into it. And I'll use salmonella Saintpaul as an example.

So, we want speed in the early stages to identify cases. So this is at the human end of it. People are getting sick and samples are arriving in clinical labs. How can we push that through faster? Then it reaches the point where we've identified a food and we want to determine is the salmonella present in that food sample. Again, speed is of the essence.

And then, once you have determined, "Yes, there's salmonella in that pepper or there's E.coli in that spinach sample," we then have to be able to serotype it in the context of the salmonella quickly, and to do the genetic typing because you need to be able to determine that that isolate is part of the outbreak.

It also has to be easy to use. Part of the goal here for rapid detection technology is not just to use it in a sophisticated lab setting, but to have it such that our field investigators can use it during investigations at a pepper farm in Mexico. I mean, that's a long shot, but let's think big here. And then during import inspections.

That has implications not only for public health, but also for industry in the context of if we stop a product to test it and it's a product that's got a short shelf-life -- fresh produce -- doing this quickly has important impacts on other issues.

So, if I now bring this back to the anatomy of an outbreak and I'm going on go through these fairly quickly -- but I want to start with somebody getting sick. They've consumed a contaminated food product. They've developed symptoms. They've gone to see their doctor, and the doctor has taken a stool sample, and sent it to the clinical microlab for analysis and they find a pathogen.

Now, that process itself is something that could faster, in terms of the actual lab part of detection. Once the clinical lab has found the salmonella, they will then start to do case finding, but sending the isolate to the local lab or the state lab. They need to confirm that it is indeed a salmonella or an E.coli 0157. So they confirm it. They will do the genetic fingerprinting. Right now, as you'll hear from my colleague Steve Musser, pulsed field gel electrophoresis is the standard that we're all using. Could we be looking at new technology

to do this faster? Absolutely.

That fingerprint is submitted to the central database, known as PulseNet, which is orchestrated and run by the Centers for Disease Control and is updated constantly. And what this is doing is looking for the patterns. It's assembling the needles in the haystack to say, "Okay, yes, we've got an outbreak going on here," as just opposed to a sporadic case.

The case exposure information is occurring in concert with this where the local health department is going to that patient and saying, "What did you eat in the week before you came sick and where did you eat it?" to begin to try to get an assessment of what may be the implicated product, because remember, at this stage, all you've got is cases of salmonellosis. You don't know whether it came from a turtle, from a colleague, from the nursery, from something that's FDA-regulated or USDA-regulated. No clue. All you're dealing

with is essentially, cases. So that's a very important part of this.

This leads to multiple case findings, through the integration of the pulsed field gel system and PulseNet, the multiplication of the food histories. Common features begin to emerge in that it looks like, "Well, yes. It's one of four or five foods because that's a common feature." Or it's a common site -- all these people who got sick ate at a specific restaurant chain.

The same genetic fingerprints are being found in multiple places. Again, the same sort of information -- setting up a case control study because then you want to know definitively is it peppers, is it tomatoes, is it spinach? What exactly is it? That leads to the identification of the most likely food.

The only part of this that's involving pathogen detection is in the human clinical part up to this point because we don't have a likely food at this point. But

once we reach this part, FDA then takes a major role in trying to identify the food problem and where it occurred.

So at this point, assuming that we have got a product that we know has been identified by CDC and the state as being the source -- and I'm going to use -- the example here would be last year when we had salmonella in peanut butter. When essentially that came through the case control studies, we knew what brand, we knew what product, and we could then call the company, and say, "Your product has been implicated." And we discussed with them what to do about it, and they initiated a recall. That's easy. It's quick.

This summer was a very, very different situation, where we didn't have a brand. We had tomatoes as being the most likely, and as you are all aware, that information shifted as we were dealing with this ongoing outbreak.

So, assuming that you have that --

you've got a press release, you're communicating to the public. The product tracing begins, for us, if we don't know that it was a certain brand of peanut butter because we've got to figure out where it came from, where it went to, because not only does contaminated product go out from a distribution center to somebody and has made them sick, it may have gone to other places, and is sitting in a distribution center or about to go onto a retail shelf that somebody's going to purchase. So that can lead to secondary recalls.

We need to get into what's going on with the process of the distributor and ultimately, in the case of a fresh produce item, back to the farm. This is where the rapid detection technology comes in again in terms of the importance of it. We may be testing leftover product from case patients. Example -- when we had spinach 0157 in 2006, we were able to get leftover bags of spinach

from patients' homes, test it, find E.coli 0157:H7 in it. That goes quicker than salmonella, as you'll hear from Steve, but it could go faster yet.

Food samples obtained during inspections -- that's something, when we are going out to the distributor or the retailer, and saying, "Do you have any of this lot left over, and if so, can we get some and can we test it?"

Now, obviously, in some of these situations, you don't have product left over from the cases because they've consumed it or it's way past it's used-by date and it's been thrown it. Ultimately, these investigations lead us back to the environment where we are looking to test the environmental samples -- the soil, animal fecal material, water -- to see if we can find problems actually on a farm.

What this allows us to do is that if we can identify problems quickly in a

distribution center through environmental testing, through product testing, then you've got a much better handle on shutting the problem down earlier. So the advantages of rapid detection is very clearly public health implicated, because you get to the solutions quicker.

The key part for us here through this testing is source determination, where, as I've said, where inspecting and taking samples in the plant or on the farm. And that is going to help us orient the consumer communication so that we're able to say, "Yes. It's likely that the contamination occurred at this point because we've rapidly been able to figure out it was an environmental contamination in a certain processing facility. We know where that product has gone, and it helps address public health issues.

It also allows us to prevent recurrence. If we're able to do a bunch of environmental testing or sample testing in an

establishment, determine what went wrong -- you can then think down the line. What do you do to prevent recurrence, which is a key part of the lessons learned out of any kind of an outbreak response. And as I'm saying here, it's important to learn how and where did the contamination occur so we can put in preventative controls.

To finally put this in the context of the recent outbreak, and to try to sort of play this into some of the time-lines, this is kind of where we ended up in this outbreak, over 1,450 cases of salmonella Saintpaul last year in multiple states dealing with multiple food types with a very complicated trace-back process and sampling strategy to try to identify the source.

It was late May in 2008 when CDC were able to give us the alert that it was salmonella Saintpaul and that tomatoes were the likely vehicle. I want to point out that the first cases occurred in mid-April. So,

we're there dealing with a gap that is certainly not all due to lack of rapid signal detection, but there is a piece of it that is. There are many other factors around the public health infrastructure related to this, but faster tools at the clinical microlab, faster genetic typing -- which certainly shortened the time-frame a little bit.

Beginning of June, end of May, we're notified that tomatoes are implicated. We initiate product tracing on tomatoes and we are then going into these facilities tracing back from retail distributer back to the farm, doing the sampling that I've talked about, looking for salmonella on tomatoes. And we tested many tomato samples in the course of this outbreak.

As many of you are aware, those tomatoes traced back to two geographic locations in Florida and Mexico, so we go down to those farms. Inspections are initiated on the farms and in the distribution centers

between the retail outlets and the farms in Mexico and Florida. Meanwhile, the outbreak continues.

Centers for Disease Control in the states undertake a second case control studies in which tomatoes are still implicated, but this time jalapeno and serrano peppers are implicated as well, so the same thing is then kicking in with them. We're starting to trace back the peppers. And as I've said, we're going to the distribution centers, and we find a positive sample of jalapeno peppers in a distribution center in Texas that traced back to Mexico.

Again, this is a time issue. We get the answer, but the time-frame between going into that distribution center and knowing that we've got a matched isolate out of that distribution center is about a week, if not longer. And in that time-frame, the distribution is continuing, the recall has not happened of those peppers, so they're still

going out into distribution because we don't have confirmation that it is definitely a salmonella of the serotype that we're concerned about.

