rate constant k such that in the end the dissolution rate dC/dt is a function of an apparent rate constant and S, the exposed surface area.

So, where am I taking you with this? For a freely soluble drug, S, the surface area, is not critical because we already have a large value of k as a consequence of the large saturation solubility of a highly water soluble material.

However, for a poorly water-soluble drug where the value of k will be very small, the surface area increase will allow us to overcome what is otherwise a very slow dissolution rate for the material.

Now, to what extent can we actually increase the surface area, can we really make a difference that is that dramatic? Well, if we consider a cube, a single cube, with a side length of 2L, of course we know that each face of that cube will have a surface

area of 4L-2, and of course there are six surfaces to the cube, we start off with a surface area of 24L-2. If we now subdivide this cube into 8 equally sized cubes, with the side length is now half of the original side length, we end up with 8 cubes having a total surface area of 48L-2 or effectively by reducing the size of the particle by 50 percent, we effectively double the surface area of the material. And we can do that time and time again and here's a very pertinent example that illustrates the power of size reduction in these systems.

If we begin with 2 cubic centimeters, of a pharmaceutical material, and if we consider that the average bulk density might be in the range of 1.25 to 1.4 grams per cubic centimeter, we're looking at 2.5 to 3 grams of the pharmaceutical substance. If that's starting off as a single cube with a 1.25cm length, and we go through this process of subdivision 24 times,

we'll actually end up with enough 1nm sized cubes to completely cover the surface area of this rugby field in a single layer.

Now in reality we're not talking about nanoparticles that are 1 nanometer in size, we're actually talking about 2 orders of magnitude larger, but still we're looking at specific surfaces in the order of 50 to 75 square meters per gram, which is very, very large.

Now of course in the oral arena, the applicability here is very clear. Based upon the biopharmaceutical classification system, we're targeting drugs that have free permeability in the GI tract, but have comparatively low solubility. These are the Class 2 compounds, and it's been estimated that about 40 percent of all new drugs coming through combinatorial and high frequent screening, are insoluble to this degree and hence present tremendous drug delivery problems.

In terms of what these particles can do in oral delivery, certainly they can increase the bioavailability of the drug and if this is an enhancement of an existing product, we can reduce the dose, sometimes dramatically over the micronized or larger formulation version of the product. We can increase the rate of absorption which certainly has huge benefits in terms of certain types of drugs such as analgesics, where getting the drug on board quickly is very important.

We can reduce or all together eliminate fed/fasted variable absorption, improve dose proportionality, and avoid uncontrolled precipitation after dosing if you are working with a traditional sybilized system employing surfactants or sybilizers and these images actually show tablets that contain these nanoparticles and also capsules filled with multi- particulates that also contain these nanoparticle materials.

One of the nice things about these technologies is that once you get past the process of actually making the particles themselves, that you can rely on traditional, well-established (off mike) operations in the pharmaceutical industry for producing solid dosage forms of these materials.

Now, the fundamental reason why particle size makes a difference here, why faster dissolution makes a difference, is because it allows us to improve the absorption efficiency of the drug in the GI tract. If we consider large particles of API as they move through an absorption window, and by absorption window, I mean a preferential area within the GI tract where the drug is most likely to be absorbed, we find that for large particles, the dissolution time can be much larger in the GI transit time through this region and hence, much drug can be passed unabsorbed beyond the absorption window.

For nano-scale materials, specifically for nano-scale APIs, the dissolution time can be much less than the GI transit time for this same window and hence a substantially greater fraction of the drug, in some cases the entire amount of drug, will be absorbed efficiently prior to passing through the end point of the absorption window.

So conceptually it's actually very simple in terms of what we're doing. We're basically just utilizing surface area increase in order to achieve an increase in dissolution rate. And a good example of particle size effects on oral absorption comes by a paper authored by Dr. Henry Wu at Merck. This is an example of MK-0869 which is known commercially as (off mike) or by the trade name Emend used for treatment of chemotherapy induced emesis and what's interesting about this molecule is that it does have an absorption window and so it

becomes a great candidate for this kind of technology. And we see that as we progress from a micronized form of the drug, at about 5 microns, to a jet milled version at about 2 microns, further down to a wet milled version at.5 microns, and to the final smallest particle size, of about 100 nanometers, we can see the corresponding increase in bioavailability, the corresponding increase in cmax and also the corresponding increase in the rate of absorption of the drug. This is in a Beagle model, but Merck did indicate that the same kinds of effects were seen in humans, and in fact, this technology enabled Merck to decrease the fed/fasted variability ratio from about 5:1 down to essentially 1:1 to there was no food effect.

Now moving on past oral delivery, there are exciting opportunities and benefits of these systems in parenteral delivery and one of those is the ability to achieve very high drug loaded formulations for parenteral

administration. Obviously one of the problems with a traditional formulation approach would be that you'd need very large volumes of an aqueous vehicle that will be untenable for parenteral delivery. These kinds of systems can produce particle drug loading up to 45 percent on a weight/weight basis which allows a very large amount of drug to be administered using a very small volume formulation.

