Event ID: 1086059
Event Started: 9/8/2008 9:49:29 AM ET
Please stand by for realtime captions.

Good morning, it looks like by my watch it is 10:00, and I know that a variety of people have been sitting here for at least a half hour or so for us to get started. Nakissa will join us in the few moments, but I am Linda Katz and I am the director of the Office of Cosmetics and Colors in CFSAN and I would like to welcome you to the cosmetic breakout and prescription drug opening session. What we have as decided to do for the first hour is combine both cosmetic and over-the-counter prescription drugs to begin our talk. The initial talk that we will be presented by the personal-care products Council and that will be an hour discussion. We thought for the sake of everyone and even those of our presenter is, that we do the talk just once rather than divided into two sessions to have as presented twice. That is the reason for having this session combined.

Following the session, what we will do is after the discussion if there are any questions, we will take those, and that we will once again have a short break to divide the room into two. The drugs section will remain in the top part of them had cosmetics will go to the back, and that we will go on with our agenda for each respective session as they were originally scheduled. I hope this doesn't create too much confusion that but not this was the best way to get started.

With that, but like to do is invite Jay Ensel to get the opening presentation for the first part of a three part discussion from PCPC. The information you are going to hear relates to a survey that was done by the council, that those of us who had attended the ICCR meeting, which is the International, cooperation on cosmetics regulation back in July and August had heard the preliminary results.

Listening to the results of the survey, I thought that the data itself was interesting it was a good way for us to take off on the subject of nanotechnology, on both over-the-counter drug products and cosmetics products that will be relevant to this discussion to follow today. With that, but like to invite Jay Ansell two begin.

Thank you.

Okay, I think and will be speaking from here. Okay, I hope everyone can hear me. Now that we have that slides up for that part of the workshop, let me introduce myself. I and Jay Ansell, I and the senior director of cosmetics programs of the personal care products council. Let me start by saying we are keenly interested in this topic, and have been participating with FDA for some time. Originally presented data on safety and characterization, presenting information on the safety characterization of animal material at the October -- first October 2006 meeting.

What I'd like to talk today about disparate -- give a brief introduction to some of the conclusions, what I have seen over the last two years is to build a consensus within the

scientific community. I would like to talk a little bit about the ICCR process as a background and ultimately lead into the survey results.

Starting with the FDA's task force report. It is one of the areas that I see the most consensus building and indeed is probably consistent with the council's own positions. For example, in the area of challenges, we agreed that nano materials represent [indiscernible] in the past and we're certainly sympathetic with the difficulty and their conclusion not to recommend it formal fix definition of terms for regulatory purposes. Now that the task force testing, we certainly agree that purer or staged testing evaluation perches are appropriate, and that issue is not so much whether the tests themselves are valid, but whether the familiarity with predictive of the value of these tests. In the area of labeling, we agreed that the use of nanotechnology does not think guaranteed the products safety and effectives is not increase, decreased, or affected in any particular way. In the area of safety, we agree whether or not -- we especially agree whether or not a material is subject to premarket authorization or not, it must be safe and effective and color additives and cosmetics must be safe.

We are broadly in agreement therefore with the task force position. The council's position that the resulting paradigm are robust and testing is reliable. Testing approaches remain realistic. We do agree that challenges to remain particularly in the area of characterization of material. We agreed regulations should not be Technology neutral and no labeling is needed. And that the definitions are intrinsically difficult when assuming the role of product assessment. Basically, we agree that products must be safe and appropriately effective.

That lets talk about the ICCR process.

The ICCR initiative is a voluntary group of cosmetic regulatory group of cosmetic regulatory authorities from the U.S., Japan, EU, and Canada. And [indiscernible] definitions products that are regulated as drugs, U.S. OTC are covered with because by definition of the ICCR process. And the intent is to remove regulatory obstacles while maintaining the highest level of consumer protection. The ICCR mission is to agree to implement decisions and subsequent actions while recognizing the boundaries of members legal and institutional constraints. And also to seek convergence on regulatory practices a of the members.

Industry is a participant. With trade associations from each region, gathering the input of their members, so that we represent all of the affected industry sectors. Prior to the ICCR meetings, industry gets together and suggest items that should be priority actions, and during the ICCR meetings, there is an opportunity for the trade associations to give their opinion in particular with the directions for further work. In the first ICCR meeting in September of 07, six priority items were identified. These included GMP 's in manufacturing practices, nanotechnology, market surveillance, authorized substances, and in animal testing and alternatives. Specifically Fort nanotechnology, ICCR invited the industry to develop a common definition of nanotechnology in the field of cosmetics,

and set up in inventory of current applications, and ICCR would be using this information in order to determine the path forward in this area.

The Association to pull together a working group and composed of some members of the Canadian ... cosmetology and fragrance Association. CALEPA the European Association, the Japanese cosmetic Industry Association as well as the U.S. personal care products Council, the council.

In the first meeting, we realized the scope was really quite extensive. Nanotechnology itself covers a dizzying array of [indiscernible] applications, not all [indiscernible]. We realized quickly that the clarification of nano materials was quick to be a critical moment relevant to defining of the survey, and we would need to provide written guidance to the members to help enable the generation of that inventory.

We also face a challenge. The survey needed to be inclusive, yet still focused on cosmetic applications. So we wanted to include all materials of interest, which included, as we imagine, you as OTC, and certain Japanese quasi drugs. We also want to make sure we could all of the material that the scientific community wants to distinguish from a universal materials which we have been conducting safety assessment on pork decades successfully, if not longer. We certainly didn't want to include -- we certainly did want to include gases, aerosols', the quits for which there is no concern about the safety assessment, and of course we needed documentation to support the participants -- inform the participants so they gift to understand that a simple definition based on size was insignificant. And they needed to address issues like stability, manufacturing and form.

We do want to mention that the inventory has limitations. The inclusion of the material on the inventory does not in and of itself explicitly or implicitly suggest any conclusions on safety. The generation of the inventory cannot be considered surrogate for identification, it has no exposure to assessment element, and it is certainly not a risk assessment.

We're most sympathetic for FDA's own Task Force conclusions, because as with many new technologies, the use of nanotechnology does not mean that a product's safety or effectiveness as necessarily increase, decrease or affected in any way.

There are other limitations to the inventory as well. We understand a number of different groups are working on definitions, including ASTN, ISO, and ISPD. At least they have a definition that defers to some extent with the one we work with here. So the key characteristics that we developed must be understood to be used solely in the confines of the ICCR process.

Definition. We're for first asked to find nanotechnology, simply put, nanotechnology is in knowledge and expertise developed a back manipulate material at nano level. It certainly seems trivial but it is a very powerful and important concept. IBM 's ability to spell out their name by manipulating one atom at a time was truly remarkable. But it goes to the expert manipulation and says nothing about the materials themselves. Building this

little engine was really remarkable but unfortunately it does not help inform us in terms of developing our survey. So we understood immediately that we really needed to go farther within the ICCR and we needed to characterize nanomaterials, and to talk about whether they should be included or excluded from this inventory.

We identified a number of key characteristics which we thought were important to make the inclusion or exclusion decisions. First, it is generally recognized that there are two groups of nanomaterials, those characterized as labile which disintegrate upon applications, and those materials which are insoluble particles like titanium dioxide, zinc oxide, fullerines or quantum dots. And the working group would agree with the conclusions of the European SCCP exclude labile and soluble materials. Thus liposomes, micro emotions, nano emullsions would not be included. The key characteristic for cosmetic material is that they are stable and soluble.

Next looked at it is intentionally manufactured. It was important to be excluded the entire universe of naturally occurring cosmetic materials. The 1 to 5 to the ten particles per cubic meter that are present in nano air. But also wanted to exclude byproducts. For example, tend to the third or ten to the fifth particles per cubic meter that are found above the gas bubble, and we did not want to make a candle a nanotechnology producing on the item. And this was adopted and this reflects the [indiscernible] of the U.K. itself [speaker/audio faint and unclear] voluntary reporting scheme where the language they use there is, deliberately engineer. In other words, the material on the inventory should be the product of nanotechnology, the expert [indiscernible] manipulation.

The next key characteristic is nano metric form. Nano particles are typically described within nanotechnology we typically talk about nano particles. And typically speaking, this would be a material with three dimensions and generally in comparable sized, but we know that want it to be broader than that and it included in other things, so particles, rods, and tubes would also be included in our inventory.

We also understand that material behaviour support. So we see aggregates or conglomerates within the scope of the inventory, although we did not expect all would be found in cosmetic products. The next, it determines that nano metric form goes to size. It is amazing that we struggle so much with the definition. Nano itself, nine times ten to the ninth meters was introduced as a prefix in 1951 and is clearly understood, deriving from the nano Greek word meaning, dwarf. Yet we struggle because what we are interested in is not size par say, but behavior. And this is a problem we have faced for many years, the issue of inhalation toxicology and air pollution dynamics, and even though those engineers working in fluid dynamics understand the behavior of [indiscernible]. So in the inhalation [indiscernible] we do not try to pretend in terms of size and shape, but we crypt the particles together the way they behave. If you look at an inhalation study, they did not talk about their size but about aerodynamic behavior, a group of materials which behaves similarly together.

We look at the novel properties themselves, with see the novel properties may exist and be imparted by materials below one nanometer, or about above 100 nanometers. For

example, [indiscernible] [speaker/audio faint and unclear] and that seems to be preferential in the range of 300 nanometers. In fact, some of the data we show that biological activity may be inversely proportionate to size. So we allow ourselves that area of size, but there is no bright chemical or physiologic line. This has been addressed by number of bodies. For example, NNI talks about this being roughly 100 nanometers, where a unique phenomenon allowed for application, Woodrow Wilson uses in the realm of. In fact, different bodies come up with different numbers. We mentioned in the U.K. Department of Food and rural affairs inventory. There they talk about materials having two or more dimensions. Up to 200 nanometers. And of course, The Royal Society has a maximum of 100 but no minimum that they reported including Cirrus at the atomic scale. -- zeros at the atomic scale.

The issue of size is further complicated. You get different results depending on how you conduct your analysis. Thus, we see significant differences between the nominal and actual size of particles depending on their measurements. Conglomerates, aggregates, versus the primary particles that form them, or in fact, the number average of weights versus weight average giving significantly different characterization of materials. How the working group felt in recognition of the value of the uniform, even if it was understandably recognized as an arbitrary value that we would include on the order of 1 to 100 nanometers. Ultimately, we would want to reference back to the FDA 's Task Force statement itself, and where it might have meaning in one context, a definition may be too narrow or too broad to used in another.

With that, let me go to the survey results. We undertook our survey, which provided a discussion paper to the lead Associations, and that would be the [speaker/audio faint and unclear] at the council. We conducted a survey of their key committees and companies, and this would include most major multinationals and certainly the most significant users.

We do understand our limitations, and I will discuss them briefly, but a second level survey would be taken without outreach to many more members, potentially thousands of companies. However, we do believe that it is our expectation that the final results will not differ significantly from what we are reporting today. We understand that this is first level survey of major players. Even when we do the second level survey, we understand we are only reaching out to association members, so we understand that even the second level survey will not include every cosmetic product in the world. And some ingredients advertised as being used may be not caught within our inventory. Although let me emphasize that the members that we did contact clearly represent a vast majority of the products sold world wide. We need to emphasize that the characterization is really multifaceted as I discussed earlier. And we will hear that more in the following speakers. We only ask people to report the nano materials. We did not confirm what they were saying we did not scrutinize the report to any real significant [indiscernible]. [indiscernible] announces. In fact, the materials may be nano in only one of the methods, and only in a minor fraction. It may be only nano during the one stage of manufacturing, it would not to glib to say that their might not be any nano materials in what meets the definition of nanoscale. We got our survey to identify six materials, aluminum, carbon black, iron oxide, silica, titanium, and zinc. These are predominantly used in titanium and

zinc in drugs, carbon black and iron oxide are predominantly in colors and silica in cosmetic applications. These preliminary survey results, we recognize that they will not include every cosmetics [indiscernible]. And some increase its may be missing and some maybe reported outside the U.S. For example, we know from Japan, they report cerium oxide, fulerine and platinum.

In conclusion, let me say, which are broadly in agreement with the FDA task force. It is our position that we are risk-assessment pardigms that we currently use and are robust. The testing is reliable and the approaches we use remain realistic. We do recognize that many challenges remain, particularly in the area of material characterization. We agree regulation should be Technology neutral, and that labeling might not be necessay, and the size alone, it is not what we are interested in. We're interested in behavior and the two to move those discussions into that area as quickly as possible, because it is clear that the association [indiscernible] fully agree that products must be safe and where appropriate, effective.

Thank you. [APPLAUSE]

Our next speaker is Francis Quinn from L'Oreal and will be discussing materials characterization.

Ladies and gentleman good morning to you all. I am pleased to come here this morning and address you all, and talk to you about the characterization of mineral sunscreens. My name is Francis Quinn, I am physicist and I work at L'Oreal in the Paris, but as you can probably guess, accent, I am not French, and Iris and I am here to speak on behalf of the council.

Due to time constraints, I will not go into reams and reams of detail on this subject, but if anyone does have any questions, any burden issues that you'd really like to get off of your test, obviously I will be here all day is accused of hesitate to come back and see me later on if there is a particular topic you wish to discuss that I did not get too, in significant detail.

Two materials that I am going to discuss with you today are titanium dioxide and zinc oxide. The first thing I will say to you about titanium dioxide is that it is an extremely common substance; you dig it out of the ground. On a worldwide scale we dig between five and 6 million pounds per year. Including some form of sand that contain up to 95% titanium dioxide to give you an idea.