We get then back to say, "Okay. We know these come from Mexico, back to the farms in Mexico. This time, we're looking at the pepper farms, and again, we find positive samples found on a farm in Mexico in serrano peppers and in irrigation water. And once again, this is a question of -- our investigators are going down to Mexico. They're taking the samples in Mexico and they're either shipping them or bringing them back with them, and wouldn't it be nice to have a tool that would allow these investigators to rapidly say, "Yes. We found it. It's salmonella Saintpaul and it's the right genetic fingerprint -- while they're on-site in Mexico. It just moves the whole thing so much faster.

So, in summary, rapid detection

certainly during the formative stages of an outbreak are key. That's not an FDA role, but it's a clear important part of public health, protecting public health at the local, state level.

And then once we know that there's an implicated food, rapid detection for the food and the environmental samples. It all helps shorten down these multiple steps that we have to go through. It will allow us to identify the problem faster, and importantly, eliminate negatives faster too, because this isn't all about finding positives. If it takes you a week or three or four days to say, "This is a negative," that's also an impact on communication to consumers, availability of safe product, and frankly, also, on the industry.

And there are very clear public health gains, which is obviously the major mission here. It provides better protection because you shut it down faster. And it

provides greater ability of products not implicated in the outbreak, and when you're talking about fresh produce, from the health perspectives, we don't want people to stop eating fresh produce -- spinach, tomatoes, whatever it may be, because there's obviously health benefits from consuming that. And the consumer reaction to any of these situations is we just don't want to take the risk. So, there's multiple benefits to be gained from rapid detection.

What we're going to do now is Steve is going to give you more specifics on the methodologies that we're using, and then I'm going to just sort of come back and wrap up and say how we're planning to move this forward, just very briefly, and then we'll have some questions.

DR. MUSSER: Thanks, David. I'm going to try and build on what David has talked about, and also try and highlight some of the issues that the task force made --

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which we would really like them to try and address and take on and make recommendations for us.

This is a very complicated situation with salmonella, as well as testing and the way we do testing, and it's very compacted. I'm going to move fast, so I hope I'm clear in my explanations.

FDA does numerous types of testing. We test products all the time in a surveillance mode. We also switch to different gears when we do outbreaks, and we're doing tracking and identifying sources. We're also doing testing as a part of our routine advancement of science in our laboratories -- how we get new methodologies, new technologies, new approaches -- out into our labs. They also have to be validated in a real-time environment using real world samples.

The point is that they all require different levels of confirmation. So, if you

look at this little chart here with specificity and sensitivity and discrimination -- if you take salmonella, for example, our code of Federal Regulations says any salmonella is a violation. So, we're doing routine surveillance. Our techniques and out technology really just look for salmonella. They don't look for Newport. They don't look for Saintpaul. They just look for, "Is it salmonella or not?"

In the case of a trace-back where we got an outbreak, we need to go all the way down to the far right to very high specificity multiple pulsed field electrophoresis matches. That's a considerably more time expenditure. It requires much more genetic resolution of the test and a much finer degree of validation of the genetic information, and it takes longer. So, the type of testing that we do spans a great continuum and thus represents a fairly high need for diversity in methods.

I'd just like to point out there's

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a very significant difference between testing that we do for E.coli and testing that we do for salmonella. Not insofar as the way we do the testing, but in the difficulty of the testing. So, in terms of E.coli, we have 0157:H7 or shiga-producing E.coli, and they represent a very distinct genetic group from other E.colis.

Salmonella, on the other hand, are very homologous, and they are all pathogenic. They all make you sick. None of them are particularly good for you and all make you sick, unlike E.colis, which there are numerous ones you could have and not even know that you had a particular E.coli.

So, here's where salmonella really gets complicated and differs substantially from E.coli and some of the other pathogens that we're dealing with. And this is what really makes our trace-back difficult.

So within salmonella, you can look at the species and sub-species, primarily the

sub-species enterica, represent 99 percent of all the human pathogens that we typically encounter.

Salmonella Bongori, at the bottom, is linked with reptiles, so if you have pet turtles and you get a salmonella infection, it's probably from that particular species.

The interesting thing to point out here is that our probes right now only detect salmonella, so the rapid probes that everybody has -- and I'm not just talking about FDA -- The probes that everyone has just detect salmonella. They don't differentiate even at the species level between Enterica and Bongori. Doesn't mean it can't be developed. It's one of the things we'd like to see, but it dramatically lengthens the time and complicates trace-back.

It gets further made difficult by the fact that within Enterica, there are 1,531 and probably more, individual serovars -- like Typhimurium, like Paratyphi, like Newport,

like Saintpaul. And there are no individual tests, molecular tests, that can differentiate one from the other.

So, when we're out doing an outbreak -- And this is where the impact of this is particularly represented. If we're doing an outbreak investigation and we're looking for Saintpaul, in the case of the most recent outbreak, and our test only says there's salmonella -- We get real excited when we find a salmonella on say, a pepper or a tomato, or whatever it is we happen to be looking for, only to find out that, "Oh, it's not the salmonella that's implicated in the outbreak." And we go out and we do sampling and it's not pointed. It's not well targeted at the places that we need to be looking.

I put this slide in because I wanted the task force to be particularly cognizant of the continuum of sample analysis that exists in foods that's not really present in clinical samples. Food samples don't

present themselves to us. We have to go out and get them. They don't let us know that they've got an infection, and so somebody has to go out and collect them in the field. They have to pick them up and they have to take them to a laboratory for testing. Samples have to be prepared. The samples have to be analyzed by some kind of technology, and then a report has to be generated. And this is all kind of a continuous process.

So if you have a technique, a new great widget for us to use that can run a 1,000 samples a day, but we can only process 50, then that thing is just sitting there not really helping us a whole lot.

Or, if the report generation -- You know, we can do one report a day and we have a technique that can run 1,000, it just -- You have to recognize that each point in this process is a choke point for getting information out in the course of an outbreak. And just having a really cool new fast

instrument doesn't solve the problems with food testing.

You might not be able to see this slide. I just wanted to point this one out because of some common misconceptions. It's not possible for us to test every tomato or leaf of lettuce that's out there. Just think about the volumes that are present and the fact that tomatoes are not bar-coded. Lettuce is not bar-coded. You go into a grocery store. There's a mound of lettuce there. There's a mound of tomatoes. Now, you go into another grocery store. Same thing. Same thing.

Across the United States, there are thousands and thousands and thousands of grocery stores filled with millions and millions of heads of lettuce, leafs of lettuce, and tomatoes. Some of them could be local. Some of them could be imported. We don't know. They're not tracked that way. So finding out where they came from and how they might be implicated in this particular

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outbreak is a critical need of ours.

Another common misconception is that microbial contamination of produce is uniform, and it's not. If you look at these pictures -- The one happens to be a Roma tomato field on the left, and then a close-up of one of those Roma tomatoes. The ones on the bottom can have a lot of spatter, and one side of the tomato could have some spatter on it, and the other side may not. The ones higher up on the vine tend to be a little cleaner and don't have any mud spatter on from rain or irrigation. And we know that 10 to 100 organisms are enough to make people sick.

Well, 10 to 100 organisms -- You can't see that spot, and they could be on one little part of the tomato. So, you can't just go out and take tomatoes and say, "Oh, I'm going to find this product." You have to have good sampling techniques, sample a lot of product to find the contamination.

And lastly, we need an enrichment

step -- And this is slow process, and this is one of the things that we really need help in figuring out where to move next. These pathogens that are low-levels, we need to enrich them. There's competitive microflora that might be there, so if you just swab a tomato, which would really not be very helpful, you're going to get the most abundant organism, which could just be a bacillus, or some other environmental sample that happens to be there. And if you do a non-selective enrichment, you're going to grow out the more higher volume organism, if you will.