In addition, there are benefits to avoiding harsh vehicles that may be employed in alternative formulations and these might be cosolvents or solubilizers that have some sort of undesirable effect or pH extremes that can cause pain at the injection site or perhaps irritation at the injection site.

Equally important, these formulations, even at a very high concentration on a weight/weight basis are readily syringe-able and can be used with traditional small bore needles and the safety

has been established for the IV, IM, and subcutaneous realms in human studies, and I reference this paper at the bottom for anyone who would care to look at the itraconazole study which was authored and published by Johnson & Johnson.

This is an example of compound X in a pre- clinical model and we're looking at the PK profile following intravenous and intramuscular administration and for reference we see the commercial product profile in purple, which is typical of what we'd expect to see for an IV solution. What's surprising here is that when we dose the nanoparticle dispersion, IV, we get effectively the same concentration versus time profile. The reason for that is, again from a formulator's perspective, these drugs are poorly water soluble, but when they have access to the much larger volume of the blood pool, they can dissolve quite readily in the larger volume of the aqueous environment and

in a sense take on solution-like properties.

If we choose instead to deliver the drug either subcutaneously or by intramuscular administration, which we show here in red, then we get more of a depo effect which we might expect because the particles have much less access to the aqueous fluids in the muscle tissue.

There are also benefits of these kinds of particles in pulmonary delivery and again, they can take on some solution-like properties in terms of their ability to be delivered to the lung. One of the great problems with traditional suspension delivery to the lung is the fact that the particle size of the suspended particle essentially dictates the particle size distribution of the droplets from a nebulized device and because of the fact that we can make these particles so small, they become much smaller than the droplets that are produced by the nebulization device and the nebulizers can

truly be used efficiently to customize a droplet sized distribution for the particular application in mind.

If it's deep lung, the nebulizers can dial in the distribution of droplets that would allow that to happen and the suspended particles, which are very, very small in comparison to those droplets, then are delivered very efficiently.

To illustrate this example, we see the percentage of the emitted dose from a nebulized device, for a nanoparticle formulation relative to a micronized formulation, so the amount of drug delivered to the deep lung is actually more than twice the amount delivered to the deep lung from the micronized formulation.

We also see that because we can produce these materials at very high concentrations on a weight/weight basis, that we can deliver the drug very, very quickly relative to conventional systems, and for a

concentration of 50mg per mil, or 5 percent weight/weight, we see that we can actually deliver a therapeutic amount of a drug in a 2-second activation using this particular formulation approach.

So a lot of exciting opportunities for pulmonary delivery -- precision delivery to the target site, increased uniformity of surface coverage, and shorter nebulization times, all of which have significant medical importance.

Now, how are these particles produced? Well, there are a number of ways of producing these particles and early on we classified them as bottom up/top down. This is just a sampling of the many ways these particles are produced. The first five are of the bottom up version -- the deposition or precipitation version of the production. One is spray freezing the liquid. This involves -- it's a cryogenic process involving liquid nitrogen. Emulsification, which many of us

are familiar with. The idea here is that once you produce the emulsion, you can flash off the organic component and have nanoparticles remaining in an aqueous environment.

The PCA and RESS -- these are basically approaches that involve super critical carbon dioxide or other appropriate super critical fluids, and another approach, which involves precipitation from an aqueous solution using heat, abbreviated EPAS.

The bottom three approaches are what we call top down. These are the attrition processes. High pressure homogenization and microfluidization which both rely on sheer end capitation and high energy wet milling which is dominated by sheer forces, and actually I'm going to show you in the next couple of slides a few examples of the wet milling process.

Largely the reason for that is that this is one of the oldest ways of producing

nanoparticles. It's very well established in other industries and only more recently was applied to the pharmaceutical industry. All the paint on this wall was produced using a high energy wet milling process. Many of the super peremetic particles that are in the cassette tapes and VCR tapes are produced by the same process. Photosensitizing agents for films -- so this technology has been around in other industries for many decades. It's only been more recently we've applied it to pharmaceutical systems.

So this is a schematic of a basic horizontal high energy mill and what we see here is a milling chamber that has been produced to pharmaceutical specifications, in this case produced with 316L grade stainless steel, and with a very high polish. Inside the chamber we have an agitator shaft which runs along the horizontal access of the chamber and inside the chamber also we had a grinding media and these media take different

forms and I'll discuss that in a little bit.

Now, there are many ways to run through this process. One permutation is to make a slurry of the course material by introducing the unmilled API, the stabilizers, and the water, and to pump that course slurry into the top of the mill. As we're doing that, we initiate the agitator, and the agitator then drives the bed of media which creates millions of points of contact during the process and when a drug particle, then sandwiched in between two adjacent media particles, the drug particles fracture into smaller bits. And that's the principle behind the wet milling process.

Now as you might imagine, this does take some period of time and typically what we do is recirculate the material back into the recirculation vessel so that we have essentially a recirculating system that runs through some period of time until the desired particle size distribution for the material

is achieved.