For all intents and purposes, titanium oxide is a totally insoluble substance and I will speak, the conditions under which you can solubilize titanium dioxide. All intents and purposes but particularly for [speaker/audio faint and unclear] widely used in a lot of different kind of applications [speaker/audio faint and unclear] and it also [speaker/audio faint and unclear]. What's known on the back neutralized [indiscernible] and we're going to get that today.

Zinc oxide is also very common, not quite as, as common, titanium oxide would be in the top-10 of all of theoxides. Zinc oxide is the top 25 [indiscernible] so it is quite common as well, and liked titanium oxide it has been used in a number of studies and has an excellent safety record.

Does it down to business here, because I am hoping that for many of you this might be fairly new to you and actually how these things are made.

Now in the case of –I'm going to take the example of titanium dioxide, but the general principle is the physics and the engineering are very general and can be applied to both titanium oxide and zinc oxide. You start off with a raw material from which you are one to make the titanium dioxide. [indiscernible] this idea, and a lot of people have but somehow you can take a raw material from the ground and you can grind it down to the nanometers scale. I say forget that, because the physics of it just doesn't work. And if you want to imagine why, if you have a milling devices using ball bearings to grind something down in between the ball bearings you have small spaces that will limit what you can grind down. [speaker/audio faint and unclear]. [speaker/audio faint and unclear] application and [speaker/audio faint and unclear]. Those small spaces set the limits of what you can grind down to. [speaker/audio faint and unclear] So if you're going to make these materials you have to grow them up. You take an ore which is then treated to extract in a liquid form those materials, a source of titanium and a source of oxygen that you going to make the titanium oxide from so it is a bottom up approach [indiscernible] is every one here familiar with that kind of language. So you're going to [indiscernible] you have two paths one of them is a precipitation path one is called hydrolysis, they are just two fancy chemical engineering terms that mean in one you take the liquid you have tiny atomic size species that start to grow, like crystals of snow. The other say you have a precipitations process whereby you have all of this stuff in solutions whereby snow falls it precipitates out. Whatever route you chose to take, and manufactures chose to take different routes, but basically what happens is that you produce tiny crystals. These tiny crystals, we'll look at the sized of them in a few minute, talking about something that is typically, in the case of titanium oxide between 10 and 60 or 50 nanometers. In the case of zinc oxide it is between 20 to 70 nanometers, roughly.

These crystals aren't just produced [indiscernible] at the bottom of your reactor, these are dynamic processes. You could have crystals as a form as nuclei, and it grows into the crystal and continues the growth process. These are very dynamic processes so you musn't think you recover from a reactor, a 50-pound bag of crystals [indiscernible] small crystals fall down to the bottom together and as they fall together they continuously aggregate that the aggregates they form continuously agglomerate. And the reason is very, very simple. When you make these crystals inside the reactor, in the reactor medium where they are around them they can see the precursor they were made from. From a simple [indiscernible] perspective, their only objective in life is to gather as much of the material around them as they can, find as many of common species they can and stick together is so it lowers thermodynamic energy. From the point of view of the physics they want to stick together as quickly as they can. Which is exactly what they to do. Through the growth process, filtration, purification. Which means, by the time

needed to the end of the reactor and the material comes out you actually something that is in its microscopic form, big lumps of material. Then this big lump of material has to be milled. You mill them down. You start off with something that is on the nanoscale, and it aggregates and conglomerates through the manufacturing process and then you have to mill it down. You mill it down because you want to [indiscernible] to optimize the dispersion. Optimizing dispersion is critical for the performance of a sunscreen filter. If it is not well dispersed you get very poor protection. You need to have these coatings and to do that this must be milled. But then, during the coating process, you adding material to the surface of a mineral that causes the material stick together again. Remember, these object that's what they like to do. Mother Nature drives them to stick together as long as they can and then [indiscernible] based on the physical form that the final cosmetic product manufacturer is looking for either a powder or a dispersion, you then have some treatments to make slurries or to make powder form. That is how you make the material. Now, to give you an idea, I did a little cartoon to show you how it works. You have a crystal that we talked about at the beginning of the manufacturing process represented in this cartoon here, and you are significantly below the 100 nanometers scale. However, when you have the crystals that are aggregating together forming the aggregates during the manufacturing process, and then much bigger in size, and the agglomerates which are basically collections of these aggregates that stick together with different physical forces like dispersion forces or Van der Waals forces and you're talking about something that's even bigger. And so, I wanted to show you just give you an idea, this is just very much a represented curve of the kind of thing that the pigment manufacture whose made a titanium dioxide mineral sunscreen this is typically what would come to a manufacturing plant.

Now this material, it crystal size during the manufacturing process is 15 nanometers. So for all intents and purposes, it says, this is 15 nanometer titanium dioxide this is often the way it is referred to in scientific publications, okay. But when you actually look at the size distribution of the final material with the aggregation of the conglomeration, this size scale is microns, the average is somewhere around the 3-5 micron size, and typically the cut off point is around 500 nanometers. This is what is delivered to the manufacture who will then take and introduce into the final product. And so, these are pigment particles these are not meant that were taken out of a sunscreen product. The scale bar here is a micron, a thousand nanometers, so you can see the particle is about 3 nanometers in size. Here, we can see the particle on the uppermost layer of skin, and you can see about a couple microns in size and this is what you typically find in the final product.

The question is, all of this work that's done inside the reactor where we are making these crystals, what's the interest? What are we doing it for? On this chart here [side conversation]. Basically we're looking at is different kinds of titanium dioxide materials. We have five different types of titanium materials. And we have an index for the materials [indiscernible] This index refers to the crystal size that we were talking about earlier on. We're not talking about the final size of the material; we're talking about crystal size. It's like is a nominal index for the materials. On this curve, we have wave length, so this is the visible part of the spectrum from 400 outwards, and in here we have the visible part of the spectrum. Ultraviolet A, B. On this side of the curve here, we're

looking at transmission which means the lower down you are on the curve, the more you are attenuating Ultraviolet light. And right here, you can see that if you organize your chemical engineering properly, when you are precipitating these crystals inside the reactor, if you play around with the size, you actually can get different curves that will either be much higher absorption, or it can give you the broad absorption of your UVA UVB and allows you to fine tune the material performance. Compared to traditional gray titanium dioxide you can see that have you have a net improvement in your capacity to attenuate ultraviolet light. You get a better filter. But there is also a second advantage you get not in the ultraviolet part of the spectrum; it's in the visible part of the spectrum. This is white. It is absorbing uniformly in all parts of the visible spectrum. It takes all colors in the spectrum and mixes them together uniformly, that means white. [indiscernible] However, if you look at the grays that have a much lower index in the visible part of the spectrum they are much more transparent, which means you have a product that is much less white. Which means that people are a lot more likely to use it and reuse it.

This is an example. Here we have five simple formulas made with the five materials I've just shown you. And this is for different skin tones going from Caucasian down to sub Saharan African skin. That is the only difference is the skin tone, the skin carnation it gets darker each time. And what you can clearly see is that it gets more transparent. Now I underline the word "more transparent." It is never completely transparent; we have realize it can't be, given the physics of what I have just described. But you certainly have a net increase, and you can see in the skin that is a little darker that even though it is much more transparent than the others there is still the white that we are seeing in the cream which is indicating the presence of the aggregates of the conglomerates. But you certainly have a product that I were to put that on and then decide to go to the pool you're obviously not going to be complete white.

Lastly, what I want to close with is to give you a bit of an indication about what these things look like in final products. Here what we have is two formulas that are the same, okay, except there's one difference. In one case, you have a nanograde titanium dioxide and the other case you have pigmentary grade. And this is what Jay was referring to earlier on, talking about the way you measure the size will change the value of the size that you measure. Even though that may seem like a very strange thing. So what we have here is we're looking at the distribution in terms of size for the whole product, and this is measure in volume. Looking at the volumes that these pigments occupy in space. The first is not very intuitive is that the curves are very similar. Maybe before this morning you might have thought the nano titanium dioxide might be to the left of the pigmentary line, but of course now you realize is that it doesn't have to be because what is in the final product are agglomerate aggregates that are independent of the size you started with. The second thing you notice is again here is your scale bar in microns one hundred nanometers is down here and we're talking about something that is center more around the ten micron size. It is the same data, except instead of presenting it to you in volume, the volume that the pigment occupies; now I'm presenting it to you as a number. In the case of number the reason why we put number up is, can you go back to the last graph? Now we're telling you the distribution by weight of the material. Most of the weight of

the material is in pigments that are about this size. But small pigment particles don't weight a lot so they don't contribute very much to the curve. That is why we go and do the same data sets, this is the same measurement, [indiscernible]. This way we're allowed to see the number and focus on the number of particles that are at this size. So what it is telling you is a lot of the particles are around the one micron size. But the curves almost overlap which as we all now know makes a lot of sense.

I haven't gone into this in reams and reams of detail but I would hardly be happy to talk more with anyone has any questions or want to talk specifically point of detail. I would like to finish this presentation by saying three things: yes, nanoparticles exist at a very early stage of the manufacturing process, but that is not what you get out of the machine at the end of the manufacturing process, and it is certainly not what is delivered to the manufacturing plant. Where nanotechnology does have an interest is it allows us to develop mineral sunscreens that are very efficient that are very good at neutralizing ultraviolet light, and being that much more transparent facilitates use amongst consumers.

Thank you very much for your attention. [APPLAUSE]

Next, with like to invite at Dan Caldwell from Johnson and Johnson who will talk about the safety assessment of these materials.

Good morning. I am here at the request of the personal care products Council to talk about activities undergoing on in our nanotechnology Technology working group. What I'd like to do today is to talk about four major points regarding the use of nanomaterials in sunscreens. Namely, first that there is no common toxicity profile for nanomaterials. Now as a corollary to that and also consistent with the recent guidelines coming out of the European Commission each individual nanomaterial is evaluated on its own characteristics. The second the safety of the nanoscale ingredients should be evaluated just as any other ingredient that we use, and looking at that you would have to consider the intended use. In this case they are sunscreens, dermal applications, route of exposure. We are going to concentrate on dermal effects. We believe that available toxicological studies and existing protocols are appropriate for evaluating the safety of nanomaterials regardless of their size. Last, the nanoparticles being used in cosmetics have proven to be safe [indiscernible].

I put this slide up for two major recent major reasons. Why use sunscreens? If you consider the fact that roughly 20% of American citizens will develop some type of cancer in their lifetime. And over this year, one million cases of skin cancer will be diagnosed and 60,000 cases of melanoma. You really set the stage for requiring the use of some type of sunscreen. [indiscernible] Skin cancer incidents exceed the total of most common cancers in the US. And regular use of sunscreen has been found to be the safest, easiest ways to reduce this cancer. Now to make a material acceptable for consumer use, you have to make it aesthetically pleasing. If you look at why we use inorganic sunscreens, scattering is influenced by particle size and when they are uniformly dispersed as pointed out before, maximum scattering occurs when size is half the wavelength. Why use nanoparticles? We have wonderful presentation on that; the bottom line is that any grade

particle scatters in the light we want to be transparent to ensure acceptance of use of the product. Again, we saw this curve; the point is if you see a 15 nanometer particle you get very good attenuation of the UVA UVB you also get reasonable attenuation of visible light. The point of this slide is the point out that both titanium dioxide and zinc in nanoscale formulations has been used for over 25 years. This is a safe track record of use of these material in consumer products. The reason that these are safe is if you look at the data on dermal penetration for a lot of different materials material, you can see a 500 [indiscernible] molecular weight cut off for materials trying to penetrate the skin. All these nanomaterials are much, much larger. Here we have the zinc oxide probably on the order here of 7 nanometers, and things that do penetrate though the skin. But the cut point here appears to be. [speaker/audio faint and unclear] looking at it a different way, looking at the molecular mass involved, he could see that it would be fairly small penetration. The skin is a very effective barrier which we don't have exit [indiscernible] leaking through our skin on a normal basis.

A little bit of history and physiology, these studies have been conducted for over 10 years of unspecific nanomaterial. But looking at this skin, you have the epidermis, the strata [indiscernible], a hair follicle penetrates through that, and if you look on the left, you can see three rounds of exposure where materials could penetrate through this skin, possibly. One is intracellular where the material goes around the intact cells, the other one is transcellular where the material penetrates through the cells, and the third is down the hair shaft [indiscernible]. And if you look at that, that is a contiguous lining of cells that penetrates. And what we've seen, if I could ask you to skip a few slides

---

This is the one of first studies that looked at penetration of nano titanium dioxide through the skin. It looked at surface applied titanium dioxide, and a series of tape strips. If you look at the first five tape strips, we see that most of the material is recovered. What that says is that the material does not penetrate to the stratum [indiscernible] is a very effective barrier. But it does show that it is penetrate was accumulated in the follicle, in the hair cells. Go back a few slides.

This is recent publication that presents the results from a European study nanoderm. The report is dated 2007 but just came out earlier this year. What this shows is that particle induced x-ray emission of titanium dioxide particles on the surface of the skin do not penetrate. If you look at the electron microscopy, you can see the penetrate, the particles on the skin that did not penetrate. These particles were formulated in the typical sunscreen vehicle, and did not have any contributing defects on the vehicle to the surface of the epidermis.

If you look at the same side in a different way, what you can see the titanium, which is the blue, shows up on the surface and also in the hair follicle. The slide on the right has filtered out the phosphorus and the sulfur and is focused in on the titanium. And what you can see is that the titanium does penetrate, but does not go through. It stays on the surface. Also, you see a similar effect with crevices and folds in the skin into wrinkles but does not penetrate through the dermis. Again another study of titanium and zinc shows

essentially the same thing. They stay on the surface of the skin. And again, a ten year old study so nothing new here.