There are biofilms and the pathogens are actually injured. They don't -- Growing on tomatoes, growing on produce is not their preferred way of living. They would much rather live in us, or in an animal, or in a nice 37 degree environment. Living outside and living on the surface or slightly inside of a particular piece of produce puts them under stress and they're constantly dying and going

through a difficult process of life. So they have to be essentially nursed back to health and allowed to grow in a selective medium or we can't detect them.

One of the real critical things that we need to do is work on sample preparation. Sample preparation, until about two or three years ago, was largely done by taking the sample -- be it lettuce or tomatoes -- shaking it up in a bag, and then taking the sample out of the bag, and processing that particular rinsed material.

And then, we've simply moved now to incubating that whole product over the course of 24 hours in the enrichment media. And each one of these processes takes a long time. 24 hours for the initial pre-enrichment, 24 hours for the selective enrichment, and then selective plating. Each one taking longer, about the same amount of time.

The interesting thing to point out here is the difference between the sample

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preparation techniques and how it changes. So -- and the difference also between individual products.

So, if you look at cantaloupes, and you just try and rinse them -- and swabbing would be even more ineffective -- we get very, very low recoveries of organisms. If we soak then overnight and allow them to grow out of the environment they're living in into the broth, we get much higher recoveries, more than a factor of ten-fold recovery.

But we don't see that with tomatoes, which indicates we need a little more development on how we might get salmonella out on tomatoes. There's a significant difference between soaking and rinsing them. But we're not getting anywhere need the recovery that we do with cantaloupes, which points out a need for better sample preparation.

So, right now, it takes us 10 to 14 days to go from collecting a sample,

processing it, getting it a pulsed field gel electrophoresis pattern, and matching that with the outbreak pattern.

We can speed that up a little bit by using a -- Once we have sort of a presumptive positive salmonella, taking that and then running pulsed field gel electrophoresis on it before we have the serotyping. The thing to point out here is the real-time choke points in this particular assay, if you will, or process.

Serological confirmation takes three to five days. It just -- Even if you're ready to do it, it takes along time with salmonella because there are so many different serovars. And it's just not easy. It takes time.

Pulsed field gel electrophoresis -- The CDC's protocol is a day, but in practice, it takes labs two to three days to do it properly. And even then, there can be smearing across the gels and have to be

repeated.

So, those last two techniques, which are really key to trace-backs, take a week. In a week, we could go back and try to re-sample that product, and it's gone. So, those two steps really are in need of improvement in terms of time.

Just a word about -- These aren't going to show up very well, so I'll just move on. Basically, what pulsed field gel electrophoresis does is chops the DNA of the organism up into large pieces that are run on a gel to produce something like a fingerprint -- In our case, I like to refer to them as bar-codes -- to get basically a genetic bar-code for that particular strain of organism.

And you can see by the steps up here that this takes a couple of days. First you have to grow the organism. Has to be a peer culture. You can't have mixed cultures or you get, obviously, different bands of DNA produced. And then we often use multiple

enzymes because the enzymes give us higher resolution if we use more than one.

And then we run the gel, and the gel has to be read into an image. The image has to be transmitted and matched up with CDC. This is all an automated process, but it does take some time.

PulseNet is how this all works, and how all the PFGE patterns come together. The key point to make note of here is that these are all validated protocols. If you do this in Minnesota, if you do it in any certified lab across the nation, you'll get exactly the same result. And that's one of the keys to doing this well. You can't just have some new technology that only works in one laboratory or two laboratories. It has to be a very consistent, highly reproducible method that works throughout public health labs, environmental labs, FDA labs, food laboratories around the world and in the United States, and gives the exact same result

every time it's run.

The other important point here is that CDC has invested a very significant amount of money in producing a very high quality database similar to what the FBI would do with fingerprinting. If you only have six fingerprints in your database, it’s not very helpful in matching anything. You have to have enormous quantities of data, in a database, for any kind of match to occur. So, just having a really nice instrument that does identification isn't helpful if you don't have the corresponding database to go along with it to allow you to match those patterns.

Oh, this is really not very good. Basically, what I wanted to show you here is the fingerprinting that occurs, or the bar-coding that occurs -- We use this just to match. This is just an example of -- We matched these bar-codes. When they match, you can take a clinical sample and an environmental sample; compare them. They're

identical, and we know that they're related to the outbreak.

We know this is all problem. It's not something that we've just suddenly woken up after the salmonella outbreak with tomatoes and said, "We've got some problems here." We've been working on this for some time, and we've been looking at points in the process that we can improve and speed up.

One of the things that we did in this particular outbreak was add real-time PCR detection following the enrichment step. And this is basically a stop-go, "Can we do more?" analysis type of approach. So, bring a lot of samples in, enrich them, is there salmonella there?

If there's no salmonella there, then we're going to throw them away and just concentrate on the ones that we can actually detect positive salmonella samples. So, this improves our laboratory through-put.

The other thing we've done is

we've integrated a device called a Bio-Plex, which is actually a fancy flow cytometer using color-coded beads to do serovar identification. This is a method that's been developed, again, at CDC. It's about ten years of work, and it uses ONH antigens to identify the serovar of the salmonella.

And unfortunately, it's only good for the top 100 most commonly occurring, so we could get a match but then not be able to actually serotype it. In our case, it's worked. And then PFGE again. But, we can basically take the time we used to process samples and improve that by two. Half as much time.

Just another word about the Bio-Plex, the Bio-Plex takes 45 minutes to do the assay. So, in 45 minutes, you have the serology if your organism is one of the top most commonly occurring human pathogens.

Again, the great part about this is it's been well-validated. It's in 17 --

Well, actually, more public health -- Almost every public health lab in the United States has this technology now. So, we could do any kind of serology with this. We could do any clinical samples. We could do MRSA with this. We could do anything that you were particularly interested in. It doesn't have to be salmonella. It's just that the platform is out there. And ORA labs have been adding this and we've been adding it and trying to improve the technology and adapt it for use with foods.

There are lots and lots and lots of other technology out there that we're looking at in our labs right now -- New approaches to ribotyping , new approaches to multilocus variable number tandem repeat analysis, optical arrays, which aren't even a commercial product yet, snip analysis using the Bio-Plex -- Bio-Plex was originally developed for single nucleotide polymorphism analysis -- Pyrosequencing, and whole genome

sequencing.

And while this seems a little odd, we're working with Virginia Tech right now. It costs about -- It takes about three days and about $2,500 to produce a whole genome sequence of a serovar. We can't actually slurp that up and do anything with it from a computer and bioinformatic standpoint, but again, it shows that technology is improving and we need to be aware of it and be thinking about how we might take that technology -- how we might adapt IT to looking at that particular information and using it in the most complete fashion.

Another one that we're working on right now, and this is just one of our future -- Just highlighting this as one of our future areas of work, is this IBIS T5000 biosensor. It's basically a product that uses mass spectrometry to look at PCR products.

This platform is the product of DARPA, the Defense Advanced Research Product

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Agency. It's one of the .01 percent of products that actually are successful and make it out of that program. It will detect anything that's there. It's basically a "tree of life" type of approach. If there are viruses present with bacteria, it will detect the viruses and the bacteria. The great, nice thing about this is it also detects mixed populations, which is a concern we have with salmonella.

We know that you could have salmonella Newport and salmonella Saintpaul present or other serovars present in the same sample, which makes a real problem for us if we pick a single colony to do PFGE of and it's not the right one, but the right one happens to be present in the sample, we'll miss that food sample.

So, we're looking at this particular approach also because it has a very good database, very highly refined database, complements of the Department of Homeland

Security for virtually all of the pathogens that we know. It doesn't drill down to the level of serovar for salmonella, but we can adapt it to that, and we're in the process of working on that.