Another consideration to point out is the fact that we are taking mechanical energy and in some cases transforming it into thermal energy, so these systems must be cooled adequately in order to preserve the integrity of the particular material. And in this diagram you can see that we have, in the cooling reservoir, for the seal coolant, we have a jacket on the mill itself and we have a jacket on the recirculation vessel and through those cooling processes, we keep the temperature of these systems in check and well within satisfactory levels for the production process.

This is a photograph of a horizontal mill in action. You can see the milling chamber here. This is a two-liter mill. And again, the material is being pumped from this recirculation vessel using a peristaltic pump up through a mass flow meter in the top of the mill, and then it comes out

the dynamic separation screen and back into the recirculation chamber in the tubing that appears white. The reason it appears white is because these materials typically take on the appearance of milk.

They're white, opaque dispersions. And you can see, if you have very good eyes, some of the cooling lines for the mechanical seal reservoir, the milling chamber itself, and the recirculation vessel. And they're controlled by a PLC, very standard for the pharmaceutical industry.

And this slide just shows the morphology of unmilled material on the left, and milled particles on the right. Two things to point out. The bar here is two microns in both cases, and so one thing that we certainly see is that these particles start out in the range of say 10 microns or so and are reduced to a size that's well below a micron here in many cases. And also that the morphology of the particles is

preserved. These are short rods and the resulting mill material are also short rods and this is typically the case for this kind of a milling operation.

In terms of the time dependence of the particles size reduction process, I'll go through this very quickly. We start out with the pre-milled (off mike) which in this case is centered around 50 to 75 microns. As we mill, over time, we see that this population is reduced very quickly and a new population of particles appears. As we go further in time through the milling process, the particle size frequency here will increase and it will also shift to the left, so we get essentially a more narrow distribution that also shifts increasingly to the left.

This slide shows the scalability of the wet milling process. In this case, three different platforms or different scales for milling, four different batch sizes ranging from 4 kilos up to about 500 kilos, and as

you can see, in terms of percent frequency versus size, we have super imposable profiles for the scale up process.

In terms of reproducibility, this is data for more than 50 batches of the product, and we see that the boundaries in the line color here are for the upper and lower limits of the assay. All the dots correspond to individual batches. The purple dots are the in-process assay results. The blue dots are the finished product results, and we can see they're well within the spec in each case.

In terms of particle size, the same thing. We have a blue bar here which defines the upper limit for the mean particle size, yellow in process, blue finished product, and also we capture in this case, a D90 particle size distribution value which is bounded by the specification shown in the magenta colored line, and the individual dots, again, for each of the batches showing their

corresponding D90 values.

In terms of the commercialization, a number of these systems have been commercialized into FDA approved products. I'm showing you examples of the most recent two approved, the most recent being Megace-ES, megestrol acetate oral suspension. The issue with this drug is that in a micronized form, it experiences some substantial fed/fasted variability where the drug is poorly absorbed in the absence of food. That's a problem because this drug is used in the treatment of cachexia, or a wasting disease, in HIV/AIDS, where patients don't have any desire to eat, so if we can't get the drug on board because of the fact that the patients are in a non-fed state, we have a problem.

The nano version of the formulation allows us to achieve the same absorption of the drug irrespective of a fed or fasting condition.

Now in the case of Tricor, the second to the last product to be approved by FDA, the 160mg co micronized version of the drug showed a 35 difference in absorption favoring fed over fasted. The nanoparticle version of the product eliminated the fed/fasted variability as shown in the graph to the right, and interestingly, also dropped down the dose slightly from 160 to 145.

I'm running very short on time so I just wanted to answer these last three slides very quickly. There are potential challenges in developing nanoparticle products of these types and we expect there would be for any kind of pharmaceutical product, and I just list these for your consideration: Particle agglomeration, again, owing to the Van der Waals forces, particle size growth through an Ostwald ripening mechanism where smaller particles dissolve and result in the growth of larger particles. There could be changes in particle morphology, changes in

polymorphic form, which must be carefully monitored during the production process and during stability. There could be process related impurities, residual solvents for many of the bottom up processes as well as media attrition impurities for top down processes. These can be controlled, but they again have to be monitored to relevant standards. Process scalability and reproducibility can be problematic for certain types of processes and there is a lack of a universal particle sizing method which does create some challenges for transference, highly desirable, to utilize the exact same particle sizing methodology across all the sites in an organization to ensure there are no tight transfer issues.

And as far as key characterization needs, particle size distribution here is key as are solid- state properties dealing with morphology, and the physical form of the drug. Since we're trying to achieve rapid

dissolution, dissolution behavior becomes very important, of course. And then for other applications, microbial limits testing, if the process involves water or if the final product involves water, applications that may be specific to the route of administration or methods that are technology specific depending upon the route or method by which these particles are produced.

So to conclude, nanoparticle engineering offers significant potential to improve the delivery performance of poorly water-soluble drugs and hence the treatment outcomes of patients who will benefit from these novel products. We've seen this already in the form of a handful of products that have been approved by the FDA.