This is a photomicrograph of the transmission of electronic microscopy and also laser defraction data of a material that the use a lot of our products. Where this came from was not so much, and in vitro study or in-vivo study or an animal with penetration, but one of the unaddressed exposure concerns is what happens to the material once you use it. Where you use it where does it go? If you look at containers it tells you to reapply after swimming. So we did a study to look at effect in fish and what we found its even though the nominal particle primary particle diameter is 15 nanometers you detect aggregate's, and if you look at the scale that is 200 nanometers right there. There are large particles. We did the laser infraction data we found the distribution range of over 100 nanometers to just over 40 micrometers and with that the particles that have to be dissolved in alcohol to get into a solution in the study with the fish. So the point here is that primary particles just do not exist in formulation. It is building consensus that these materials as used in skin products and titanium and zinc [indiscernible] and the basic science and risk assessment are not changing that these are starting as nanomaterial materials. You have to identify the hazard for each of your ingredients, you have to know your exposures, the your route of exposures, and the element [indiscernible] whether or not it becomes systemically available and then you conduct your risk assessment based on those two prior data points. We think existing regulatory structures are sufficient and any regulations should be risk-based and not defined to any specific technology that may be developed in the future and that safety of all products has to be demonstrated by all manufacturers.

There are some challenges that remain, as alluded to by Dr. Ansell earlier, metrology or characterizing materials is problematic. What we know about one material may not apply equally to other materials, other classes of materials. Inorganic sunscreens are fairly well studied; the database is now developing for some of the carbon based nanomaterials. There is not evidence of a unique hazardous property from size alone; however having said that coupled with characterization pretty much cannot read across from one class across nanomaterials to another. You have to have the data for each specific material.

Lastly, the characterization contains to be an issue with a variety of techniques on the market, and I don’t know if Dr. Canady is here and he mentioned the [indiscernible] program they are going to look at a variety of endpoints for a variety of nanomaterials to try to determine if there are some commonalities that can be fed into the quantitative structure activity models that can predict [indiscernible] in the future.

Thank you. [APPLAUSE]

And then just to finish up the council’s presentation, I would like to invite up Dr. John Bailey, the executive vice president of science at the council to make a few concluding remarks.

Thanks Jay. I think this morning we heard Doctor Ansell talk about what is happening under ICCR, and the good progress is being made there and the questions that we're attempting answered and working through in a way that hopefully will lead to global harmonization, which we believe is very important. Dr. Quinn gave a very good overview of from a physicist's perspective of manufacturing and characterization; I think that is extremely important in the area of TI02 and zinc oxide. And certainly those concerns and thoughts apply to other types of nanomaterials that might be present in cosmetics. And Dr. Caldwell gave a good overview of safety substantiation perspective. These are all very quick and very brief presentations and we look forward to continuing the dialogue under ICCR and having his substantive interaction with FDA and other regulatory authorities and other partner associations.

There are a couple of takeaways. One is that that survey has been done for cosmetics the nanotechnology that is being used there is very limited, very simple, we're not talking about the little letters and machines that you see in some other applications of those nice animated slides that Jay showed. That may not always be the case. Certainly more sophisticated nanotechnology may move into the area of cosmetics and personal care products, and over-the-counter drugs. And as that happens it will be driven by the science. Out experience is that these technologies find their way through the drug area and food area and that sort of thing first, and then make their way into the cosmetics sector.

Some of the questions that have been posed by FDA for this meeting do not necessarily have concise discrete answers that you could then just take can use to develop guidelines. I think this will require a lot of working together to work through each one of these particular questions. And when we talk about products ingredients and uses, they must be dealt with on a case by case basis. The science is there, the methods for doing the toxicology and testing are all well known and well established. What is important is the characterization of the test material. Once you have done that, your test can be designed appropriately and used to establish the safety.

In looking at what Mr. Canady said earlier, the need specific guidance is not clear, exactly what that guidance should contain for cosmetics and personal care products. It is certainly different than it might be if you had an issue of efficacy, where we are talking about a food additive where there may be large scale consumption. It is very possible that existing guidance that FDA issues and guidelines, which are the things that trade association issues may be adequate. So just to close, I think this is a very good forum, we were happy to be invited and included, and we look forward to further discussions endpoints working through the ICCR process on these issues.

Update

Thank you very much for your time. [APPLAUSE]

Unless there are any questions or Q&A of the speakers, what I'd like to do to conclude the joint session, and we will take a short break so the room can be divided in half.

Are there any questions? You need to come to a microphone and identify yourself.

Alice speak loud.

He can't, because it is being transcribed. Yet to speak into a microphone. Sorry about that.

My name is [indiscernible] and I come from NCI/NIH, and my questions is do we know and how many nanoproducts [speaker/audio faint and unclear] are currently in the market regulated by FDA, and how much of an advantage or disadvantage [speaker/audio faint and unclear] [indiscernible] microsize that we know about?

I think at this point, I am not going to answer questions, because that is actually part of our discussion today is to get that information from industry and academia as opposed to directly answering that question. I can't speak to proportions because I am not in the center, that this is information we are trying to gather and find out exactly what is on the marketplace and how we need to approach these problems, and that is the purpose for this meeting.

Any other clarifications for the speakers specifically? Not for general discussion, but for the speakers?

Rick Weiss, Center for American Progress. It isn't clear to me from a physics point of view, because part of the argument I'm hearing this morning is that one of the reasons that we don't really need to worry about nanoparticles is because they're not that many and they are mostly aggregated into larger clumps so to the extent that the sunscreens are giving better protection invisibly is because the few nanoparticles in there are doing the work or are the ones that aggregate and agglomerate also providing protection invisibly. Because it raises the question why did you bother going down to this size if it going to turn to bigger clumps anyway.

Francis Quinn from L'Oreal speaking on behalf of PCPC, when you look at the overall performance on the sunscreen product you basically have three fundamental contributions. Today in our discussion of nanotechnology we talked about one of them, and that one is the intrinsic capacity of the pigment to attenuate Ultraviolet light and what we saw there was that, using the nanotechnology to make these very small primary particle sizes, it means have something that intrinsically is a better absorber. And that intrinsic property is fully maintained in the aggregate and in the conglomerate it contributes.

The second contribution comes from a diffusive effect, okay, whereby the light comes in and hits the aggregates and agglomerates and gets disperse. Now, that phenomenon is based on a nano size, it requires the micron size aggregate and agglomerates to operate. So for example, being nano grade does not give you a particular advantage in that area. You get the advantage in the first area which is intrinsic absorption. The third factor that

contributes is called a mirror effect, where basically these pigments are designed to protect the surface of the skin they represent no interest whatsoever if they were to cross the skin barrier should remain on the skin surface, that is where they work, and they act as micro mirrors. Once again, that contribution has almost nothing to do with nanotechnology its based on the micro size. So those are the three factors that contribute and where nanotechnology represents significant in advance in terms of product efficacy is that in one of the three you do get an end gain. And that last point is something I should have stressed more in my presentation. A product is never invisible. You take a sun screen product that contains a nano titanium dioxide even when you see it in the bottle, it is white. It is not transparent. When you put it on your skin, and get a good, uniform dispersion you're increasing your protection and it becomes more transparent, but never completely invisible.

Thank you. And if there are no other questions, what I would like to do is to have -- take a short break so that rim can be divided. Again, the drug session will be in front and cosmetics will be in the back of the room. They view as the key two -- thank you and thank you to our speakers.

(Meeting is on a short break at this time.)

I think we're going to get started. Welcome to the CDER breakout session of today's public meeting. My name is Nakissa Sadrieh. I'm the Association Director for Research Policy and Implementation in the Office if Pharmaceutical Science in the Center for Drugs. And I will be moderating the session. Because I might have to leave, I have asked Dr. Abby Jacob's the Associate Director for Toxicology in the Office of New Drugs is helping me out. But what I would like to do first is go over the question that were in the federal register notice because I want to reemphasize what Dr. Alderson said this morning, which is the purpose of this meeting, is to get information to the public, the public being you, and information that we would like to get we have identified some questions for the Center for Drugs and these questions are where we need inital help from their public. So I think it is very important for us to go over these questions to ensure that we stay focused on the particular topic as these are what we are most interested in at this time. Although, we are interested in other areas, you consider as well, and certainly you can raise additional questions and I would like to also remind you that there is a docket open until the 24th of October and we very much encouraged everyone to raise additional the issues we need to be aware of in the docket as that is how we are one to be aware of these issues after the docket closes we will be able to analyze all of the points that were raised.

So starting with the question number one, and I will just read these questions. Are there general parameters for screening tools by which to evaluate the likelihood that a particular material might have nanoscale specific properties and to decide when and what sort of further evaluation might be warranted? Are there characteristics and properties of materials the FDA can use to further categorize materials with respect to their likelihood of having nanoscale- specific properties warranting further review?

What are that unique manufacturing features of products containing nanoscale material and how should these be evaluated? A. Is the manufacturing process understanding and development for nanoscale materials different of that of conventional drugs? B, Does the nanoscale materials effect scale-up? and if so, how? C, If you develop nanoscale material containing products under the quality by design (QbD) paradigm does this contributes to process of understanding and manufacturing capabilities? D, Can nanoscale affect product formulation components, excipients, and processing?

What are the unique to the client psychiochemical attributes of products containing nanoscale material? How do they impact controls and standards, specifications, etc? How do they affect characteristics and performance of a product? How do they complicate development and manufacturing of these products? What has been your experience to date with products containing nanoscale materials and/or have you avoided these products due to developments in characterization and manufacturing? And my last question, focusing on characterization of manufacturing aspects of products containing nanoscale materials should be addressed in this forum or brought to the attention of CDER?

So as you can see, all five questions are very much based on characterization and manufacturing. The reason we're focusing on this because in order to try to address these issues and develop guidance we have to stay focused, and we can't develop guidance on everything at the same time. We have identified within the Center for Drugs characterization and manufacturing may be the one of the first places we need to focus on and this is why we developed these areas does the questions.

However, if you are aware of additional questions that we should be thinking about, certainly you should submit the docket and make us aware of those. As I said, this is our first attempt at trying to develop guidance as mandated by the task force report which Doctor Canady talked about this morning, and we would really like to stay focused on the area of characterization manufacturing and really I think it was discussed in the previous discussions as well. If you don't understand the product that you're dealing with, the characteristics, it is very hard to determine if what impact it has on safety and effectiveness. So the most of important to try to understand first is, how do you characterize these things, and how do you manufacture them to have a consistent product. And so the topic of today's discussion, we really would like all the presentations to be focused these issues, and try to address these issues. So I'll try to go over the agenda for today, and tell you more what to expect. We had the PCPC presentation at 10:00, and so the first presentation this morning is going to be Dr. Larry Tamarkin and that will be the only presentation in the morning before we break for lunch. Then we will go for lunch, and will come back, I think we have an hour and have for lunch. We come back about 1:10 p.m., and will have four other presentations that are listed here on the agenda. That will be Dr. George Mills, Dr. Jaydee Hansen, Doctor David Hobson, Dr. Carolyn Carnes, Dr. Rick Pleus. And I also think that anyone that would like to give additional presentations had the option this morning and anyone that you certainly can still sign up. But there are slots available, for people that do want to make presentations which we have a little bit of time at the end of the day for additional presentations. But those will be

limited to probably about five minutes, and if we don't have that many and these could take 10 minutes.

Once the presentations are finished, we will open the floor at for people to come and even if you didn’t sign up, can come and address the questions as you see fit and make comments on them at that point. And that we will adjourn when there is no discussion left. And so, I just want to reiterate, the points the points that people should be making should be focused on the questions, and that the FDA is here to listen and we are not able to answer policy questions or make policy here, but the focus is for us to take the information, go back and try to make policy at some point. If you do have questions please come speak into to the microphone because it is being transcribed, and without wasting any more time, of like to introduce the first speaker, Dr. Larry Tamarkin of CytImmune is our first presentation today, and we will have some questions afterwards and with that you very much.

Good morning, my name is Larry Tamarkin, president and CEO of CytImmune sciences. What I’d like to share with you this morning is that we're beginning to realize the promise of nanomedicines and we would like to share with you our model nanomedicine 6091 which we call [indiscernible]. The problem with cancer therapy is that most chemotherapies can't distinguish between healthy cells and cancerous cells. This problem, we believe, can be most readily addressed by the changing the biodelivery of Cancer therapy, potent but potentially toxic cancer therapies. And our solution is to engineer it so that when the manufactured these nano particles, each in a nano particle is uniformly coded, and when it is hydrated, each nano particle becomes an invisible to immune detection when it is injected into circulation, the particles are too large to exit the normal circulation but small enough to travel safely through the body. They can exit the circulation because the blood vessels that provides nutrients to going tumors are uniquely leaky, with fenestrations or holes that are approximately 200 to 400 nanometers in size. So if the nano particle is small enough it can exit the circulation and get to the site of the disease, just as, for comparison, a red blood cell is about 8,000 nanometers in size. So what we are characterizing is nano particles of gold, if you would, that are going to directly target cancer cells. Cancer tumors.

Here is a blueprint of our product, essentially, and the core of this is a 27-nanometer core of colloidal gold. On the surface of this colloidal gold are two molecules that are uniformly attached to every nano particle. One is tumor necrosis factor alpha, TNF is part of our body and we’ll talk about that in a minute. The other molecule is polyethylene glycol. We know the surface chemistry, so we combined both of these molecules very avidly through available thiols. And each of these molecules must be coded on every nanoparticle of gold. The purpose of the thiol is to hydrate, and that is but the Blue Circle is around the gold particles, hydrate each and every nano particles so that it becomes invisible to immune detection.

Why did we choose gold? Because gold has a long history of safety, the gold particles and colloidal gold itself has been used since the 1930's to treat patients with rheumatoid arthritis. We know the surface chemistry and we know that available thiols and

sulphydryls bond very avidly to the surface of gold. And it also can be used for electronic microscopy imaging.