So, in conclusion then, a few points for the Committee to consider about new methods. We get a lot of requests to look at technology from industry that's producing and selling new technology.

And we ask them, "Have you tried this on foods? Have you applied it to a food? Have you done cheese? Have you done a piece of tomato with it?"

"Well, no. It works really good on air. It works really good on, you know, on a swab."

"Well, have you tried enriching and how does this whole continuum of testing fit into your product?" And so, it's really important to look at that whole continuum of food testing and whether the application is

suitable for that particular application.

It has to be a technology that is extremely rugged and very reproducible. A lot of these public health labs are staffed by people with minimal science backgrounds. A lot if it is very turn-key. You know, "green light-red light" type of analysis. If you're looking at sophisticated gene array type of approaches, that's not going to work in a public health lab unless you have a very smart informatics program for it. It's going to be difficult to interpret that data, so there's a practicality aspect of it. And it's got to provide a better level of performance.

We get lots of things now that say, "Yes. We can do this just as well as PFGE." Well, if you can do it just as well as PFGE, we already have that. We need something that's faster, higher resolution, better than what we already have.

And finally, if we could address the issue of enrichment, and sampling, and how

that approach is taken for food samples. That's a real research project -- how to improve enrichment and sample detection out of environmental samples in contaminated produce.

That concludes my talk. Thank you. I hope I didn't go too fast.

DR. MCNEIL: No, that was -- It was a terrific write-up that you submitted in our book, and I think those were very informative presentations. Thank you very much. I actually had no idea the whole system was as complicated as it was.

So, we have time for questions -- Oh, I'm sorry, David. I forgot. Sorry.

DR. ACHESON: That's okay. Just a quick -- To sort of pull it all together because I want to do is to just focus back on some of the Commissioner's comments and some of the earlier discussion, and point out that wherever we go with this, we have to use it as a regulatory tool. And we've got to develop the detection technology that we can then use

as a regulatory tool to take regulatory actions.

So, it needs to have that level of robustness for us to be able to turn it into something useful. And we've got to keep that in mind as we go forward.

It's very pertinent right now, this whole topic, because in July, we opened for the first time a high through-put microbiology lab in Denver because part of what we want to do at FDA is to drive rapid detection technology. Because of the complexities that you've heard from Steve a little bit about taking multiple samples on the food site, we need rapid detection technology, not only from the technological side, but the high through-put side.

So, we're gearing up to be able to do this internally through high through-put labs. And as I said, we just opened one in Denver. And in terms of our next steps -- as Frank alluded to, what we're proposing is to

develop a group comprised of FDA, CDC, NIH, USDA, Department of Homeland Security, and DARPA to essentially get our heads together to look at how can we drive some of these needs because there are needs for the Department of Agriculture, for Centers for Disease Control, and locals and states, as well as us.

So, we would see that this is a win-win all the way around, and the goal would be to move this forward, and then report back to you in the future.

So, with that, I thank you, and now would be happy to take any questions. Thanks.

DR. MCNEIL: Are there questions? Yes, Erik?

Q AND A AND DISCUSSION

DR. HEWLETT: David, very nice presentation. Both of you. I need you to put this in perspective for me a little bit.

This is huge effort and technology, but in theory, much of this is

preventable by irradiating food and I realize there are all matter of economic logistical problems of doing that, but in the past, there's been a major problem of naive emotional reaction to that approach, rather than the other problems.

Can you tell me -- At the present time, I know that that's being done some now, where are we in terms of the balance here of emotional reaction, economic constraints, as opposed to other barriers to doing the radiation side, which would reduce the need for doing some of what you're talking about here.

DR. ACHESON: That's a really good question. I think, you know, the whole focus of this presentation is largely on response when things go wrong, and it would be remiss of me not to point out that the key here is prevention. I mean, that's a key part of our food protection plan, and you prevent the problems in the first place.

Part of that preventative strategy is surveillance to some level or another where you're looking to verify that the preventative controls are working, or you're just checking import samples based on risk to look for problems. So, there's definitely, outside of the reactive response element, there's a need for rapid detection technology.

In the context of a radiation for fresh fruits and vegetables -- Just recently the agency has approved the use of that for certain types of fruits and vegetables. I'm not aware that it's actually being utilized yet by many, if any, in the industry.

And you're right, there are a lot of potential concerns around the use of that in consumers' eyes; not from a scientific perspective, but consumers have a resistance to that. But the key to that is irradiation is not a silver bullet, and the preventative controls on the farm around fresh produce are what is key. That's the emphasis that the

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agency is focusing on, but there is obviously a desire to have that tool in the toolbox of the irradiation, and we've provided that -- at least for some leafy green commodities, so it's there if folks want to use it.

But it's not like, "Okay. Now, we just irradiate everything and we relax." That's not the strategy that we feel is in the best interest of public health.

DR. MCNEIL: Oh, I'm sorry. Steve?

DR. SUNDLOF: Yes. Just to follow up on the irradiation question. We are still evaluating other produce and other foods for irradiation.

I think the critical issue that you raise and it is very critical, is that consumers don't want irradiated food. We've seen this with irradiated beef. We've talked to some of the stores that still sell irradiated beef, and they're saying, you know, "We can't make a profit on it because nobody wants to buy it." So there are some real

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strong consumer messaging work that needs to be done.

I recently attended a meeting in which a person who used to be with the FDA and now runs a consulting firm -- is trying to put together a coalition of stake-holders and asked if the FDA would be involved. And the whole purpose of this is to try and develop a campaign which would alert consumers about the benefits of irradiation and the lack of any kind of adverse health issues that might result from that. So hopefully, we can change that -- the way that people feel about it.

DR. MCNEIL: I had one question. Is the line between CDC's responsibility and FDA's responsibility clear?

DR. ACHESON: Is the line between the two clear?

DR. MCNEIL: In outbreaks.

DR. ACHESON: Yes. You know, I think the line is clear. Certainly there are challenges with regard to that line because

there's some grayness, and to that end, Lonnie and I have actually met individually and with our groups to make sure that we're even more seamless than we have been before in terms of dealing with those situations. But you know, Lonnie many want to speak to that too from the CDC side.

DR. KING: No, I think they are clear. They need to be clearer, but I think that we're doing a pretty good job.

If I could just kind of follow-up on two really good presentations -- You're talking about the development of a regulatory tool. I think it also is the development of the tool that's used in epidemiology and surveillance. And the key to standardization is to be able to look at these data sets across ecological settings and surveillance and human and animal health, etcetera, so what you develop here is something that is going to be critical, and what we adopt at CDC or in public health agencies across the states.

The other part is, the development of this that might be able to be used globally. So, you had been very nice in salmonella Saintpaul to understand with our colleagues in public health in Mexico, "What are you seeing in salmonella Saintpaul with this DNA fingerprinting?" So they had the capability for pulsed field gel electrophoresis, but it really wasn't up and running very well. We couldn't do the comparison, and it really was difficult then to understand the epidemiology, and it certainly didn't help in our trace-backs.

And then the third part is just the critical need for states to go ahead and adopt this and understand that they need to be brought up to speed and have the capacity to do that.

Do you have any comments about kind of how you kind of take this technology into a broader perspective than just the regulatory tools and the need to do that kind

of collectively?

DR. ACHESON: Lonnie, I think you're right on target there. It does need to be used more broadly. I'm just coming at it from an FDA perspective of -- It's got to at least have that capacity to be a regulatory tool for us. But it also needs to have that flexibility to be able to go down to the states and locals.

We've got to build that into our thinking as we move this forward. I think we're more and more establishing the mechanisms through the food emergency response network, for example, where we've now got an infrastructure with states, some more advanced than others, to take this technology and to drive down into those food emergency response network labs.