We believe that FDA's current requirements for assessing drug product safety, efficacy, and quality, appear adequate for evaluation of these kinds of nanoparticle based products, and also believe

that future evolution of more complex nanotechnologies that may deal with drug targeting, intracellular deliver, et cetera, will likely drive the need for periodic evaluation of FDA policy and procedures for regulating nanotechnology based drug products.

Thank you very much.

MR. MORRIS: Thank you, Dr. Ruddy. So we'll take clarifying questions. I should note though that -- I should have said this before. If you could signify with raising the hands so Diem can identify you and then list everybody. Otherwise we screw up the transcript taking. Dr. Koch first. Mel, I think that's you.

DR. KOCH: Yes, I have a question relative to the end point analysis in the process. You have data of the resulting product, but do you have any methodology to determine where you are in the attrition? If you just take the wet milling as an example?

DR. RUDDY: If you use the wet milling as an example process, typically one would want to characterize samples of the product over the course of time to have a fingerprint of the particle size distribution throughout the process.

Once the process is scaled up and fully developed and there is a greater familiarity with how the process and how the product works, then one can reduce the sampling frequency or just go for a certain desired endpoint based upon an abbreviated sampling schedule.

MR. MORRIS: Art?

MR. KIBBE: I just have a couple questions about -- I think they revolve around slide 19. What methodology did you use to determine the particle size, the mean and the over 90, for the data that's described --

DR. RUDDY: That data was produced by laser diffraction.

MR. KIBBE: Do you use the same -- the USP standards for laser defraction to qualify your laser diffraction tests?

DR. RUDDY: Yes, we do.

MR. KIBBE: The RSD and the --

DR. RUDDY: That's correct.

MR. KIBBE: Okay.

MR. MORRIS: I want to just remind everybody before you start. That's okay, we know who you are. Liz?

MS. TOPP: So I'm Liz Topp. He said my name, but I'll say it again. So I have a question about the solid drug particle cores that are in the center of your nanoparticle material. A lot of the comments that you've presented suggest that they are crystalline. Do you know for a fact that these particle cores in the nanoparticulate state are crystalline material or are they amorphous or some combination?

DR. RUDDY: They can be all of the above. They can be purely crystalline. They

can be amorphous. Or they can be mixed. It depends very much on the desired application. It depends on the API itself.

MS. TOPP: How do you determine whether they're crystalline amorphous?

DR. RUDDY: Determination is typically done with traditional methodologies -- X-ray pattern diffraction, solid state MMR.

MS. TOPP: Okay. I have one more question about slide number 11. You show some PK data, basically --

DR. RUDDY: Yes.

MS. TOPP: -- following different routes of administration, and I was wondering if the bioavailabilities of the IM formulation, of the nanoparticle formulation administered IM are equivalent, or if that -- it looks to me like it might be lower but I can't integrate by eye very well. Do you have that information?

DR. RUDDY: To be completely

honest, I do not recall the relative bioavailability of the IM leg of this study.

MS. TOPP: Okay.

DR. RUDDY: I don't believe there was any major loss of bioavailability but I can't tell you that they're identical to the IV dose.

MS. TOPP: Thank you.

MR. MORRIS: Any other questions? Well, this is Ken Morris. One quick question. Talking about the wet milling operation on slide 14, you don't have to go to the slide, are there -- you talk about how they're used in other industries, which I know. Are there ASTM standards for most of these? This is relevant to what we're going to talk about later.

DR. RUDDY: I actually don't know.

MR. MORRIS: That's okay. I just thought you might because I'm assuming that might come up in our discussion. Well thank you very much.

DR. RUDDY: Thank you.

MR. MORRIS: So our next speaker is Darin Furgeson who's from the University of Wisconsin, assistant professor in pharmaceutical sciences and biomedical engineering and we have his title -- oh, you have your own lap top Darin?

MR. FURGESON: Yes.

MR. MORRIS: You don't trust us?

MR. FURGESON: No.

MR. MORRIS: But in any case, he's going to talk about Nanotools for Toxicity Assessment of Nanomedicines which is obviously a relevant part of the discussion.

And Darin, can you see this? This will be your counter.

MR. FURGESON: Yes, and I want to thank you for the shock caller, too.

MR. MORRIS: No problem. No problem. We're not going to need them after next January.

MR. FURGESON: Okay. Good morning.

I would like to -- this is really a unique opportunity for me to come speak to this Committee and what I'm going to present today is very dissimilar to what you've already heard. And this is a primary focus -- I think it's a waking giant area of research when it comes to assessing nanomaterial toxicity, but I'm directing it more so towards nanomedicines and trying to give an idea of some sort of tool kit that we can come up with to help accelerate the (off mike) clinical development and ultimately get these from the bench to the bedside faster.

So there are three primary areas I'm going to talk about at first. One is, what drug delivery systems right now are using nanotech, and what goes into the manufacturing of these nanoparticle-containing drugs, or nanomedicines. And then try to identify some issues that need to be addressed by the FDA. I mean, I don't think it needs to be said, but safety and efficacy

are the primary impetus for all this, and that's the FDA's standard, but I also believe validation is a primary concern when it comes to the FDA and trying to find some toolkits that will do this.