The history have TNF is very interesting is part of our immune system and it was discovered back in 1975 and in 1985 Genetech made a genetically engineered form of this. And over the next decade, over 100 clinical trials try to harness the therapeutic potential of this very interesting immuno-surveillant molecule. But no clinical benefit could be realized because it was too toxic. In 1982, two surgical oncologists realized that they could isolate limbs surgically, they could actually infuse a high dose of this TNF molecule, 1 milligram, followed by chemotherapy and between 60 and 85 percent local response rate. So that was our target. Could the actually deliver approximately one milligram of this molecule formulated as 6091 systemically rather than locally? And what is the role of TNF? The TNF even on our drug is a vascular disrupting agent. This is a new class of therapies that destroys the blood vessels that support tumor growth.

So as Nakissa suggested, the challenge of going from the bench to the bedside is climbing the mountain called manufacturing, and manufacturing these nanoparticles, nano medicines, uniformly and to some established standards. Basically again, if we go back to our blueprint, what is the unique properties? And I highlight unique properties of our nano construct. And I like to share with you one of the messages that this is going to be on the case by case basis that we can evaluate the analytics and properties of each of these nano medicines. This is our particular core product and will share with you and our specific analytics. The unique things about this simple, number one, because the particles of gold has weight, we can actually centrifuge it or spin it down, and we can separate those molecules which are bound to the surface of gold from those which are not bound to the surface of gold. So we understand what is free and what is in fact properly bound. The second thing we know about the service chemistry is that we can actually use strong reducing agents and actually strip off all of the components that you see on the surface of gold nano particle. So we can interrogate both the finished product as well as each of the components.

Here is the list of analytical tests that we do that we do, that are special to our unique product. We have to analyze how much gold there is in the product and we have to analyze the size. Because what I showed you, not only do we have to understand the size of the product, that’s the core size, which I showed you was 27 nanometers. But also, what is the hydrodynamic volume? What is the body appear this to the body. And it is actually 70 nanometers. We then have to anlyze the active Pharmaceutical ingredient [indiscernible]. We also have to evaluate that each and every particle has the appropriate amount of the immune avoiding molecule's, polyethylene glycol, and finally, and most importantly, what is the service charge? It has to be either neutral or negative otherwise we run the risk of inadvertent toxicity.

So here is how we analyzed our gold nano particles. The characterization here for size, for in process sampling, is done by UV spectroscopy, and differential sedimentation by centrifugation. Each of these methods have been correlated to electoral microscopy, which is, if you will, the gold standard for analyzing the particle size. Quantitatively we

use inductively coupled plasma atomic emissions spectroscopy to give us a quantitative analysis of how much gold did we start with and after the manufacturing process, how much did we end up with?

So for the TNF analysis, we have a number of different ways. Number one, because of each and every molecule of TNF on the surface of the gold particle is biologically active; we can interrogate or analyzed the TNF on the surface of the finished product without disturbing the TNF and without disturbing the product. And because of the centrifugation properties I shared with you, we can spin down the product and determine how much of the TNF is actually bound to the particle and how much is not bound, by which we call free. We can also strip off the TNF to make sure that the purity hasn't a changed during the process of manufacturing. Finally, for dosing purposes, we have to know the biologic activity of a product and this is best defined by an in-vitro bioassay.

The polyethylene glycol, a critical component in avoiding immune detections, is analyzed also into different ways. One we can measure in the final drug product the total amount of polyethylene glycol, and then through the centrifugation and stripping process, we can determine how much of that polyethylene glycol was actually bound to the gold nano particles. Finally, we can determine surface charge by imaging zeta potential, all of these characteristics together it gets us away upon interrogating in analyzing our core product. Very quickly, I will read through the actual manufacturing process.

This process, this chemistry, believe it or not dates back to 1857. Michael Ferede did the first publication of this chemistry, where you use gold chloride and sodium citrate or a reducing agent to ultimately get mono dispersed, you're seeing on your right, gold particles by electron microscopy. So we are going to a number of reducing processes. I will show you that very quickly. This is on the bench scale. You're going to boil some water, and add gold chloride, this yellow solution you'll see in a second.

And then, very quickly, we'll add sodium citrate. Very quickly to this spinning vortex solution and three reactions happen. First they form nuclei that then aggregate and turn into a black, the solution gets clear, then to a black, and then it is going to turn red. And that in real time is 27 nanometer colloidal gold nanoparticles ready for manufacture. Now how are we going to take all of those golden nanoparticles and ensure that every nanoparticle is a uniformly coded with both our active pharmaceutical ingredients and the immune avoiding molecule?

First of all, I'd jump ahead of myself. This is the reproducibility. Size matters. It matters in the nano medicine business because if a particle has a large distribution and the particles are under between seven to ten nanometers they will be filtered out by our kidneys, we have to make sure that we are above that threshold. So 85% of our particles are between 15 and 35 nanometers in size. So again, here's how we do it now on a larger scale when we talk about manufacturing and how we take it from the bench to the manufacturing process to the bedside. This is now on a 150-liter scale when we were doing it only four liters at a time or 80 liters at a time. Now we are doing 150 liters at a time. This is going up to about 5000 clinical uses per unit. Here is how we manufacture

like I said, how do we make sure that every nanoparticle is uniformly coded? You see the T connector right there, right where you are looking right now, in those two reservoirs', one has a red colloidal gold nanoparticle and another has a mixture of TNF and polyethylene glycol. And it's pulled together in that T connector and right there in that small volume our drug is formed, and the question is, can we scale that up? And here is to show you, you take that 150 liters of TNF and you have now[Indiscernible], the Y connector is where the drug is actually formed. And the drug is formed and is concentrated an [Indiscernible]. So this is the strategy that we have adopted to create a uniform nanomedicine that we can analyze and well characterize. This drug in its current form [Indiscernible], and I will share with you what again, we are beginning to realize the promise of nanomedicine. One of those is to take the toxic molecules' and see if we can reduce or greatly eliminate their toxicities. And to do that we have the cooperation of the National Cancer Institute's in Bethesda Maryland that ran our phase one clinical trial in advance stage cancer patients with cancer tumors, three patients per group, each patient was only treated twice once on day zero and once on day 14. And our challenge was to determine maximum tolerated dose and to also what we wanted to do was to find the tumor in this particle, find this nanoparticle. And the result of that clinical trial was that this 6091 was very well tolerated and our target dose was achieved, remember we wanted to achieve approximately 1 milligram, we exceeded that and went to 1.2 milligrams per patient. And we saw no dose limiting toxic effects and no significant adverse effects that were unexpected and related to treatment. The gold particles were found in the tumor. This is the patient's listing here, basically doubling that number give the active amount of that patient. And the 200 or 400 micrograms per dose was the previous MTD, and you can see in the green, it is significant exceeded. And showing, what is the promise of nanomedicine. TNF is a molecule, that causes us to have fever [Indiscernible] but we can control that fever, this is patient number one, you see the red, the first dose the patient developed a large fever but with treatment with [Indiscernible] we can completely eliminate that. [Indiscernible] And each patient was treated with this P treatment -- pre treatment [Indiscernible] and causes low blood pressure renal failure [Indiscernible] that complete organ failure. So that is something that we wanted to avoid at all costs. So the question is, have we eliminated that? And in the next slide, all of the patients are summarized here. None of the patients were experiencing hypertension. So with the nanomedicine, those were managed, and eliminate toxic effects that are going to lead to clinical problem. So the question is now does it get to the site of disease? This is a patient with an up inoperable breast cancer, and you can see on your right -- with inoperable breast cancer and you see on your right, those black dots are nanoparticles of gold and comparison to normal healthy breast tissue where no gold particles were seen, so now we have an indication that we are actually getting the medicine to the site of the disease. And we basically confirmed our proof of principle that we can get exposures 30 fold above TNF alone because we were able to keep the drug away from cytotoxicity we achieved, quantitative, the amount of TNF [Indiscernible] in combination with chemotherapy, 60-85% local response rate. And we will begin phase II clinical trials mimicking that clinical design. And we are just in the beginning of a series of colloidal gold [Indiscernible]. And what I want to leave you with this morning. One size does not fit all. [Indiscernible] our program was supposed by the advanced technology program at NIST and Dr. Laboudie who ran the [Indiscernible] at NCI, I want to leave you with

this one last ideal three legs of a stool nanomedicine. The ideal nanomedicine should be designed for cancer to avoid uptake by the RES (liver and spleen) [Indiscernible]. By design, it should target tumors by two different independent ways, one would be the EPR, it exits the circulation, a passive response and it should be actively be binding to the active process and that is what our TNF provides. What is and not the least important, relevant to today's session, the products needs to be manufactured to define specifications that can be well characterized.

Thank you for your time.

[applause]

Thank you Larry. I guess we can ask the audience if you have any questions at this point directed to the speaker about the presentation. [Indiscernible]

My name is [Indiscernible] from NCI. What a wonderful presentation. Regarding your product and the [Indiscernible] it is super. And it clearly [Indiscernible] safety and comparison to the TNF. My questions is as soon as FDA prioritized the new [Indiscernible] and that is your prerogative, so I and was wondering whether or not the TNF [Indiscernible] nanoparticle and my question is, can your drug be classified as a priority, number one and so it can get approval as quick as possible?

That is not mine to answer. I thank you for your comment, but all nanomedicines in my view, I'll let FDA speak to this, but we are not seeking to change any regulation nor short cut anything and it should be product specific and it's done on a case-by-case basis. So the guidelines and everything that we are doing and working with the agency and other products of there, we are perfectly fine and satisfied with the collegiality and the way which we interact with this agency. And we are not trying to shortcut any process. And on the other side of the coin we are not trying to have any barriers to make it more difficult.

I don't think we are going to be addressing any issues specific to the drug approval today, however are there any other questions for the speaker?

Michael Shaw, Elon Drug Technologies. I have a manufacturing question first, your sterilization technique would be part of your manufacturing process and I assume this is maybe aseptic [Indiscernible] in nature. And characterizing I guess this morning a lot was made of agglomeration and how do you monitor agglomeration upon delivery.

Larry Tamarkin. To answer your question, First of all, everything is done by aseptic filling prior to final step prior to lyothilization. Basically the way that we deal with agglomeration of aggregation is that we test for that by its reconstitution, and the clarity of the product when it reconstituted from its [Indiscernible] form. Also we also know if the particles are well stabilized because of zeta potential they will not agglomerate and they will remain stabilized as long as the polyethylene glycol is on the product. That's the reason for the characterization and the manufacturing is to ensure that the particles

don't show this aggregation. One can see aggregation, visually, even by eye, with colloidal gold because it turns black, you can see black coloration on the surface and that is a clear sign of aggregation on our products. Again unique to our product.

Thank you. Any more questions? I'd like to ask a question of you Larry since your company is in the process of developing nano based products and so based on your presentation you've clearly adopted a characterization process and you're in the process of developing scale up plans for manufacturing. Would you have developed a guidance document from the FDA that would have helped you during your characterization and manufacturing like the type of advice that you think the FDA needs the provide a developer of a nano based particle product? Guidance not available right now.

Larry Tamarkin. I think that for us, we started this process back in 1994 or 1995. So what I think to answer your question specifically, going forward, is that not all of us need to fall into the same fox hole every time. And that is where I think an FDA guidance would help for those following behind us. Because we have fallen into every hole that everyone one else who is developing liposome's, we discover all of those problems. So clear guidance's on size, surface charge, and this of concept of distribution. In other words, what are the concerns of distribution that one might have? What are specifically the ways of characterizing these drugs? These are again, are going to the development and the in process as everyone else. Some of this may not generalize and may provide guidelines to help people to understand what they need to be looking for. And those are questions. In other words, if I were to have something to say to the Agency, give us a list of question -- give us the questions that you need to think about to answer. If you can answer these questions, then you will be on your way.

Thank you very much. And we rely on individuals such as yourself to identify those types of foxholes. [Indiscernible]

Thank you very much. I think at this point we have a lunch break. We are going to break for lunch. So I will ask everybody to go to lunch [inaudible] so why thank you very much, everybody if. See you this afternoon.

[Public Meeting on Nanotechnology on lunch break until 1:00 Eastern Time]

So I think we're going to get started with the afternoon session. And I wanted to mention that one of the presenters, Jaydee Hansen we don't have slides for you. And I think someone has signed up to speak today, so there will be an additional speaker today. If you have slides for your presentation, please forward them to me.

So the first presentation today after lunch is by Dr. George Mills, who we know because of his past experience at FDA. He is currently the vice-president of medical imaging consulting and Parlexel in Gaithersburg, MD. And he is going to speak for about 20 minutes, thank you.

Can you all hear me in the back row?

So what I want to do is bring a very straightforward technique, which during my years in the agency was developed and used routinely. Which has a great value and structural support for you in developing nanotechnology So we're dealing with nanotechnology assessment tool for investigational and approved drug and biologics. Because as we look at this and the documents in the background we may well associate nanotechnology with new as well as approved products. So this tool may be used in both aspects. It's whole body biodistribution imaging of organs and tissues for comparative biodistribution, retention, clearance, of radiolabeled nanoscale elements. And I'll take you through it.