And it won't happen overnight, and it will go into hundreds of labs, but it will -- I would foresee that it would work its way through the system.

DR. APPLEBAUM: David, I just have a question in terms of the statement that was in our briefing books, specifically -- and I don't want to preempt the workshop that's going to happen in 2009, but can you share any of the information that you've been able to glean from what's going on in the EU as relates to their pilots on traceability and what they're doing for the tomatoes?

DR. ACHESON: I'm not familiar with the specifics of that, Rhona. I know that it's ongoing, and I know that FDA is following that, maybe Dr. Sundlof has some component of that because I think CFSAN is directly engaged with that activity.

DR. SUNDLOF: Actually, we had a public meeting on traceability a couple weeks ago, I guess it was, in which we invited a representative from the European Union to speak to us on what they are doing and how far along they are in their efforts.

Unfortunately, we didn't --

unfortunately, he wasn't even very much aware of the tomato pilot that they were putting on, and so we didn't really get very much information. But we will be following that very closely.

DR. SLIKKER: Steve and David, excellent presentations. My question is, is that as these newer field rugged technologies become available, is there a possibility to build on the synergy between the various centers of FDA and between FDA and other agencies to actually have industry utilize this technology in the field -- in the processing plants to prevent these kinds of exposures. Do you see that as something in the future that we can help complement from the FDA perspective?

DR. ACHESON: I'd love to hear Steve's perspective on this, but I think the short answer is "yes." I mean, our goal, obviously, Bill, is to look at it in a purely selfish way for what tools can we develop for

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a purely public health benefit.

But, certainly there are people here representing the food industry, or have expertise in the food industry, on the Science Board -- Rhona, I'm looking at. And you know, I think in essence, part of our challenge, which has come out in some of the earlier discussions, is the partnership question.

And a key part of protecting the food supply is building those partnerships with industry around preventative controls, but also around technology. And in that context, if you look at the technology industry, if they're moving forward in certain areas and we can utilize that technology in a more specific way for the regulatory side, I could see this could both ways.

Steve, any thoughts?

DR. MUSSER: I think you have to keep in mind that industry has sort of different needs and different approaches to looking at some of these problems.

If you look at the produce industry, for example, they don't really care whether the 0157:H7 pattern matches the one from another field. They only care whether there is a shiga-producing E.coli there. So, they have a real good PCR test for that, and if they get a positive, they dump the whole load.

Their needs are in many ways being met by some assisting technology. Salmonella, for example, they don't care whether it's Newport or Javiana, or any of the serovars. The Food Code says "No Salmonella." They detect salmonella, they do a cleaning process.

So, you have to be very mindful that there's often a very significant difference between industry's requirements and needs and a regulatory authority and scientific needs in terms of trace-back and what industry may or may not need or do.

We routinely work with the industry to, you know, "What are your

questions? What are your problems? How do you -- are your needs being met? Is there something we can work together on?"

But, it is important to remember that industry has very different needs in the way they approach the regulatory compliance with our programs.

DR. MCNEIL: So, maybe one final comment from Frank before we move on.

DR. TORTI: So, you know, just turning that comment of Bill's and looking at it in a different way, however. One of the -- I think the intent of this task force, which is sort of an inter-governmental task force, is first to assess and be sure that we have a top-down approach to investing in the most promising of these new technologies and that everyone in agrees that these are the ways to go.

But part of the task will be also to engage industry, academia, and others who are interested in these issues to bring their

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knowledge and their skills to also bear in on this problem so that at the end of the day, the scientific contribution that we can make to this is that everybody has had an opportunity to think and to reflect on where the science is that is going to deliver the products we need.

Now, it may be that they are a little bit different products, but I think there may be also a core of centrality of needs as well. So we'll have to see, but at least the process will be inclusive, and I think that's an important part of what we're communicating to you today.

DR. MCNEIL: Why don't we move on the next section on melamine, and if we have additional time at the end of that, we can come back to the presentation on salmonella. But I'd like to thank our speakers very much. They were just terrific.

So, Steve, you're up first?

OVERVIEW OF CURRENT METHODS FOR DETECTION OF

CONTAMINANTS IN FDA-REGULATED PRODUCTS:
INTENTIONAL AND ECONOMICALLY MOTIVATED
ADULTERATION (melamine paradigm)

DR. SUNDLOF: Thank you. I'm just going to tell the melamine story, and I probably know it as well as anybody because a year ago, I was the director of the Center for Veterinary Medicine dealing with the pet food issue, and when I made the move over to CFSAN, melamine followed me.

So, basically, this is an interesting story. There are many side stories. I can't get into them all, but we'll just kind of walk you through this, and some of you have already heard some of this.

How we learned about it? So, we're going to talk about how we first learned about melamine, the current situation with melamine in China, and infant formula. What we've learned about melamine and melamine plus cyanuric acid -- kind of the mechanistic reason for the health problems, and then some

of the information that we still continue to seek on this.

How we learned about it? Well, in March of 2007 -- The date is indelibly etched in my memory. It was March 15. We received a call from Menu Foods, which is a pet food manufacturer in Emporia, Kansas -- they indicated that they were going to be recalling 60 million units of pet food on the next day, on Friday. So, once they announced that, we were absolutely deluged with phone calls from concerned pet owners about what pet food -- which of the pet food brands, and was their pet involved.

In the first three weeks, we had over 12,000 calls. Now, we generally get somewhere around 3,000 calls every year in our complaint centers on all the products that FDA regulates. So within three weeks, we had more complaint calls than we normally receive over a period of two years for everything that FDA regulates. And in fact, we actually received

many more calls. Many people couldn't get through. We found this out -- we have complaint centers in all 50 states, and people just couldn't get through. It was that bad.

During that period of time, we held over 13 press conferences and media calls just to keep the information flowing to consumers who were extremely concerned about the health of their pets.

So here begins in March 16, in Menu Foods, there is three things there. Las Vegas -- that was the supplier of what turned out to be false, counterfeit wheat gluten that was used in the manufacture of pet food.

Emporia, Kansas is where the main plant was located, and we also know that some of that shipment made it out to their pet food plant in Pennsauken, New Jersey.

So, we started the trace-back at that point. It was, in many ways like the recent salmonella outbreak in that it became very complex very quickly. So many products,

so much material being distributed throughout the country, and very widely distributed and quickly.

We didn't know what it was. All we knew was that pets were dying, and that the company had been -- They had taste-test cats that they use to release lots or release batches of pet food, and if the cats liked the food, then it went out. That was how part of their quality control.

Well, they lost a significant number of cats in one of these palatability trials. That's how the company found out that they had a problem, but we had no clue as to what was the cause. It was diagnosed as acute renal failure. That's all we knew.

We started looking for everything that we normally associate with acute renal failure. We looked for heavy metals. We looked for ochratoxins. We looked for ethylene glycol and a lot of other things that potentially cause -- Nothing turned up positive.

But eventually -- and this is, I think, a testament to the creativity and ingenuity of chemists that they were able to identify melamine as a compound within two weeks of our being alerted to this problem.

That was very well received. I mean, we knew that we had melamine. Next question is, why should melamine be causing this? All of our toxicologists now are sitting around scratching their heads saying, "Melamine is pretty inert stuff." When you look it up in the literature, it says that it takes about three grams per kilogram in order to cause toxicity in rodents. So this was the next problem that needed to be dealt with.

In the meantime, we had a second importer that was importing a product called "rice protein concentrate." Again, it didn't turn out to be rice protein concentrate, but was a substance that was actually turned out to be what flour that had melamine. Wheat flour plus melamine equals wheat gluten and

rice protein concentrate, I guess. They had supplied other pet food manufacturers in the United States, so we had another recall on going with an entirely different firm.