I just threw this in just to give you some stats. This isn't in the slides, but just to give you an idea where the nanotechnology is going. So these are from the Freedonia Group and they project that the nanotechnology is going to reach around $53 billion in 2011 and that the drug delivery and the biomedical product demand of this is going to be around $3.7 billion in 2009. And if you compare that to 2004, we're talking about more than an order of magnitude difference. And the largest share of opportunities will emerge in pharmaceutical applications. This is also reiterated from Advance Tech Monitor in 2006 which has now been taken over by Industry Matter, that this might be a little bit outdated but at least

12 nanomedicines right now are already approved and there are a lot right now in preclinical development both in industry, academia, and in the next 5 years, we're going to see an exponential growth, I believe, in the area of nanotherapeutics.

But the most active areas, again, are going to be in drug delivery and in in vivo imaging, and then the coupling of those two together in theragnostics where you can simultaneously image and also deliver the therapeutic that you need.

So this comes from the amount of funding going towards EHS research from the NNI and these numbers look impressive, okay, it's steadily growing. We're at $58.6 this year, projected next year it's going to be $76 million, but when you consider the amount of the budget that's (off mike) to the NNI, this is less than 3 percent. So we still have a long way to go when it comes to developing some sort of methodology to

provide some rapid data when it comes to toxicity.

So I think this has sort of a tripartite relationship here between the nanocharacterization, nanotherapeutics, and nanotoxicology and when we're looking at these nanotools for that, all of these need to be addressed. I think the previous speakers have done an excellent job of talking about nanotherapeutics, nanocharacterization, and nanotoxicity in and of themselves. They may not have used those same nanotoxicity words, but the ideas are the same -- chemical, physical, biological characterization, safety, efficacy, reproducibility and toxicity.

So this is from Ernst & Young. It gives you an idea of what, right now, is out there when it comes to nanotech components that are in medicine. On the left panel here we have medical products. The field of applications are here in these blue boxes,

and then we have the functional nanotech components, so what is the actual delivery vehicle.

This is what I'm going to focus on right now. So our first speaker was speaking about liposomes and these polymer nanoparticles, (off mike) cells, now we have these new advanced delivery systems, carbon nanotubes, fullerenes, you have antibody drug conjugates that are emerging, quantum dots for diagnostics, nanospheres, even inorganics that are being used now, gold and silver nanoparticles, silver nanoparticles, almost every issue of C&E News now has some sort of alert-alert or some kind of concern about silver nanoparticles and what not only is it going to do to the environment, but what ultimately is it going to do with the patient.

For both the FDA and the EU, the regulatory approval, there's a distinction here between medicinal products when it comes

to the drugs, and also to the devices. And so this is an action achieved on the drug side by pharmacological, immunological, or metabolic means.

On the device side, we have the action achieved by physical means whether it's through mechanical or structural action, replacement, some support to the organs or to the body functions in and of themselves, and that is relying on the principle intended action which is why the FDA is not, from my reading anyway, focused on tracking polymer synthesis more with the applications of those polymers to the therapeutics.

So here's a slide showing -- we have 10,000 drug candidates down here at the bottom, and the challenge here with drug discovery is that as we start to move up this staircase here, we're looking from the selection, can we target them, the solubility issues, are they going to be stable, are they nontoxic. By the time we reach the pinnacle

here, there's around one, maybe two candidates that seem like they're going to move into the second stage.

But 70 percent of these new drugs are going to be insoluble, in fact, many of them are toxic especially when we're talking about cancer, small molecules, it's essentially a poison that we're going to deliver to a patient in the hopes of killing a tumor and being from both a pharmaceutical background -- pharmaceutics, the whole design here, is that we're trying to improve the drug therapeutic potential. And these drug candidates here have to meet numerous, numerous selection criteria to eventually reach the marketplace here at the top. And if we could go in with some pharmaceutical reengineering, almost, rethinking, down here, at the early, early stages, the amount of time, money, and patients suffering, ultimately, could substantially be decreased in my opinion.

So this looks great on my computer, it looks terrible -- oh, there we go. So this -- I'm sure everyone has seen this, but this is what eventually the process of being approved is. In the preclinical stages, it takes about three to four years where you'd find a target, you go through and you validate it, you use some high through-put screens, you just carpet bomb it over a bunch of different cell lines, see what hits you get, take some of those hits and move them into a lead candidate. Now we're moving into the preclinical stage, Phase 1 and it now can take place over four to six years. And then move that through looking at patient's tolerance and everything else up to market.

So at the very minimum, we're looking at years and costs somewhere projected between $800 million to $1 billion for a single pharmaceutical drug.