The objectives, assess the in-vivo biodistribution and of nano sized drugs and biologics for the following, and note you can do this for drugs, small molecule with biologics, you can assess organ and tissue localization, I'll show you pictures of how it's been done and on label already. Organ and tissue retention. One of the real challenges around nanoscale particles was to determine if they're ever going to leave, so you want to determine where they're going to do your assessment. Routes and rates of excretion. To identify these are key elements and all of these can be done quickly in the course of 5-7 days. And I'll show you the timing onto it and how to do it. To identify organs and tissues for potential toxicity and planning for safety monitoring. Those doing regulatory know that we need to find out where these products are going, and where they are staying so that we can potentially modify safety and efficacy criteria for assessment. Assess for localization and retention in inaccessible organs and tissues. This technique will give you the first step to be able to survey for elements in nanoscale technology, crossing blood/brain barrier for example, going to cornea and other areas that we don't typical anticipate that our drugs and biologics will move to. Comparative biodistribution for alterations. Because necessarily if we start to incorporate nanoscale materials into approved products you're going to want to do comparative biodistribution to see if nanoscale material is altered in its biodistribution as compared to the approved product. So we need to be able to investigation nanoscale material and do comparative side by side biodistribution with the approved product. IND phase one safety. This should be one of the entry criteria that you want to utilize as you make your first step into phase one. First in human clinical trials biodistribution studies. Assessment and confirmation of preclinical findings to determine if you've done animal model studies preclinically to determine if the biodistribution in humans is giving you a diagnostics pattern to be able to associate the nanoscale material, especially as compared to standard non nano material. Diagnostic doses can be used with this so you can get micro dose strategies which can be incorporated in USFDA and Europe. Plan future human clinical trials. Probably the best essence as to why to put this into the early phase development is so that you can plan phase 1,2, and 3 in terms of biodistribution imagining as well as to determine where you're going to associate biodistribution for efficacy and safety. Non target, unexpected organ localization and retention is a significant focused issue with nanoscale material which is why this technique will give you that first imaging to be able to associate and routes and rights of clearance. Efficacy schema can be selected and determined both for localization retention for tumors and abscesses, targets of abnormal localization with this technique. Especially when doing comparative modeling to see in your change to nanoscale material has altered targeting.

Comparative biodistribution imaging design, how to do it. First off, in accordance with the release for this meeting, this is well established, cost effective, generally available in any diagnostic nuclear medicine associated department. So the applications these techniques are generally well established. And they are incorporated in therapeutic FDA biologics labels today. Bexar, for non Hodgkin's lymphoma, acts as a safety gatekeeper is biodistribution studies. Zevalin, the same way for a safety gatekeeper. All diagnostics and therapeutics for nuclear medicine drugs and biologics incorporate the same technique, and on label when you look their radiation [inaudible]. So we've established a simple, direct, cost effective tool for you.

Basic technique, one, radio label the approved and investigational drug or biologic approved candidates. Both for nano and non nano. Two, comparative whole body biodistribtion imaging over time. The over time is the piece. You don't want a snap shot and go away with one image. You want to do it over time. And I'll show you that.

The radio labeling technique, and again these techniques are well established. We're looking at 50 – 60 years of iodine labeling techniques to understand this. Typically non destructive biologics of the drug. Linker technology may be necessary if you go to such labels as indium. In-vivo stability of the radio labels is essential to identify and we have an extensive history and experience as I've described so that you're working with a well founded technique.

Imaging time points, when do you image? The essential piece here is to work off the pre-clinical PK data, and I should show you too baseline 30, 60, 90 minutes. That's typically a small molecule pattern, that's the drug pattern so they clear much more quickly. The baseline 34, 48, 72, 96 is a biologic timeline so you begin to recognize that the patterns will be associated with this. If indeed we take this to the next degree I wonder if the nano will be even shorter. But that's necessarily what we need to see for the individual product. But these are two comparative timelines.

Labels. If you're in to PET radio labeling these are the patterns that you would typically use. C-11 has a 20 minute half life. It's well readily available, currently in many research institutions. F-28 is commonly available through the US and Europe, with a 110 minute half life. So you can see that you can put a label on as fast as the material will necessary be uptake, clearance and retain. And I-124 is a PET label which is quite effective and has a 4.18 day half life. So if we're looking at biologics we can label for a long period of time. So effectively the technique is well established and the labels are readily available.

Gamma radio labels, typically the nuclear medicine labels. I-123 has a 13.5 hour half life. Indium 111, 2.8 days, and I-131, 8.01 days. So we begin to see that this technique can readily arm your ability to come immediately into phase one development, label your drug or biologic that is in nano or non nano, and effectively do comparative whole body biodistribution.

And this is the picture that you are basically looking for. This is the picture of Zelin and it's technique is exactly the same that you would use for nano. You're seeing whole body biodistribution 1, 2, and 3. The time points are labeled as that, because whether you're dealing with a biologic, a drug, or a nanoscale we're going to change it depending on the PK. But we can see very quickly the bio distribution within the vascular structures; the liver, the spleen, the major organs are distributed but not localized. The tumor, the target is demonstrated in the second time point. The clearance through the large bowl is demonstrated in the second time point, localization is retained in the liver and we demonstrate bone marrow. The third time point demonstrates all of those we've seen before. You can associate this in terms of anatomy with CT or MRI or other types of imaging modalities so you can effectively determine where it's localizing. Now you can take various scoped down pictures and look very closely at specific areas, such as brain localization or even the cornea of the eye. But from that standpoint, this is the pattern, its readily available, and its on label already.

So you can do, competitive and comparative if biodistributionre for portfolio analysis if you're working from the drug or biologic development side, and you put this together to determine if the size, or charge, or shape is affecting you nanoscale particle. And you can do the comparative biodistribution to see if you are affecting the distribution.

Typically a horizontal portfolio analysis you can incorporate into all of the subjects at once with different types of labeling for the different nanoparticles. Or you can use a vertical approach where you can actually identify what you want the nanoscale particle to do and determine which one effectively meets your expectation. Faster, more quality information, more expensive. Faster, cheaper, not as all informative of all so it depends if you're a large sponsor with a lot of information and money to be put forward or you're a small sponsor to be able to use this technique.

Now related signals, expected imaging of radio labeled. Is going to tumor considered efficacy? That is a question if you're doing your first product versus an approved product versus a nanoscale. An expected localization, an organ localization, and or retention is that the safety concern? These two issues is where you do your design going through phase 1, 2, and 3.

Bottom line. Comparative radiolabeled biodistribution imaging for you. Long term effective, FDA established, cost effective, generally available tool for the in-vivo assessment of the biodistribution, retention, clearance of nanotechnology drugs, biologics in human tissues and organs.

Thank you.

[applause]

Thank you. We will now open up for questions, if anybody would like to ask questions.

Larry Tamarkin, CytImmune Sciences, a quick question, with the labeling, if you would label some of these nano particles, would that change the hydrodynamic volume and ultimately change the biodistribution?

One of the concerns with breaking it down, that's why I put one slide in there on not stepping on or altering the nanoscale particle, is that frankly speaking I think that most of your nanoscale particles are not going to be as effective as large scale biologics which could cause some folding and unfolding. What I have seen is the technique used with many of the nanoparticles quite effective. Most of them are built with various hooks and labels already on them. While I recognize the theoretical concern, frankly speaking is this is your first step into it and what you would want to do is model both in the preclinical, animal models, as well this to make sure you're confirming your findings in both.

Any other questions?

[Indiscernible] from NCI. Do we need to figure out how long it takes for the [Indiscernible] molecule to be eliminated out of the body? Because you didn't show that data.

In terms of the question, let me make sure I get the question right, if we are going to label the PET material are we concerned about the speed of the PET materials being cleared or the background material?

[speaker in audience faint and unclear]

Elimination? So if, indeed, we have the free isotope, such as I-124 are you concerned about the competitive imaging that may be available from the free isotope versus the radio label nanscale particle? Is that the questions?

[Speaker/Audio faint or unclear]

Let me focus for you that there is a well known biodistribution for each of these labels, to make sure that you are not watching the isotope that's free while the nanoparticles going in other direction. So you can effectively identify that for background information which is the free isotope and sequester that well away from the radio labeled nanoscale material. You can identify how much clean material there is so that you can clean these very nicely in phase one to make sure that you're giving very clean nanoscal label as well as non nanoscale material.

Any other questions?

I was wondering with the drug that you worked with, how much variation that you see in the drug that you are testing itself and if that a effects your results at all?

Yeah, more in terms of how clean are these products. That is kind of the hidden message to it all is to recognize that these products aren't typically; even the ones are approved, uniform in size. And that is what I saw for years within the Agency. So as we label these materials we really want to understand that if we have an approved product or a non nanoscale product you want to do your biodistribution on that first and you're going to see that these things aren't uniform. Frankly speaking I saw wide variations on them and I expect that is what is going to be the issue. Some of the nanoscale particles appear to be much better definded and uniform in their sizing than non nanoscale materials.

Any other questions? Nakissa I think we're done.

I would like to ask one small question and it has to do with [Indiscernible] secretion type studies preclinically and while there is benefit of looking at where the drug is going, how quantitative are these studies and can they be used in terms of trying to do mass balance studies and figuring out how long does it take for the drug to get out of your body and where does it distribute and what the concentration is over time?

That is actually one of the interesting parts. You can get very quantitative and you can get down to essentially accounting for 100% here because you know the activity the number of [Indiscernible] you are administering to the animal model or human and account right down to all of that activity. So recognize that there is a small, maybe 2 or 3% that I would readily admit to that they couldn't get down to but the rest is going to be there. So you can come very close on these. And you can do great quantitation to it what I have shown you is the biodistribution on the subjective qualitative [Indiscernible] but if you want to get down there we can do the uptake studies, which frankly have been well identified for 60 years in thyroid work. You can do uptake studies over each of these organs, we've worked out all of the technology under the radiation [Indiscernible] model, to do those same uptake studies, and that is how all of the radiation [Indiscernible] on all of the radiation [Indiscernible] products that are radio labeled in diagnostics and therapeutics are found on the labels today. There is a program called Olinda and that is actually cleared by CDRH.

And are there any characterization methodologies that might be specific to these types of products that you know when we're trying to evaluate the nanoparticle aversion that would be useful to us in terms of incorporating into a guidance document.

Now you are talking about the actual radio labeling techniques, there are a number of radio labeling techniques and we can actually define them down to various materials for it, and from that standpoint [Indiscernible] is an excellent resource within in the agency, who I worked with for years within the agency and can identify all of those techniques from within the agency, those that would be acceptable and reproduceable from that standpoint. So there are excellent resources on this. And again a long of history and it's going down by the various isotopes and so we should have no difficulty at all putting that guidance together.

Thank you for offering to help put that guidance together. [laughter] Thanks George.

So we will go on to our next speaker is Dr. Jaydee Hansen he's a policy direction with the International Center for Technology Assessment in Washington, DC.

Good afternoon. I am glad to be here with you. Actually, my conclusion aren't going to be that different from Dr. Tamarkin or Doctor Mills. I get there in a different way. I don't think I come to a different conclusion in the end.

I do think it is important -- I do think it is important that we understand the context that many other people in the country are dealing with nanotechnology within. They hear from people at the National Nanotechnology Institute or people in other parts of government that nanotechnology is going to solve all of their problems. This quote has been well used, but "on the human level, nano's potential rises to nearly biblical proportions. It is not inconceivable that these technologies could eventually achieve the truly miraculous. Enabling the blind to see, the lame to walk, and the deaf to hear. curing AIDS, diabetes cancers, and other afflictions: ending hunger, and even supplementing the power of our minds, enabling us to think great thoughts, create new knowledge and gain new insights." Now, this is not someone from the transhumanist community, but rather Philip Bond who was the under Secretary of Commerce for technology. On a societal level, nanotechnology will deliver higher standards of living allow us to live longer, healthier life. Nano also, hold extraordinary potential for the global environment through waste free energy proficient production of processes that cause no harm to the environment or human health. Nano is showing great potential for repairing existing environmental damage. Okay, all of you that are working on nano issues, this is what is expected of you.

The patent office thinks that an awful lot is coming down the pike. This a that review appeared in Nature a few years ago. The patents are out racing the publications, not unusual. Patents are out racing the drugs. And this was what had been done up to 2004 and since then, even more. A whole variety of nano products are coming, from drugs and vaccines which as the subject of this from in vivo imaging to in vitro diagnostics to bio materials. FDA has actually, by my standard, been doing approvals of nano drugs, since about 1990. And in 1990, Digivan at [indiscernible] encapsulated anesthetic made by [indiscernible] was approved. And by my count, since then at least 10 other liposomal or lipid encapsulated drugs have been approved.

If you use the definition that the cosmetic folks used, basically, that lipsomoses aren't nano, and that is a different discussion. Abraxane is probably the first nano Product and, correct me if not, and so far, it doesn't help patients live longer, but any of you that have had a family member go to breast cancer treatment with Taxol know that it is a really toxic drug. So that does help overcome major side effects.

But an even bigger advantage for drug companies is, the cost per dose is phenomenally higher. Another product approved around the same time, actually a few months later. Actually, Biolock is approved for dental implant technology. It is a time release tool

bone augmentation product that forms a new calcium phosphate lattice. It is not a new way of remineralizing bone, but it is a new delivering the agent and a smaller form. And by the way, sometimes getting FDA approval means you are a bigger public better target for someone else too buy, and the company was bought by Health point capitol six months after FDA approval.

We have identified, at the International Center for Technology Assessment, we have identified about 270 so far that use nano silver. This is a nano Silver antimicrobial agent was approved by the FDA about a year ago.

We have had some discussion of how you measure things as a whole group of technologies that are going to be important for measuring the presence of various things, and at the very end, maybe using nanotechnology to actually measure our presence of genes very quickly so we can prescribe drugs better.

Gene therapy has been regulated one way or the other by the FDA since 1990, when the first gene transfer experiments for children with severe combined immune deficiency were approved. In most gene transfer research to date, a normal gene is inserted in the genome to replace an abnormal disease causing gene. A carrier called a vector must be used to deliver the therapeutic gene to the patients target cells. There have been a number of concerns about the virus is used as vectors, and some researchers are now looking to nano vectors as away around some of this viral problems. The scientists have already conducted the classic transfer experiments in rodents to see if the gene transferred, avoids some of the kinds of problems found by vectors. Using more [speaker/audio faint and unclear] fullerenes and other nano materials.