Okay, so I think most people know this story, but a year -- year and a half ago -- when we said "melamine," and the response that we got back was mela-who? It just was not something that was on our radar screens. It was not something that we routinely tested for. It was not something that we thought was a particular hazard.

Melamine is in many, many products. I think this is formica on this podium, and that's melamine. It's in so many different products. But the reason that it was used in this case was because, as you can see from the chemical structure, there's about 2/3 nitrogen, by weight. It was the nitrogen content that was used to artificially boost the protein level in these products.

Wheat gluten is supposed to be

high in protein. Generally, it's purchased on the basis of its protein content, so it should be around 85 percent protein, as my understanding. And the way protein is measured in the food industry is to do a very old method called a Kjeldahl determination which only measure nitrogen and then you multiply that number times something, to some number, to get to the overall protein content. So, it's a surrogate for actually measuring true protein, and that's how it was used for economic gains.

Okay, so, here are some of the industrial uses of melamine. Fertilizer, a lot of plastic resins, and I don't know -- It doesn't show up very well, but that's kind of the polymer of melamine that gives it its value because it is used in plastics and such. It's also used in some pharmaceuticals.

One of the other problems then -- Once we've determined that melamine was the adulterant that we were concerned about, we

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need a way of actually measuring it reliably for regulatory purposes. And so, again, our chemists came to the rescue and developed a gas chromatography mass spectrometry method for analyzing melamine in various pet foods and components of pet foods.

And then, we put it up on the website, on our website, so that everybody who was wanting to measure melamine in pet foods could do so. And there was a lot of demand for that. The state laboratories needed a method. It was being used in other countries. Everybody needed a method. So putting that method up there quickly really helped multiple our efforts because so many other people were working to bring us information.

So, just as we thought we were getting things under control and product was being removed from grocery shelves, we found out that -- What turns out to be a fairly common practice is that pet food that can't be sold for one reason or another because it got

moisture damage or it was a bad run or had quality issues, it had expired on its sell-by date -- gets transferred over to the animal feed industry. And so it was for live-stock.

So, now we had melamine-contaminated pet food being fed to live-stock, and the question became, "What do we do with those animals?" It turns out there were several million chickens that were involved, over 50,000 pigs involved, and it also ended up in some fish food.

So we needed to do a risk assessment, and the reason we needed to do a risk assessment very quickly is because the US Department of Agriculture would have to indemnify all of those producers that had contaminated feed and again, millions of chickens, over 50,000 pigs. It was a lot of money.

They needed to know whether or not those animals could be sent to slaughter safely. Time was of the essence because

chickens generally only are around about six to seven weeks. That's their life-span. They grow extremely rapidly and they would have outgrown their facilities. Same with the pigs. They market them at a certain weight, and if they can't sell them, the pigs actually outgrow the facility, so there was an urgent need for a risk assessment to determine whether or not those products could be consumed safely.

We did this risk assessment, published it, put it up on the web. It was peer-reviewed. It basically said that on our best estimates, that a 132 pound person could eat 800 pounds of contaminated meat and still be under the acceptable daily intake. So, turned out that there was very, very little risk, if any, to the public, and that allowed the USDA to then go ahead and approve those animals for slaughter.

So, after months, we finally got the situation under control and we thought we

were done with it forever, and then -- What do you know? We have the current situation in China.

So, here's again -- melamine, and it was found in infant formula. On September 11, another date that is easier to remember, but again, this is the date that it was announced that the Chinese had this problem with melamine in an infant formula, and subsequently with kidney problems in infants.

We've learned from one of our counterparts in another country a couple days before that China was having this problem. We immediately sent out people, our investigators from our field offices, to the various Asian markets in the major cities to determine whether or not there was any Chinese-made infant formula in the United States.

We knew all of the infant formula manufacturers in the US -- There's only really five of them. We contacted them immediately, asked them if they were sourcing any of their

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milk-based ingredients from China. All of them assured us that they were not, so we were starting to understand the scope of what might be out there. We did not find any infant formulas from China in any of the Asian markets that we visited, and there were several thousands of visits that occurred during that time, so -- So, we were well on our way to having a good message to tell the public when the Chinese actually announced that they had this problem.

The current situation -- Again, this is according to Chinese government, they haven't changed their numbers in many, many weeks now it seems like, but we know that there is at least 53,000 ill infants, the vast majority under 2 years old, over 13,000 hospitalizations, four deaths -- Three of those are attributed directly to melamine. The last one cannot be confirmed.

In addition to infant formula, just like the pet food issue, it started

spilling over into other products. And here is some candy from the Cadbury company that didn't make it into the United States. They distributed that -- It was produced in Asia and distributed in the Asian market.

But we started finding melamine in candies. There are several candies that came to the United States that were Chinese-manufactured in which we did find melamine. We put those products up on our website. The company has initiated recalls. We have had no cases that we're aware of any adverse health effects in the United States as a result of melamine, and we trust that will continue.

Other states were also testing products. So, Connecticut, California -- a number of states started testing products that they felt might contain melamine and we're finding them. We confirmed many of these.

And then in China, these look like racoons, but apparently they are dogs. They raise these dogs in China for their pelts to

look like racoons, and 1500 Chinese racoon dogs died from this tainted pet food. So it was also a pet food issue there.

We know now that it has also been found in things like eggs because the Chinese -- This practice has been going on for a fairly long time where feed materials are contaminated with, adulterated with the melamine in order to improve their protein content so that they can get a higher price.

One of the things -- And I think Randy Lutter is going to talk about this, about why this is attractive. And it's attractive because certain products are purchased based on their protein content, so anything that can be initiated to artificially increase that has higher value.

The method that we had developed the year before, gas chromatography mass spectrometry, was not sensitive enough to get down to the levels that we really needed to in this outbreak. So, since the last outbreak, a

lot of chemists were working on other methods and we were ready to go with a liquid chromatography mass spec method. Again, we published that on our website, and so everybody that had that kind of equipment and expertise could be using that method. And this is the method that is being used fairly universally now for all the countries.

In the face of this, we re-evaluated our risk assessment because now we were dealing with a much more direct problem. Rather than the melamine actually going through an animal and then getting into the food supply, now we had it directly in the food supply.

So we conducted an additional risk assessment. It came out differently. It was based largely on the first one, but based on new information that we have acquired since the pet food outbreak. We were able to use that in coming up with a new risk assessment. We published it. Again, it is out for peer

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review, so that we can see if it needs to be adjusted.

Here are some of the things that we've learned about melamine and cyanuric acid since the pet food outbreak. Well, the working hypothesis -- and it was very interesting that before we even found cyanuric acid along with the melamine, people were speculating that it can't be melamine alone. It must be melamine in combination with something else.

And the pathologist looked at this and said, "This looks very much like urate nephropathy, acute urate nephropathy, in people, when you look at the crystals." So, the colored one there -- That is actually from a dog that was poisoned by melamine and those amber-colored lumps there are the crystals of melamine plus cyanuric acid.

In fact, one of the -- From Proctor and Gamble, one of the chemists who helped identify melamine as the contaminant -- Once he identified melamine, actually said,

"There must be cyanuric acid here." Their methods didn't pick up cyanuric acid, but he said, "It's got to be here. Let's look for it." He did and he found it.

So, it's easy to see how this occurs then, because one of the tubes, I think -- There's two tubes here and then the third one, the white one. One of those is a dilute solution of melamine. One of them is dilute solution of cyanuric acid, and if you just pipette one of them into the other, you get this reaction immediately. And under the microscope, this is what those crystals look like.