Now, in the future, or what's going on right now, we have a lot of exciting new

therapies on the horizon and this is from a paper from Nature Nanotech this year actually and the one are is with biosynthetic and bio organic polymer systems. Biosynthetic, what I mean by that, are recombinant polymer systems or genetically engineered systems. You eliminate a lot of the variables when it comes to synthetic polymer synthesis, monodisbursity, you can ensure, biocompatibility, even the block architecture, you can simply make these mRNA templates, drop them into an expression cloning vector, have them produced, and you have the polymer that you want.

Bio organic systems are sort of a hybrid where you take a recombinant polymer and you have conjugated a synthetic polymer along with it.

Theragnostics, this is going to be huge where you have both the therapeutic and also the imaging agent here, and multimodalities and combination therapy which

I'll get to in the next slide, but returning here to this panel, we have here in the gray, the tumor, we have carbon nanotubes that have ligands that are going after these tumor receptors, and they're bearing quantum dots for imaging and they could also potentially be bearing a therapeutic as well, say small molecule or a drug. So we can image the animal and show that we can have tight specific targeting both through active and passive means that's already been reiterated by previous speakers, and so we could then show that, well there's where our delivery vehicle is, and if that's where the delivery vehicle is, hopefully that's where our drug is as well.

So further applications of these systems, I believe, are going to be with synergistic or multimodalities. We are taking, for example, like hyperthermia, and you're combining it with imaging and therapy as well.

Again, mRNA templates, this goes back to recombinant or genetically engineered systems. A lot of -- like Perceptin and Avastin -- some of these regimens cost $100,000 to $250,000 a year per patient. And the substantial cost for that is a lot due to the production that has to go into that. But now with new technologies that we have, when it comes to protein production, we can get higher yields of these proteins in a faster route.

When I was in graduate school I did a lot of synthetic polymer chemistry and beat my head against the wall a lot of times because it just simply wouldn't work. I did a postdoc in genetic engineering where I moved into using DNA to make these polymers and what I loved about this system was that once you got the gene designed the way you wanted it to, you had in that expression vector, all you had to do was throw that thing into the -80 freezer and that's your

polymer right there. You need another batch of it, you take it out, you spike the culture, you come back the next day and you purify it because these were all thermosensitive, you can purify them simply by heat. So rather than going through this laborious process of organic solvents and MMR, MMR, mass spec, la, la, la, you can do this in a quick manner. And with yields we can get right now, 200mg of some of our polymers in a 1L culture.

So this, I think, is one of the most outstanding pieces of work. This was developed by Mark Davis at Cal Tech and this is now, again, in the May 2008 Phase 1, and it's a siRNA gene therapy therapeutic against this ribonucleotide, but they're using cyclodextrin containing polymer, so it's biocompatible, they're delivering these siRNAs which are similar between 19 and 23 residues, they're targeting them through a transferring, which are hyper expressed on

the surfaces of tumors, and they're using polyethylene glycol to stabilize these particles. And this is really, I think, a very -- I think it's paramount to look at a system like this where gene therapy has all this potential where it would be like Star Trek where they can just walk up to you and spray something into your arm, and hey, I'm cured by whatever I got bit by. But it has yet to really evolve both on the non-viral side and on the viral side. There are pros and cons to each. But this system, I think, is one of the most promising in my opinion.

Now what makes these so challenging when we're looking at not just with gene therapy but with nanomedicines as whole, is the Nano Design Complexity. When you take material from the bulk and you take it down to these nanoparticle sizes, you get these quantum effects. You bring these free electrons up to the surface and behaviors aren't always what you would expect, as you

would expect in the bulk, and with that being said, you just cannot assume that it's worked before, it works fine when we use it in the bulk, it doesn't necessarily mean when you get down to it nanometer scale that it's going to behave the same.

Another problem with nanotechnology when it comes to therapeutics is that we still have -- I mean, long term or chronic exposure studies are still years and years away. This is just a very nascent technology in the grand scheme of things and what's even more sad, I think, is that there's really a lack of correlative in vitro and in vivo data that we have. I know that I have a great collaborator at the NC, Marina Dobrovolskaia. I spoke with her and they're sitting on just a ton of human data and trying to find ways to -- she and I are trying to find a way to make a correlative model between what they have and what they've found in vitro as well.

So is there something that we can

use then to bridge these areas -- from in vitro cell culture where we are testing these particles against fibroblasts, endothelial cells, cancer cells, macro(off mike), and mammalian data? And the answer is, yes. And what I've begun to use, in addition to my drug delivery focus in my lab, is to look at Zebrafish. It's a model organism that has genome very similar to our own in a way that we can then use medium through-put screening, hopefully with the utility of robotics, many move this even into high through-put screening, and use it as an ability to assess developmental toxicity. This is a very conservative nanotoxicity screen. Using Zebrafish, adult Zebrafish or Zebrafish embryos, we can look at developmental toxicity, phenotypic abnormalities, these cannot be linked to genetic mutations. We could also then take the fish that survive, cross breed them, look at future generations, look at any kind of epigenetic problems that

might arise, and then look at limited long term studies for these with the fish.

The epigenetic, I'm not a geneticist by any stretch, but I think this is really interesting.