The first human transfer experiment with a reportably nano vector is for, [indiscernible] muscular dystrophy and was approved in 2006. In reality, I would say this is not nano so much as a synthetic [indiscernible] and the vector is really a synthetic virus made from the reassociated parts of adenovirus. And I think that means a number of things. It means additional problems for medical ethics. It means informed consent for trials may become more difficult as if – Nanoscale Technology means new toxicity for all durgs. Nano surgery, may allow direct manipulation of chromosomes and genes not just removement and replacement of defective ones. The National Institute of arthritis and musculoskeletal skin disease are using stem cells and nano lattices for research on a replacement of tissues destroyed by arthritis.

The convergence of stem cell synthetic biology and genetic manipulation debates, is made possible through nanotechnology may need that biological and chemical effect may need to be more thoroughly studied. And especially, we need to look at what is the ability of a nano particle to actually enter into the nucleus intentionally or unintentionally, and I realize that some of the last studies did address that.

So what do we think the FDA should do? We think they should treat all nano formulations of a drug as a new drug and require data commensurate with a new drug application, whether it is human of animal drugs. We think the FDA should develop nano

specific documents, such as the FDA already has for [indiscernible] drugs. I think that should probably be separate guidances depending on the kind of nano particle being used as well as general guidances. We would urge that the cosmetic and industry also demonstrates that they are following these guidance as they come out.

And finally, measurement technologies are probably one of the most important things, that we've already discussed that here today. In short, we can't measure what is being done, it should not be marketed. The FDA must require that metrics that can measure the performance and possible effects of the drug or simply not approve the drug. And certainly not just approved in nanosized versions of existing drugs.

Thank you. [APPLAUSE]

Thank you very much. Now any questions to the speaker?

[indiscernible] you propose that the FDA should (indiscernible due to heavy accent) and [indiscernible] I attended several AAPI meetings [indiscernible] if a well-known drug that is already on the market, then the nanotechnology can't improve the power of the drug. Can (indiscernible due to heavy accent) can show that [indiscernible] equivalent. And if you push the [indiscernible] A new drug, the (indiscernible due to heavy accent) goes over the [speaker/audio faint and unclear]. Is that fair or not fair? I am not quite sure, but I wanted to debate with you.

I realize that a drug trials are expensive and timely. But as we are arguing that this is a new product, and I used the example of Cairo drugs deliberately. It took the FDA a while to required to a separate guidance for Cairo Drugs, which now seems just obvious. It may be that some kinds of nano materials work exactly the same way. But others the answer is it would be nice to have the data that shows if it worked better, and that they work safer. It seems that the drug approval process can do that for us. The FDA has tools that could speed up things that need to be speeded up. And I think that our default position should be, if you are going to be hyping it as all new, then you ought to be testing it as all new.

Keith Weber with FDA, if you have a particle that is soluble, do you feel that necessary as well once you move from a non nano to a nano sized particle stance?

I think that is why some of the people feel that the liposome's are a different kind of category. But, if the question is, is the product getting into places that couldn't have gotten into without that new delivery system, then, yes, I would say we need to make sure it is working the way that it did before. And that is recognizing that there been nano versions in every drug mix before. These are engineered to do a particular task, and you ought to see whether it does that task and whether it does it better.

Rick Weis, Center for American Progress. I was just wondering what the history is [speaker/audio faint and unclear] what is process FDA has gone through and the micron process [speaker/audio faint and unclear].

I'd think you probably need to ask FDA about that.

I just want to clarify that a new formulation is a new product and is evaluated as a new product. While it might not be considered a new molecular entity, it will still be evaluated as a new product and there will be additional bridging studies conducted evaluating that product. So I think that maybe that is where the confusion is, that the nano formulation is not scrutinized is wrong, it will be a new formulation and evaluated as a new product. So, if you have a formulation with a different release profile and the dosage form is different, clearly that is a new application that is evaluating separately.

So, just to be clear Jaydee, are you recommending that a nano drugs be treated differently [speaker/audio faint and unclear].

What I am recommending is that at least for now the be treated as new drugs. As at the FDA has issues nano specific guidances', they may be finding from their research that certain drugs do fit the extended release formuation, but right now, we will say, until they demonstrated that treat it a certain drug.

I'm not sure [indiscernible] [speaker/audio faint and unclear]but I think that if you treat the nanoformulated drug as a new one [indiscernible] [indiscernible] the company has to go over [speaker/audio faint and unclear] information, and then [speaker/audio faint and unclear] [indiscernible] [speaker/audio faint and unclear].

I just want to say, I think that is the place to discuss this issue, however I do want to clarify that there are additional studies not just the PK studies in humans that are required. There are additional studies, preclinical studies in humans. I don't think this question addressed the questions that we had regarding the guidances that are needed which are aimed at understanding and characterizing nanomaterials for the purpose of manufacturing. I am glad in your presentation you called for the FDA to develop guidance documents which is what we're here for today. And any guidance we can get for the direction of these guidances I think that would be useful. And please submit any comments you have to the docket.

So we will go on to the next presentation by Dr. David Hobson who is the chief scientific officer at Nanotox Inc. in Austin, Texas and also Nanotox BV in the Netherlands.

Thank you very much. Nanotox is involved with a number of different types of products including energy products and pharmaceuticals. The comments today will be on behalf of the pharmaceutical products and the work the company has done since the company began about two and a half years ago.

I am going to cover these five different areas briefly, in terms of things that we have seen over the years, as this has progressed toward some policy thinking and some guidance document work. I was very pleased actually to see the White paper come out last year

from FDA and to read the content, because I think you're going to see that there is sort of an underlying theme in experiencing and handling these materials we're beginning to come to some consensus on what should be done.

In terms of international harmonization, I think it is an comment. In order to avoid issues of duplications world wide, including repeat animal studies and things, we need to be able to come up with a common language, and the best mechanism that I know of that FDA is engaged in, last year is the ICH activity and there could be another program I'm sure. That is one particular interest, and this should focus very heavily on a common language for dose descriptions an expression for nano materials and nano products. Especially in terms of our preclinical studies and preclinical work.

There is also recognition that there are many potential uses and there is some innovative nature to nano materials and nano sciences, that approaches to safety assessment of these new nano materials and nano products really need to take on a case by case basis. This has been our real experience in looking at a variety of different products. I wouldn't see as a practicing toxicologists [indiscernible] There may be a way over years of time ways to do it otherwise but I don't think we're there yet. We also should not be too restrictive of as nanomaterials offer very valuable advances that may not be completely appreciated by us at this time. I think that we should give some thought at least at this point in time towards substantial equivalence if we are thinking about guidance, because eventually nano materials will have to be generics. I realize that is a long time down the road for people that are not just getting patents; it is the last thing we want to think about. But if you're our rule making and you are always thinking about develop guidance, it always seems to me to be prudent about where you rgoing to when we get to that point. But I just offer that as a suggestion.

Nanohype, snd I don't know if I mean if same way the previous speaker it meant, but really in terms of the scientific quality of information out there, it is a wide variety of really good and well documented and well done repeatable science, and stuff that is really just -- I don't know if you would call it junk, but it might be a junk science. The problem with it is the toxicology professional community and the nano industries are becoming increasingly concerned. They do watch this and it is not useless in the sense of making public concerns known, but the quality of literature and scientific nature may not be appropriate for setting guidance recommendations at this point in time, particularly because some of the studies may not be consistent with good laboratory practices or even good laboratory practices like studies and that would need to be looked at very carefully particularly since this was a pivotal piece of work that you wanted to pull from the literature.

The FDA should not utilize, although they should be aware of the information but should probably not utilize the support of this information in the promulgation of guidance. Guidance should be developed accordingly to scientifically sound, valid, and well documented procedures. It has always been my statement with regard to the interactions I have had over the years with FDA and also where I personally believe in [indiscernible] the FDA is chartered. It has not been decided to support bad science or promote bad

science, and to my knowledge it never has and it doesn't. So hopefully that will go forward to a cadenced [indiscernible]. As far as those instruction, again, there have been much higher service area which could occur at any time [indiscernible]. They do have some unique particulate characteristics, and if you can't forget that they decided for that purpose and they pay us. So we need to make sure we take these into consideration when we develop and determine dosages, particularly even with preclinical work and clinical studies. Some of the speakers this morning indicated that they had gone through that experience already had had even come up with some solutions for how we might approach doing that better. We also need to -- we have been reminded once or twice this morning that the FDA already has experience with in the materials, and there are a number of previously approved products in a number of different divisions and at different centers, including nuclear medicine.

There is information out there with regard to the previous experience that I would hope would be brought together and focus on this particular guidance setting as well, because we are well aware that there are other experiences and they will be brought into consideration when they prepare any guide says related to this.

Therefore, there is a clear need for the FDA to provide at least a draft general guidance for dosage expression, contact and stability of dosage of 4Z antsy, even for pharmacology and toxicology and the preclinical areas and also the clinical studies. Some general guidance, even if it is dropped is useful at this time because it allows to kind of use sort of a Navy board, shake down the process so we can focus on [speaker/audio faint and unclear].

The ability and determination should be required for all formulated doses so they can assure that the nano material that is tested is that that is intended to be tested, including whether or not it is free bound or aggregate or conglomerate. We see this in the laboratory literally weekly. Some materials are very stable and some materials as you might suspect, or expect that it would be stable or not as stable as you think they might be. There was a comment earlier about particle size distribution, and you can see sometimes that the particle sizes will begin to ship with stability. That may be a useful reported perimeter and the stability study. There may be limits in which you may want to set with regard to how far you allow that material to shift before you have some concerns for safety or otherwise. Or quality.

More sense of stability testing appears necessary, because [indiscernible] often relate to mechanism by action of distribution of pharmacokinetics. What comet in regard to that is, we talked about silver and gold nano particles, and some of these things being thought of as a second generational nano particle, we are now moving and IMC particles that would be considered in the third or fourth generation where they are now in particle has been a fictionalized, and then you need to count the number of functions on the particle. And this has been a challenge to deal with, but it is happening in their needs to be techniques and it may be unique to that particular panel particle on how you accomplish those.

There are notes to change different particles [speaker/audio faint and unclear]

So consideration testability testings, I did the frequency is correct, the current I.C.H., I don't see any problems with that, per southeast. It seems to work okay. I think [indiscernible] recommended storage temperatures in your facility and maybe some projections, because in some cases, holding Kingsport increased stability and then making a prediction on that likely would a drug product does not work for nano materials very well. They conglomerates and they actually colas in some cases. [indiscernible] should be included in additional chemistry as imagined many times this morning, particle size and particle shape, it's Assyria, forming aggregates and conglomerates [speaker/audio faint and unclear] and I always like to be until have an image analysis, a T EM4 [indiscernible] [indiscernible] stability conditions. It sounds real easy, but if you go to make [indiscernible], people will say, that is the gold standard because of tedium or as a am, but it has been considered semis off or semi soft panel particles where it is required to go after the freeze factor as the MR T EN. Net for those of you that maybe in a medical center, that may be easy to go get. But if you try to go kaput [indiscernible] imaging done for a commercial setting like GMB or something like that, that can be difficult.

Safety assessment procedures, or the safety assessment, clinical studies need to have substantial focus on particle [indiscernible] two medics, [speaker/audio faint and unclear] and George kind of pointed that out. And imaging techniques are available and being used to facilitate nano particle vocalization and quantification. Again, Beijing as and [indiscernible] as doctor bills presented at, there are actually some radioisotopes required that are emerging right now that might be able to localize the article and [indiscernible] sections, which are very interesting. But those types of storage instability are very significant issues support some engineered metal particles. And many engineered metal particles are often been expensive to produce, in fact, I was talking to Dr. Markham earlier, and his particles are more expensive than gold. [laughter] but keep in mind that many of these particles were created by making the decision on whether they even want to cut down the pharmaceutical Route. They're very expensive. Net for that reason, I think we need to work poured innovative research methods and continue in that way to work with nano particles in mind to improve the design and deficiency used to allow some in vitro in and in-vivo designs that are in a more efficient, and those could be suggested or at least recognized that it is for the fact of [indiscernible]. And that is what I have to present. Thank you very much. [APPLAUSE]

Thank you very much. Are there any questions for the speaker? I just [indiscernible] and the size that [speaker/audio faint and unclear] that is actually what is going to be necessary because [speaker/audio faint and unclear] (indiscernible due to poor audio quality).

Exactly. And that is exactly right. And in any type of imaging, of course the and there it makes a lot of difference. And let me go to provide guidance documents, we need to make it very clear as two what volume [indiscernible] images [speaker/audio faint and unclear].

Thank-you. At the ink [speaker/audio faint and unclear] (indiscernible due to poor audio quality) I think we will do the next presentation [indiscernible] will be speaking to us at this time. They give Thank you very much.

I don't have a presentation, I just wanted to speak. I pretty much [indiscernible] if he were in the session earlier today on cosmetics, I am [indiscernible] and I and program leader of Product Safety and Consumers Union and we're happy to get to present comments on the need for FDA regulation and materials of unique substances. In a lot of what has been set earlier in the session, and that is [indiscernible] as well, as I said before. It has been a few years since the FDA 's first public meeting on this issue, and [indiscernible] more specific questions being posed here, and hope that that is bringing us closer to getting some more specific regulatory action on the panel materials. My comments today, I will discuss what we do know about [indiscernible] assistive nano materials and what we yet the tittle to ensure their safety. One of my comments will speak more to over-the-counter products, especially sunscreen, and the other will pertain to new drugs as well.