So, as we started to zero in on the cause, it became very apparent how this was all working. This is some experimental studies that were done in FDA Center for Veterinary Medicine, in which trout were fed diets of melamine alone, cyanuric acid alone, and then melamine plus cyanuric acid. Didn't see any lesions in the melamine alone. Didn't

see any lesions in the cyanuric acid alone. When you combine the two, you get these crystals that are identical to the ones we saw in cats.

Why is this occurring? Why are we seeing both melamine and cyanuric acid occurring in these feeds? Well, there's a couple hypotheses. Either melamine is breaking down through microbial degradation or it's just an incomplete synthesis that the manufacturer of the melamine that was being used was not very high quality melamine. It was melamine that was produced under poor conditions.

The arrows are pointing in one direction. That's the degradation pathway, but you can flip those arrows around and it's exactly the same for the synthetic pathway. And you can see in that pathway that in addition to cyanuric acid, there are there intermediates, ammeline and ammelide. Those were also found in pet food last year. So,

that's how we think this whole thing actually happened.

Cyanuric acid polymerizes with melamine very easily. That's the green structure, is melamine. The non-green structure -- I guess it's the orange structure, is cyanuric acid, and those are hydrogen bonds. They bond at a 1:1 ratio, and we found crystals in cats that looked like 30 percent melamine, 70 percent cyanuric acid. Most of them had been reported since are about a 50/50 mixture.

One of the other problems that we encountered early in the outbreak of pet food was that people weren't seeing these crystals when they were doing histopathology. The animals died of acute renal failure, but they didn't see many crystals. They saw a few, but not very many. Well, we found out that was that these crystals dissolve in formalin. So, as they were fixing the kidney tissues -- you let it set over the weekend -- before we

actually prepared the slides, the crystals are gone.

So, getting that information was very helpful. Then once that information was out, pathologists started picking it up much more readily.

One of the really interesting papers that has come out since the pet food outbreak was one that came out of the University of California at Davis, in which they actually dosed cats, again, with melamine alone, cyanuric acid alone, and then the combination, at very low levels up to fairly high levels. What they found was that at the lowest level in which you had melamine and cyanuric acid, the lowest level that they fed, cats developed acute renal failure within a day.

So, one day at relatively low levels -- It was 34 milligrams per kilogram, cyanuric acid and 34 milligrams per kilogram melamine, which gives a total melamine content

of about 64 milligrams per kilogram. When we did our original risk assessment, the lowest level that we could find for a no-effect level in any rodent species was 63 milligrams per kilogram.

So, our NOAEL -- When you have half of that -- melamine and half cyanuric acid caused acute renal failure in cats after a single dose. So, our whole concept of how you measure the toxicity of these kind of compounds when it's not -- When you're looking at a single compound, melamine -- It's something that we'll talk about here as information needs.

So, here's some of the things that we still need to be able to understand better -- The toxicology studies and investigate the synergistic action of the combination of melamine and cyanuric acid, and possibly the other analogs, so we get a better understanding about exactly what concentration in the blood would cause crystallization in

the urine. Obviously, cyanuric acid and melamine are soluble in the blood and are not precipitating out because we don't see crystals in any other organ except for the kidney. As urine formation occurs that what is in the plasma gets concentrated significantly, and at some point precipitates out.

We need to understand that process better, about the solubility and the PH influence, and how that might affect toxicity, and at what level do we not have any concern anymore about that because it just is too low to cause crystallization. We need pharmacokinetics studies in mammalian species to look at the clearance rates of these products.

It may -- You know, one of the concerns we have was that infants don't have very good renal function. Well, that actually might be beneficial in this case because the better you're able to concentrate urine, the

more risk you are of developing crystals. But we need to know more about how that all works.

We need information from the Chinese medical authorities about what they're actually finding -- what do these crystals contain that they're finding in infants? We don't have any of that material in the United States. We have asked, but we need to know a lot more about just how that syndrome developed. We need to develop some rapid test methods to be able to detect melamine and related compounds in a lot of the products that we regulate -- not just foods, but other products as well. We need to identify other economic adulterants that might be used.

This is the oldest game in the world is to adulterate food for economic purposes, whether that's substitution, whether that's adding something to it to increase the weight, or whether it's adding things like melamine to increase protein content. We need to start looking at that as part of our food

defense program. And Randy is going to be talking about that in a second here.

Other information we need -- We don't know what background levels of melamine in food are. Melamine is a food contact substance. It's regulated as food contact substance. Melamine is used to make plastic-ware that's used for food. Again, surfaces like formica, on which food is prepared, and some of that is -- Obviously, there are very low levels that do leech into food.

We need to know what those background levels are so that as we continue to test and our methodology gets even more sensitive, we need to know what's naturally there and what might have occurred through contamination or adulteration. And then we need to have an ongoing surveillance of a wide variety of protein commodities, not just milk proteins, but soy proteins and other kinds of proteins, and make that a regular part of our surveillance efforts.

Well, so the lessons that we learned from that is that global connections make safe-guarding the food supply more complex. You've heard about this over and over again. I think in the melamine case, both with the pet food and with the current outbreak, that FDA has really stepped up to the plate and did all that it could do in the face of great uncertainty and in uncovering this new syndrome. But we welcome the Science Board's feedback as we continue to address these issues of intentional economic adulteration.

So, I think that is the last slide. Yes, it is. Thanks.

DR. LUTTER: I think you've heard from my colleague, Dr. Sundlof about how we've intervened a and responded to threats caused by melamine in animal feed and the food supply, and I think that presentation also lays a really good argument why we believe within the agency our response has been both

rapid and agile, and we've benefited from some really exceptional scientific sleuthing by staff in the labs and in the field offices.

But what I'd like to talk about here is a broader problem than simply melamine, and that's really the problem of addressing challenges from economically motivated adulteration of FDA-regulated products in general.

What I'd like to talk about is first, a little bit, the recent context and the history behind economically motivated adulteration and some of the causes. What we'd like to present is a structure, if you will -- a framework, for thinking about the next major case of economically-motivated adulteration, and share with you some actions that we're taking to anticipate and prepare for that next case.

And melamine is not unique. You've heard today really two stories entwined into

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one. It was apparently added to infant formula and dairy products to increase the apparent protein content. That's what Dr. Sundlof talked about. It was also apparently added to gluten, actually, that is a typo, to wheat flour intended for pet food to increase apparent protein content and sold as wheat gluten. But there's broader episodes than that recently.

Heparin has been in the news a lot because heparin has been adulterated with over-sulfated chondroitin sulfate and that's been associated with a significant number of adverse events in the United States. And again, that's an instance where FDA has played a leadership role in sharing test methods internationally with our counterpart regulatory agencies abroad, and based on use of those tests methods, discovered exactly the same type of contamination in their drug supplies as occurred here.

Diethylene glycol is another

example that's been on and off in the news for some time. It's apparently added to drugs and food in place of glycerin.

The problem that this poses is not new, as Dr. Sundlof has mentioned. And I point that out just to indicate that in some sense, there's good news and bad news here. The good news is it's one problem that we've solved. The bad news is it used to cause a lot of harm.

As early as 1858, there was an issue of swill milk in New York. It was derived from cows who were fed alcoholic mash, and it was allegedly responsible for the deaths of up to 8,000 children. And here's a quote from the "New York Times" of August 13, 1890.

So this is, as has been mentioned, an old problem, and we're fortunate that in the United States at least, it's been solved. Congress took action more than 100 years ago with the Federal Food and Drugs Act

proscribing adulteration. And if you look carefully at the words here, it's clearly their intent to capture economically-motivated adulteration.

They have "lower or injuriously affect its quality or strength." "Substitute wholly or in part for the article." "Any valuable constituent of the article has been wholly or in part abstracted." "Mixed, colored, powdered, coated, or stained in a matter whereby damage or inferiority is concealed." The entire purpose of this language is intended, clearly, to get at economically-motivated adulteration.