And when I teach the PharmD students drug delivery systems, back in World War II when the German soldiers would use polymers as a plasma expander until they could get transfusions, and then these men would later come into the clinic and be complaining about disease, they'd go in there and they'd get a biopsy done, and, lo and behold, they'd find this pvp polymer still residing in their cells. And they called this, if you look back in the literature, if you dig really, really hard, they call this the macromolecular syndrome where these macromolecules will be localized in the cells. They're not degraded, they're not exocytose, and no one knows what the long-term effects of that are. It's a term

in an area of research that there doesn't seem to be really much concern for, but I would venture and go out on a limb here and say that I think that really needs to be looked at.

So this gives you an idea of how we do our Zebrafish experiments. We have a 96 well plate. We take one, we cross the fish, we take within each well we put one Zebrafish embryo, so they have a chorion around them to protect them as they develop.

Now they hatch usually at around five days. This is cut off over here, but this is "HPF" hours post fertilization, so 120 hours post fertilization the Zebrafish emerges and we can do one of two tests. We can either incubate the embryos where we place them into 96 well plate with (off mike) or (off mike) solution, something that has the ionic strength and what the embryos need to survive at the temperature. Then we can also drop in gold nanoparticles, silver

nanoparticles, polymers, around them, and look to see if they can get through that chorion, that protective barrier, or what we can do is we can take a syringe and directly inject it through the embryo.

So if we do this continuous waterborne exposure, that would be one where we have the embryo, it's incubating in the presence of gold nanoparticles, let's say, we can look at developmental toxicity. Paul Tanguay up at Oregon State, he does a great job of looking at dechorinated work and also with a nanotoxicity where they basically dechorinate the embryo here, and then look at some exposures and then we turn around and we look at assessing these. We can even wait until the fish have already hatched and then place the materials in there and see when they uptake these. When they ingest these, where do these particles go? What do they do? What sort of genetic abnormalities do we see?

In my lab we've done two systems, primarily, gold and silver nanoparticles, and also looked at some FDA approved polymers, some pluronics, also known as poloxamers, and polyethylene glycol.

So here's a pluronic, representative pluronic. It has a hydrophilic, hydrophobic hydrophilic block, and we went and we did some exposures to the Zebrafish with these. Now, pluronics are widely used to deliver water insoluble materials. They're amphiphilic, they have both hydrophilic and hydrophobic nature. So here's our control fish here. Here's the eye, the jaw down here, this is the yolk sac, this is the swim bladder. I didn't want to overload with what different variables we can look at, but when it comes to toxicity, as we began to increase the amount of pluronic here at 0.65MM, all the way up to 650MM, you can see some changes begin to occur. One, you know, the eyes begin to get some different

shapes, they get bigger, they could get smaller. The yolk sac can begin to enlarge or decrease or degrade. Even the number of vertebrae will change. You can get curvature in the spine both up and down. You can also get an excess of fluid around the hearts. You get a tamponade effect preventing profusion throughout the body. So it's a -- I think really a great model.

So then as a control, we went back and we looked at polyethylene glycol 2000. It has everything in it from your food to your shampoo. We use it every day. And we exposed these to greater concentrations again. We started off with 0.001MM up to 10MM so we did a large concentration. Of course there were some viscosity effects, but as we began to increase the concentrations, again, we began to see changes in the fish after they had hatched.

So are the FDA requirements that we have right now for preclinical assessment and

QA, are they adequate to safely evaluate nanomedicines? I'm going to say no. I hope that doesn't affect my RO-1, my RO-21s are being submitted by the people who are at the NIH, but no. And part of the problem here is that the people who are working on nanotechnology are so far ahead with developing these materials and the people who are trying to catch up with looking at the toxicity and development issues or epigenetic issues, we're years behind, and the number of people working on these, not only is the time gap huge, but the number of people working on this area are very small.

We need to find some in vitro models that we can help to correlate to in vivo systems. If we could do that and then find some way to have some predictive nanotoxicity that would be huge. Not only could we then go back and say, hey, look, yeah this is a great drug, but we dropped it on to these fish, and this is a conservative

estimate, and it just wiped them all out.

Now, okay, well you could then take that back to the higher ups and say, well we could maybe do intra to oral delivery or parenteral to oral delivery with this, but if we try to do systemic delivery, we're going to run into a bunch of problems.

And as I'm in a hurry and speed up here, one example I want to give from the literature where there are two different groups of thought, and this is with gold nanoparticles, and the ancient Egyptians used to use gold nanoparticles as elixirs to drink for vitality, so they've been around for millennia. This isn't new.

Jahnen-Dechent, at (off mike), he looked at different sizes of gold nanoparticles, and he stabilized these with triphenylophosphine, extremely toxic, these derivatives, and he tested it against four cell lines -- fibroblasts, epithelial, macrophages, and melanoma cells -- and what

he found was pretty interesting. Now, these were all in vitro assays, and he found that 1.4 nanometer gold nanoparticles, showed the highest toxicity IC-50 of 30 to 56MM. Fifteen nanometer gold nanoparticles were completely nontoxic even up to 100-fold higher concentrations.