We've been investigating [indiscernible] from nano materials and consumer products for several years now, and my comments are based mostly on our experience with sunscreen and some other nano enabled products that test Consumer reports. Our recommendation about the type of analytical data that FDA should be demanding for premarket approval from over-the-counter treatments can be summarized in four basic points. One, we think that the materials should be treated across the board as if you and they should not be given generally recognized save status. We think that all material should be characterized according to futures known to the safety, as discussed earlier, size, church, Service shape and [indiscernible] using [indiscernible] nomenclature. I think that is the most important issue I see on the horizon here, and a lot of people have spoken about that earlier.

And then [indiscernible] to access a direct and indirect pace of nano material, including [indiscernible]. And did did that in a way that ensures that the test accurately reflect the true condition in which the product will be used. As I mentioned earlier, the formulation can be affect performance as well as safety, and we really need to get that information right now with so many ingredients into the battle for [indiscernible] over the counter products as equivalent to their other counterparts who are really missing that critical and permission.

So I just went through the questions that were opposed. So the next part we will really focus on the first question, which is, are the general parameters of screening tools by which to evaluate the likelihood that nano material may have nanoscale specific properties, and whether they are characteristics that the FDA can use to broaden characterize materials. At at this point generally, that has prevented [indiscernible]. Because it has been manipulated at a nanoscale level and so many different ways, tainting of chemical to physical properties and having a biological impact, we have to look at a case by case basis and look at how they're being used in order to really evaluate their [indiscernible]. And that is why we think the most required safety assessments for new drugs for all [speaker/audio faint and unclear] even if the macros conversions are

substances that have already entered the marketplace. And a lot of the reasons were mentioned earlier.

We got back with features at the nanoscale. And we think they need to be regulating [indiscernible] not on the likelihood that the valdez knowledge is of what exactly are we dealing with, whether these materials being with [indiscernible]. We do know the nanoscale properties of black biotechnology turgid etc., it can take to toxicity -- contained toxicity and [indiscernible] how the changes can't effect biologically pact. And [speaker/audio faint and unclear] to this increase in the ratio of [indiscernible] who can really change the exposure and toxicity relationship and that is why we think [indiscernible] regulated.

As I mentioned this morning, research at the University of Oregon and Oregon State University and [indiscernible] are developing new battle materials to develop these [indiscernible] materials and how they are behaving in basic toxicity, and that is great. But we are one to need a lot more information just because of back which is behind the materials and products, and so really, they have not been able to draw any kind of general conclusions about structure activities and relationships.

And bat as Alza discussed this morning, the variability of them materials and the purity of that is really an issue, and it. Because [indiscernible] previous speakers, together is a new drug or over-the-counter product that the variability is likely to be seen, particularly because, many [indiscernible] are not being acquired and characterized as [speaker/audio faint and unclear] to include information that tells us how [speaker/audio faint and unclear] is a talent. And I am sitting here in this meeting hearing more of the taka what we're learning about drugs, that we have to go to a new drug application and testing, and compare that to what we don't know about over the counter drugs and cosmetics and [indiscernible] -- .

Basic and permission to start with.

Referring to question two, referring to whether unique product manufacturing a bacterial [speaker/audio faint and unclear] formulation, certainly, as we discussed, and the materials and related contaminants and the impurities and. Buildings and toxicity as a well as efficacy, and certainly have seen with sunscreen that all together, for related products are not equal. And depending on the is very important precedent relying on [indiscernible]. [indiscernible] that these minerals can take [indiscernible] [speaker/audio faint and unclear] can vary, and it does have an impact. And tell [indiscernible] how many of you are familiar with the studies in Austria finding [indiscernible] [indiscernible] vacancy that hand prints in this are the settings are [indiscernible] the residents of sunscreen was stomach but the hands of the group. So that is a physical effect, certainly [indiscernible] a group for people getting new routes, but that is just one example and how many other unintended consequences of that happening of the results of that different form of these ingredients going into per commercial products. That is certainly something Napa [speaker/audio faint and unclear].

The reactive nature [indiscernible] makes it difficult to answer [indiscernible] security as we talked about, and how these ingredients are specified in the manufacturing product, that is a big issue, I'd think. And again, without companies being required to do that testing and characterize their ingredients in that way, which had had a situation of, don't test, don't tell. And we're left with the same situation we're in right now.

The correct [indiscernible] cents in active ingredients don't normally include requirements for disclosure or control of these characteristics, and nor do we know how much if any of this information is detailed to the suppliers of formulas. Consumers have some people the term of mechanized, which really is not defined anyway, and our test of different brands of sunscreen found that a range of [indiscernible] particles in Napa products we tested, but yet few of these products actually disclosed that they contain no particles.

Finally, the point about dental materials inadvertently reacting with other ingredients is a big concern. I mentioned this morning is study finding that [indiscernible] in sunscreens seem to increase the absorption of insect repellent with DEET when there are co formulated. And it seems to be [indiscernible] when it comes out on the market.

The third question are, what are the unique technical attributes of products contained with in the materials that have to take affect the characteristics and performance of a product?

The nature of the properties that are engineered and in nano materials depend on how they are changed from their backers scale counterpart. Is normally a concerned shaped by the structure we talked about before. All particles cannot invade them commune system or pass through the blood-brain barrier and sells an average price of the body that conventional material cannot. And we seem to think that is a flag that we should be looking at. Is this change who are making affecting where the product goes in the body, and how much gets to the different parts of the body, and and think we have to ask that question, even if we think assets changing in a nanoscale [speaker/audio faint and unclear] we have to face the fact that that kind of change could bring about changes in biological impact in those areas, or unable paint a [indiscernible] to get further into the body.

And I also discussed this morning in the cosmetic section, the impact on the in-depth [indiscernible] light, the accumulation of nano materials into things like drinking water and a veritable media. As with a dearth pharmaceutical materials we have to consider what will happen with those products as well, so the FDA really needs to evaluate the downstream impact of their use in other environmental health and safety impacts.

Finally, it has been our experience with nanoscale materials, I mentioned that Veritas and nano for belated sunscreen suggested that their performance can vary considerably, some products with nanoscale titanium or zinc oxide perform. Well, and others less so, and compared to organic formulation, they did not perform exceptionally better. So again, we can't consider all products formulated that ingredients are always treated it equal, we have to look at them individually.

And finally, but additional assessments do we have a? Due to the variable nature that the materials, is particularly important to invited to toxicity in a way that we can accept the conditions [speaker/audio faint and unclear] spoke a lot about that, but [indiscernible] product testing organization, we are always working two that and I think that is [indiscernible] things that we've buy off the shelf in a way that no one is 20's them, and I think that is definitely with over the counter [indiscernible] we have to think the same way. There is too much potential [indiscernible] variable formulations and one that is excellent to have [speaker/audio faint and unclear]. So that is my talk, think is very much, and the questions? [APPLAUSE]

[speaker/audio faint and unclear] I have a couple questions about your and nano materials. (indiscernible due to poor audio quality) at bulletpoints [indiscernible].

At what point did it become nano? We don't know, because it has been labeled as such. I'd think you could say that it became clearer on the skin, and you could expect [speaker/audio faint and unclear]

[speaker/audio faint and unclear]

Again, you're talking about "it." A different products and different manufacturers have different types of CO2, and I think scene from the commercial literature, the [indiscernible] being made and aluminum, and [speaker/audio faint and unclear]. It is not [speaker/audio faint and unclear] different forms that it is being used in indicative for permission, that could very well affect [indiscernible].

Again, unless the testing of the some formulation [indiscernible] there is no way to know.

[indiscernible] testing [speaker/audio faint and unclear]

Was awesome products did well, some of back [speaker/audio faint and unclear] FDA Clinton some percentage of the EPA got back necessary.

[speaker/audio faint and unclear] defined by the FDA but [speaker/audio faint and unclear] (indiscernible due to poor audio quality).

Well that is not because they a study in the lab with a sun screen, and [indiscernible]. You are right. Is actually a different type where they evaluation [indiscernible] TIFF results with different [speaker/audio faint and unclear].

(indiscernible due to poor audio quality) I just wanted to ask a question, and I heard you say attacked tested [indiscernible] and that was final formulations?

Move.

[indiscernible] T TM andSTM.

(indiscernible due to poor audio quality)

USB definitions and [speaker/audio faint and unclear] because [speaker/audio faint and unclear] is simple as that. And that would explain [speaker/audio faint and unclear] earlier (indiscernible due to poor audio quality) and [indiscernible] all testing [indiscernible].

Again, the other night and meet again, to three companies have different data, but unless we're talking about a specific formulation, we [speaker/audio faint and unclear]. But [indiscernible] were they using, and this is something was at the same on [indiscernible] or was it something different?

And Ed think that is specific to what conditions of the skin [indiscernible] [indiscernible] scant can't behave differently. In the ink [speaker/audio faint and unclear]

[indiscernible] are you familiar with the [indiscernible] method to [indiscernible] of men exposed in the same spigot.

Actually, yes. They're is a different [indiscernible] for different techniques, and I think [indiscernible] [indiscernible] the sunscreen evaporates on the skin, so I think that is pretty much significant up as you can get. [indiscernible] [indiscernible] [speaker/audio faint and unclear] in the kind of use or products. I think what Mark [speaker/audio faint and unclear] on how --

We did look at different techniques, and and think [indiscernible] the people that did the testing [indiscernible] get a step further and -- but nonetheless, that raises the issue again, how well does the test that they're using represent the real world conditions, it can't, I think that people will argue that there are different ways, different techniques to use with TEM and SEM [speaker/audio faint and unclear].

I guess that answers my question for you. [laughter]

And is wanted to follow up on [indiscernible]. The company (indiscernible due to poor audio quality) skin penetration for nano products [speaker/audio faint and unclear] [indiscernible] (indiscernible due to poor audio quality).

Are you familiar with the [indiscernible] paper on quantum (indiscernible due to poor audio quality) [indiscernible] penetration on dead skin I think [indiscernible].

And specifically, that is just generally [indiscernible] you're speaking [speaker/audio faint and unclear] Yuma to make sure that those methods represent [indiscernible] and [indiscernible] which they are using it. [indiscernible] the have a banner [speaker/audio faint and unclear]. Their [indiscernible] and dates are pretend Hiked. Talking about [indiscernible], talking about a number of business products, and the point here is that,

you want to make sure that that method [speaker/audio faint and unclear] [indiscernible] file formulation [indiscernible] in-depth [indiscernible] [speaker/audio faint and unclear]

We can talk as as the studies later on in GMP.

That does raise another interesting issue for me. There are adverse effects that we're concerned about with this actually getting into the body and going to live notes and other urban systems, but I'm not sure [indiscernible], the question I had and how was hoping that some of you at Maury permission about this, what effect might occur within strata, empower blood is a torch into the body is the only mechanism by which you have is toxicity. I think that is [indiscernible].

Is a there [indiscernible] on your skin, or [indiscernible] to remain system for your body clocks or is there any [indiscernible] that is heard from the [speaker/audio faint and unclear].

Link you very much. I think [indiscernible] some interesting points. And was it like you took after the last presentation, we have been talking about the final formulation, have [speaker/audio faint and unclear] that representative of the actual formulation [indiscernible] [speaker/audio faint and unclear]. The questions we have raised [speaker/audio faint and unclear] [indiscernible] is her mission, [indiscernible] 800 [indiscernible]. Cell, I need we have [speaker/audio faint and unclear] and have an additional person signed up, so okay if we just continue to presentations at this point? [indiscernible] introduce the next speaker, Doctor [indiscernible] national director Upper [indiscernible] think you're very much.

Thank-you. Good afternoon. And I have a short presentation here.

Good afternoon, I am very proud to be here. All the way of this is a Northwest to a Baez lovely sunny and warm and now it is hot. I want to talk to you a little bit about some work that is being done. One of the endings that I have been able to [indiscernible] in the meeting today, I think an area of need an understanding, and it was [indiscernible] the work that I myself and my colleagues are engaged in [indiscernible] were you, I hope that is something that will be useful. Basically, is to try to list if you will, the chemical and physical parameters for toxicological testing. And this is work that is being done by [indiscernible] TT 229. What we call, working for free, it is a lot of numbers and that kind of thing. But working group three is what we call the Air Medal health and safety group. There are four of them and this is the third one.

I am the Project Leader of this technical [indiscernible], and I had a number of colleagues from around the world that are assisting me in this process. They are from Canada, Czech Republic, France, Germany,I ran, Germany and the U.S. And also liaisons with [indiscernible] and JWT. So these are works that are being done. The timeline for this work is to be completed by June 2009, and I feel at this point I feel like we are on track. So what I am going to show you today is all the work in progress. In fact, we were supposed to be getting data in from a colleague this week after about a week or so,

actually about a month and a half doing some ongoing research. So why chemicals prepared in characteristics? And E could come up with it in a fairly simple way. In fact was doing experiments at the pharmacology Institute of Minnesota, and later people are doing [speaker/audio faint and unclear] [indiscernible] whatever your testing is kind of important. And so, if you extrapolate that to where we are today in terms of nano materials, panel objects, however you want to describe them, the point would be, what are the chemicals physical characteristics? Why would that be important collects Brothers of this is some interest, if you are testing something today, 20 years from now you're testing something, if you want to know what it is. So we hope by putting the list of chemical characteristics we would be recommended, he will get off that help the process. It will tell us a lot more about it purity or [indiscernible]. And it will tell us more about pathological possible outcome. Well [speaker/audio faint and unclear] and it puzzles and my colleagues around the world that are working on desperate.