Similarly, with the language in the Filled Milk Act of 1923. This is an old problem, Fortunately, it was successfully remedied through most of the 20th century.

But that's then and this is now. And as Dr. Torti mentioned, we're in a new world, and the new word is essentially driven by a very important phenomenon of

globalization. And FDA has responsibilities for the safety of products sold here, but they aren't made here anymore in the same way that they were predominantly in the past.

You saw data earlier today and in an earlier presentation to the Science Board at least a year ago, about the growth in the volume, in the number, of imported lines of FDA-regulated products, and those indicated absolutely astronomical rate of growth.

It works out to 14 percent per annum since 1997. And anybody familiar with a little bit of high school arithmetic knows what that does over an extended period. This is a very, very high growth rate. And not surprisingly, what it implies is that as a percent of value, there's already very high shares of FDA-regulated products which aren't made in this country and instead come in from overseas.

The challenges that globalization thereby poses can be seen as we have to now

rely on protection at the border to a far greater extent than was necessary. And that's intrinsically weaker because we lack partnerships with state-based regulatory agencies, as is the case with domestic efforts and other information about the nature of the production process and the supply chain and supply chain security. It's simply lacking when the products come from overseas.

The Administration has taken a whole collection of high-profile and very energetic efforts to address this. President Bush signed an executive order -- I think it was July of last year -- initiating a Cabinet-level task force chaired by Secretary Leavitt. In November of last year, it issued an Import Safety Action Plan, parts of which dealt with FDA-regulated products, and we've been implementing aspects of that very actively since then.

More broadly, with respect to challenges, there's a fundamental need for us

to understand better the economic systems and the associated incentives that exist in other countries and cultures. And, for example, a year ago, I think most of the people in this room would not have known that there were premiums paid in China according to the protein content of milk and being cognizant of the vulnerabilities associated with that. In fact, most countries and the United States use fat content instead as a basis for value.

So, what we'd like to do is talk about and share with you a framework, if you will, a strategy for thinking about how to identify the next melamine. And I use "next melamine" as short-hand, simply for the next large scale case of economically-motivated adulteration for FDA-regulated products. We hope it doesn't happen, but I think the recent history suggests we would be remiss if we didn't start thinking now strategically and systematically about steps we can take to anticipate it and help prevent it, and that's

what I'd like to walk through with you now.

The basic idea is application of a Willie Sutton principle, who years ago was quoted when asked the question, "Why do you rob banks?" is "That's where the money is." So, what I'd like to do is put on our Willie Sutton hats for a moment and ask, "Where would Willie Sutton think about exploiting opportunities for vulnerability in adulteration to make money in the food supply?"

And the basic notion here is that he would act where the expected reward from adulteration in an economic sense exceeds the expected cost of being discovered and penalized.

I'd like to walk through what that might mean for us moving forward. So, let me focus on the expected reward. You can think about this as the per unit savings of the substitution by the contaminant times the quantity of the products sold. I'm going to

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explore what this really means in the case of melamine in just a moment, but specifically what it means is that if the cost of the substitute is really low compared to the cost of the genuine ingredient when expressed on a dollar per unit basis, and then that's their high sales, and particularly in the case of melamine, high production volume.

And based on data from press accounts, we have some ability to say what were the gains from melamine, and this serves to qualify, even validate if you will, the basic notion that the threat posed by melamine to the extent to which it was economically-motivated because we lack evidence to date to prove that definitively, though the circumstantial evidence is very, very strong. The extent to which this model might be used elsewhere in anticipating the next one.

So, what we know is that in the case of pet food, melamine costs about $1.20 per percentage increase in the protein count

per ton of the product, whereas real protein costs about $6 per ton, as indicated by the nitrogen testing.

And with respect to milk, there's a 50 fold return from the delivered adulteration. Let me walk you through how you we get that. The cost of using melamine, of just adding the melamine per kilogram of milk is about 18 US cents per kilogram, and that's from press accounts. And the return on that is -- This is the increase price per kilogram is about 8.9 cents per kilogram of milk. So, if you add the melamine and then you do the dilution that apparently was being conducted in China, and that gets you a return of 8.9 cents for a cost of about 0.18 cents, and the ratio is 50 fold, the 8.9 over the 0.18.

And that's big. For anybody, especially in the last six weeks, but even in the last six years, trying to make money on the stock market or elsewhere to turn down an opportunity to invest $1 and get back a return

of $50 is really, really difficult unless you're constrained either by a firm sense of morality or by a legal system that imposes penalties for such behavior.

So, what it gets you then is an increase in the price of 17.6 cents per kilo to 26.5 cents per kilo. That difference is the 8.9, and if you were just to presume hypothetically that a billion kilos in China was spiked, that would offer net returns to whomever was doing the spiking of $87 million dollars, and a billion kilos is about 3.7 percent of the annual production.

So, why do I walk you through this? To suggest that the economic model in some sense has some applicability and coherence if applied retrospectively. Similarly for diethylene glycol, there's less compelling data available in the press accounts, but the pharmaceutical grade syrup is priced much more expensively than the diethylene glycol.

Another part of the economic paradigm applied on this problem is that the expected costs of the consequences of doing the adulteration. And what Willie Sutton presumable cared about, not only the gains, okay, but was he going to get caught if he robbed the bank and what would happen to him if he did. So in that sense, what matters is the expected likelihood of detection and the expected penalty.

And some factors leading to a low expected cost of consequences would be first, with respect to the low expected likelihood of detection, low likelihood of detectable health affects. And actually what I think was suggested by Dr. Sundlof earlier is that if you use really high quality melamine that isn't contaminated, so to speak, with the cyanuric acid, then the likelihood of toxic or lethal effects on the animals is quite low, and therefore the detectability is low.

He mentioned that the initial

reaction of all the toxicologists, when told it was melamine, said, "Well, then the cats shouldn't be dying," until someone clever said, "Ah, but we know it's in the kidneys. There must be cyanuric acid."

But therefore, the suggestion is that some chemist was so clever to think about how to rob the bank here in a matter that, if you will, that avoided detection -- they deliberately used high-quality melamine that avoided the cyanuric acid and only later on, when the melamine was co-mingled with cyanuric acid did we find the adverse health effects, tragically in infants in China as well as in animals.

And then also another factor leading to low expected likelihood of detection is if the detection of the contaminant in the product is difficult with conventional test methods, either not practiced or expensive. Also, that there's a history of inadequate enforcement. What

matters here is how people think they might be treated if caught. Associated with a low expected penalty is that the legal system might allow for bribery or other ways of evading penalties, and simply low penalties in the from of low fines or low sentences if imprisoned.

That's not to say that there haven't been costs of consequences in the United States. There was an indictment by a US grand jury in February of this year of two Chinese nationals and businesses they operate, along with a US company and its president and chief executive officer. And that's now in court so we don't know the outcome.

I don't know, though there have been some press accounts, about the effectiveness of the criminal justice system in China. That's a difficult thing for FDA to judge, but clearly it matters in thinking about how the Willie Suttons of the food supply or looking for opportunities in FDA-

regulated products might behave.

So, what does this mean for us? And what should we be doing? And I started out by saying that melamine, in some sense, is a symbol, but one of only several. The other ones are heparin, and to a lesser extent, diethylene glycol. But they're a symbol that the world we live in is changed, and globalization and the existence of relatively weak regulatory regimes abroad means there's a new vulnerability. So how should we behave at FDA to anticipate, if you will, the next threat posed by economically-motivated adulteration.

So, here's what we're doing and we solicit feedback on this. We're establishing a science and policy workgroup within FDA to try to use this framework and other information to think about, constructively, what might be the next episodes, the next vulnerability, and take appropriate measures.

We're also soliciting information

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