In terms of the process, I think it is rather simple process and [indiscernible] International group. Any of your documents that talk about chemical and physical characteristics from around the world, having never friendly and said states, from the European Union, from Japan and other countries including now China which has also participated in the process. What we did was appropriate to those documents and collected all of the chemical characteristics with a fine get the novelist. We came up with about 80 of them. That is a lot. There was redundancy, duplication obviously, so we we did those out and went back into the Committee, all of which are a scientist in different disciplines in a will take disciplinary approach, there toxicologist and if you need it, absent from that list, which do think we're the most critical that would be sent to Beckley supported? Called the list if you will from [indiscernible] to 15 or 40, and [speaker/audio faint and unclear] and a bit more. And what we have come up with is the current list. Now let me again when you, this is a draft list. It is about 10 items and it is not completed. Fiats are interested in any feedback you might have. The thing we have been trying to do is to try to get the list small enough that makes sense for people to do. Obviously, one thing that will not make sense, and could put an exhaustive list out there, but if those characteristics part then evaluated, it probably does not mean a whole lot. So we're trying to focus of fact. So the list as it is right now, again, this is a draft and by no means the end of the road. Why have a lot more work to do. But as it stands now, exoneration had exoneration C, application, and we try to take terms that were fairly large, I remember, we're not just talking about prescription medication or over-the-counter medications, you're talking about any other application of in a material. [speaker/audio faint and unclear]. This is [indiscernible] but when we actually start working on it -- size distribution, purity, shape, stability, service area, service [indiscernible] and service charge.

This is the list that we have a right hook. We have also get some input from a number of the institutions, which must say is also part of our membership of our group [indiscernible] non-profit organizations, government organizations, to prevent those in industry as well.

If you look -- what kind of thing could we do, throughout three simple examples. If we get this and it is relatively large, there may be a way of Canada. It down depending on

what questions being asked. And that is just for material identification. The next one would be predicted toxicology, and the third would be entered of what should be recorded in terms of literature is a researcher can go back 15 or 20 or whenever years from now and go back quality that [indiscernible] was that at that particular time. And then there is some way that people could start to look at that. Bella and talk about predicted toxicology which is what we're looking at.

One thing that would be difficult but we hope to do is to get three or four of these particular components will be useful in helping to predict the toxicological outcome. I think that is relatively large, but what we have been getting from intermission around the world and developing and putting into reports, there does need to be some information that is coming out. We will see how that all adds up. If we take a look at the other best, and other organizations, not just [indiscernible] that is looking at this but OECD for example, I can show you here, I can show you there is similarity between the two. An OECD is working hard, putting a list together and keep them waiting it. These are all traps, but just keep you informed in terms of depth [indiscernible]. It is a relatively similar list of chemical and physical characteristics although there are some differences. And we're not trying to put any kind of value on it, [speaker/audio faint and unclear], those are things that are committee felt I probably was not usable, but there may be too different purposes between the list. I just want to venture that chemical [indiscernible] characteristic list is not synonymous from what is the plant two another discipline.

But anyway, you can see some similarity here.

Where this is headed is hopefully at some point, this will help draw standards. At the organization that is leading it here in the event States and head of the U.S. delegation which I am a member of is the American decimal standard Institute, which reports to [indiscernible].And ISO has the 229 nanotechnology and it is mirrored by the [indiscernible] organization which pays for [indiscernible] within the United States. It started in 2005, it has 30 participating member bodies [indiscernible] Edwards incorporation with a number of different organizations. And I will go through these kind of quickly became an idea of the relegated terminology and nomenclature. Group to is [indiscernible] and working group three is the 1I am talking about and there is a new one called material specification.

In terms of our [indiscernible] in the States, there is Doctor [indiscernible] is the head of the National coordination Office, and the organization is barely tapers as you can see a number of fairly large companies here, but it should be stated as a mission before that nongovernmental organizations are also part of government toward toward organizations such as [speaker/audio faint and unclear] and it is a very diverse group and multidisciplinary group at that.

To what questions are we asking right now in terms of where we go for there? One of the rings is, what is the definition of a [indiscernible]? What number two is what is the relevance of that term, and pepper three is, how do you measure it? This is information that I mentioned earlier in my [indiscernible] that is actually coming in this week from all

over the world in terms of helping define [indiscernible]. This is going to be the need of our document [speaker/audio faint and unclear].

The other question we have is, if that list is too long, hard we work towards reducing that? One thing we have been thinking about is, if we can't quantify it, the media should be a specific chemical parameter. If this is the parameter weirdest thing is a unit parameter in some way, it is. If it is not, then it should be. Not all parameters have benefits for qualification, in fact, there is a number that Del. We are working with working group to get talking to them about how and what is available for measuring these particular parameters. And is there some way we should be prioritizing? These are some questions we're wrestling right now and we hope to be entering very quickly here.

So the next section, [indiscernible] been developed and being edified and minutes and Hyde. Part, it is [indiscernible] within our group-would come up with its. We think that possibly test listening to Mike listing methods, not recommended methods, in other rates, taking what is out there in the literature as opposed to taking [indiscernible]. But we'd think we have a lot of work already in terms of what we're doing, but this is something we're considering. And then, we'll write it up and we'll put it out for publication.

With that, above to entertain any questions you have all the work we're doing, and I certainly hope it will be useful. [APPLAUSE]

One thing I will say is, if anyone is interested in participating in this process, please see me. I would be happy to take you involved with the right people in terms of how you can be a part of not trust this but others. If you have any comments or questions, don't hesitate to give me a call. And any thoughts on this, I would be happy to consider those.

(indiscernible due to poor audio quality)

That is a good question, and the 1I could easily answer. The work we're doing, we're not even going to touch any kind of testing, per say. These are just the chemical physical characteristics. I will say in the terms of pathological aspect of it, when they might think is, what medium like to be considering in terms of understanding a chemical physical characteristic, and that is what we're working at thinking through right at the moment. But right now, there seems to be an acquiesce solution and something that makes sense from the most pathological perspective. That is what we're thinking at the moment.

(indiscernible due to poor audio quality).

Good question.And a simple answer to that is, I [indiscernible] before, and I would be happy to send you a copy of that is just a mixture. I would say that we have the talking and are ready looking at documents [speaker/audio faint and unclear] Battista mixture we haven't missed anything, I would certainly appreciate a copy of that.

I am just curious about (indiscernible due to poor audio quality).

I am reluctant to kind of give you any definition at this point. I am not ready to "one way or the other. So from the chemical -- or any of the parameters. But I think, one of things we're considering from the chemical compositions could be it the atomic structure with their pretty much tenfold atomic structure, [speaker/audio faint and unclear].

(indiscernible due to poor audio quality).

Yes. That would be one of them.

Okay.

The link you very much. I just wanted to ask, (indiscernible due to poor audio quality) pour characteristics that may impact any kind of toxicology type [indiscernible] (indiscernible due to poor audio quality) different combinations and [speaker/audio faint and unclear] it is important for us to know [indiscernible] nano material will actually be [indiscernible] with characteristics such as the 13 toxicological assessment. Is that [speaker/audio faint and unclear].

But we think, yes. A PC if I can kind of rephrase it.

We have a list of the, let's say, Ted right now, but from a toxicological perspective, and I will speak only for myself at this point. I am not sure that all 10 will be required for the technological assessment. But what we are trying to do is take a look at that subset that is in there, which could be very useful or required or recommended that it be done in order for characterization of the material. So for example, if he were to publish someone in the University of [indiscernible] wanted to publish a paper describing the material that he or she was testing, we would want to have the intermission [indiscernible] on the chemical and physical characteristics so at some point in the future summit could come back and understand where it was that it was tested.

So that is a publication for [speaker/audio faint and unclear]

And it does. I'd think it does. From what we can tell from our colleagues at the National [indiscernible] ever Tory, I know that they are doing a number of excellent characteristics of chemical physical properties. I think it is very important to them that they understand what those are with the materials they are testing. So yes.

Thank-you very much. And I think we will go to our next speaker, and that is Kathleen [speaker/audio faint and unclear] from [indiscernible] university.

Good afternoon.Actually, I did not come here to present, and [indiscernible] this morning and I volunteered a topic, but I would like to give in other a little perspective and something to think about. Talking about is the inorganic particle. And [indiscernible] in the cosmetic industry would say, [indiscernible] are a in a particle, [speaker/audio faint and unclear]. Bud but debut [indiscernible] perspective and how some of these deadlines that we're talking about might be developing a [indiscernible] chemical characteristics

and they may not be that straight forward and that applicable when you're talking about something that is actually a complex, but a number of different particles.

I (indiscernible due to poor audio quality) very therapeutic. And over the last 10 years, we haven't developed a [indiscernible] targeted at Liposome oil delivery system. And it is actually complex and composed of three different components. Now there is a that the zone and sell, one is [indiscernible] molecule, and (indiscernible due to poor audio quality). And this is [indiscernible] we can actually is which out the targeting molecule and the [indiscernible] to give a different property delivered, etc. And currently, the delivery system using the [indiscernible] into by fragment in the [indiscernible] what would normally be [speaker/audio faint and unclear] set up the trail down at the [indiscernible] can dissenter. So one of the things out like to point out is, it is a very different [speaker/audio faint and unclear] and there is no [indiscernible] particles involved in it. Cell [indiscernible] considered. [indiscernible] recently attended the [speaker/audio faint and unclear] conference where the big discussion was going on aspect [speaker/audio faint and unclear] nano material. Some of these things have been proposed that guidelines for hard in the material may not be appropriate. Poor example, is the TEM and SEM, which you guys recently talked about. We have been [indiscernible] pour the last two or three years, and it is taking quite a bit of time and effort to be able to develop TEM and SEM at Methodist, what we can actually it correctly in the to the problem [speaker/audio faint and unclear]. Something we need to take into account when you're talking about these guidelines. We can't be so rigid where it applies to the heart of of material, and [indiscernible] soft and a material. Because he may, in doing that, actually miss what potential can't capability for developing these new products are.

I just want to show you that this new (indiscernible due to poor audio quality) on the inside had raised the nano particle.

Does digit the potential for some of these systems, this is our delivery system, [indiscernible] reporters in that turns blue to an animal [speaker/audio faint and unclear] pancreatic cancer. This is a mouse model, and I just want to say now that [indiscernible] that is Blue is where the tumor is, and it goes only with a tumor cell is and not to the normal cells at all. It is very two respond to that. And [indiscernible] these guidelines and this was approved by the FDA through the [indiscernible] process. And I think everything we had to go through was quite appropriate.

I don't think we need to go much beyond what we need to do for a new drug system to make it so rigid steady become virtually impossible for a small company torpor individual academic researchers to develop something that I've met out of the drug in the future. That is a treaty to take into consideration.

Not on an all particles are created equal. That isn't the need need to keep in mind. When but the term and a material, they think of carbon and 02 and titanium dioxide, but a lot of these systems being developed are biologic. And gentle with its, and just a fad. Perfectly natural, [indiscernible] no toxic side effects, very straightforward, and so I think we need two kind of keep in mind that there are too many different categories to try to pigeonhole

everything into one system. [speaker/audio faint and unclear] [indiscernible] composition. That would be really very difficult to convince [indiscernible] that that is elected by the year and molecules of DNA. So that is [indiscernible] oxide homage titanium is in resenting? Site is wanted to throw that out as a spur perspective as we are developing these.

Thank-you very much. Are there any questions?

(indiscernible due to poor audio quality).

Absolutely.

I think this has come up a little bit before, but I am wondering what your opinion is as FDA starts considering different values for nano, whether all of gene therapy sees detectors or engineered metal particles by back with all G. Dear Abby and everything that [indiscernible] considers has to be [speaker/audio faint and unclear] with a regulation that they are considering.

The biologic cut back to biologic, I think yes. We [speaker/audio faint and unclear] required, because of the Pac-10 are even considered [indiscernible] one of the time (indiscernible due to poor audio quality) because it is strictly to the pit and a protein [indiscernible]. We didn't have much consideration with that. But I think that you develop something that is unique, and think you probably shouldn't go through the rap. I think it is safer. [indiscernible] consideration to see what type of analysis you may need to do and what kind of consideration for [indiscernible] toxicity and safety have to consider.

But [indiscernible] does not want to be much of a problem. Most of the problems with people and [indiscernible] have not been in cancer, not one of them has been in cancer. It has all been in trying to duty replacement for [indiscernible], etc. And that is a situation where you are trying to [indiscernible] with Gene and therapy, and you really don't [indiscernible] permanently, or they are engineered to go and [speaker/audio faint and unclear] for example, if you have like (indiscernible due to poor audio quality) the teeth 53 protein disappears after about

---

So if it's totally new, yes, I think it is something [Indiscernible] I think it should work. I think it would be sufficient for that.

Any other questions?

[speaker in audience faint and unclear]

No, I agree with that but I don't want [Indiscernible] based upon organic materials. And the criteria that would be virtually impossible for physical to translate into something like a lipid. So I think that is what needs to be done in that case. The perfect example would be the [Indiscernible] of the RAC and the initial things that we need to do. There were designed for viruses and they said it was totally irrelevant to our delivery system but we

still had to come up with an answer for them. And it made it very difficult for people who just came into this to actually do this successfully. So I think that is the kind of thing that we need to consider. We can't be too specific if we may be need to do it as different categories, categories for an organic, categories for biologic, categories for the nanoparticle and so on, so that you can enter an appropriately for your particular [Indiscernible] or your particular nanoparticle.

[Speaker/Audio faint or unclear]

Right, sure.

[speaker in audience faint and unclear]

That is really great, that is a good point, thank you.

Well I believe at this point we will open up the floor for any other questions, or anything else that we like to talk about. To address anything that we have. But [Indiscernible] so I guess I will hand it over [Indiscernible due to poor audio quality]

We encourage you to submit any kind of suggestion that you have or any information that you have a discernible and we will look at it -- we will look at that very carefully and follow up based on the information that we get.

If we have no further questions, we will close the session. Thank you very much for coming.

[applause]

Captioner: Are you finished for today, or just finished with this session? Thanks!

[event concluded]