This is what was interesting if you look in the conclusions, while 1.4nm AuNPs caused rapid cell death by necrosis within 12 hours, but you drop that size by 0.2nm, we're getting down to the size of a bond length here, that they're causing rapid cell death by apoptosis.

Now, we did the same thing with the Zebrafish. We didn't use any cell lines. We just simply went back and we looked at the Zebrafish. So in the columns here, the nomenclature, we have cAu50. That means colloidal gold nanoparticles of 50 nanometers. And so we have 0.25MM of colloidal gold nanometers, and then we

increase the concentrations as you go down.

As you go across you increase the size of the particles and with a few exceptions, we've really found no size dependent toxicity that was visible compared to what he found in vitro. Now does that mean that he's wrong? No. He could certainly well be on to something. But at least it shows that there is more work that needs to be done when it comes to at least waterborne exposures that could possibly be -- dermal exposures would be better for this, but for right now, gold is inert, it's been widely used, and for all intents and purposes, it's a great vehicle.

Now, silver nanoparticles, on the other hand, are extremely toxic that we've found with our Zebrafish. Again, we have the same scheme set up. Concentrations increase with the columns and we have the particle size increasing with the rows. And if you compare, here's our control fish up here, and

we did -- these are all waterborne exposures, and you can see with increasing the concentration of even the 3 nanometer silver nanoparticles, the yolk sac begins to expand and we start to get these alien fish here, the same sort of effect begins to occur.

And what's even more interesting when looking at the data here, is that when we have -- toxicity is a function of size and concentration, but these markers for toxicity -- jaw malformation or pericardial sac edema or vertebrae number decreasing or curved spines -- some of these variables would peak sooner with different sizes or different concentrations compared to others. So that is an interesting question to answer but I can only make my graduate student work so many hours without being thrown away, but those are some things I think that also need to be looked at because silver nanoparticles, they're really hot right now. Their antimicrobial agents, I mean -- there's been

some issues with clothes, et cetera, silver socks, but you can see just from this -- this is the first study that we did and toxicity was extremely hard.

So then we thought, well maybe it was the formulation that we did, so we took the silver nanoparticles -- I'm into the red box, okay -- and we spun these down and thought, well maybe we have some of the toxic, organic solvents, maybe, as a lingering contaminant. So we took the supernatants and we dropped them onto the fish as well and we didn't see any toxicity with those.

When it comes to developing these nano toolkits, these are just the basic basal levels, I think, that have to be addressed. When it comes to physical characterization, molecular weight, particle size, surface charge, and I forgot to put this on here, but even the shape, the surface morphology, all of those are going to have an effect upon

toxicity, every single one of them and, the associated distributions with those. Molecular weight has got polydispersity, particle size has got polydispersity. What about stability? What's their stability like in aqueous media? Why don't we just incubate some of these particles in 100 percent pure plasma on the bench and see what kind of proteins, if any, absorb to that surface.

Martin Filbert at the University of Michigan does an excellent job in that area. The purity of these, when it comes to manufacture, what about lingering contaminants? You've got antioxidants that come into play. If you're looking at polymers, you have homopolymers that could be taken down the line. How reproducible are these when it comes to manufacture? Yeah, we're within our realm of particle size and everything (off mike) whatever, but what about the realm of toxicity? You're not measuring antioxidant concentrations or

anything like that. Is that something that we need to look at?

Also, drug release and biodegradability profiles, that's especially true when it comes to more of these biotherapeutics.

I'm going to skip the top part here but skip down here to the bottom. I've already talked about this paper here. Chan and others in 2008 looked at -- they found the same sort of effect of gold nanoparticles from a cellular response, but this is where -- I want to point this out because this is where discrepancy comes in the literature when you're reading these papers. They used, for their samples, they made one set of particles, they borrowed two from another investigator, and then the purchased two from outside vendors. Hopefully I got that right, but I know they had three different stocks. Now, without rigorous characterization and making sure that they're all within the same

realm, so to speak, how can you possibly jump to make any sort of conclusions when it comes to what cellular responses are occurring when it comes to toxicity?

Now clean-up of nanodispersity, it's going to be key, it's going to be very expensive, and we all know that there are molecular weight fractions of polymers that contribute high molecular weight fractions, small molecular weight fractions, those have been shown in the literature. It's well established that they have different areas of toxicity, and what really bothers me when I'm teaching this course is when we talk about cremophore. Everyone knows how toxic cremophore is, but yet it's still one of the first vehicles of choice when it comes to delivering a hydrophobic drug even though it is extremely toxic, has a fatality that was induced by it, and we have the patient, he's already suffering from cancer, we're giving him a poison, as in the drug, and then we're

using a poison for the vehicle. To me that's adding insult to injury, and there are much smarter ways to do these things.

And that comes back to reeducating the pharmaceutical development and using pharmaceutical chemistry. We have outstanding pharmaceutical programs in the nation, outstanding pharmaceutical scientists that are being produced to optimize these formulations so beginning with the initial concept, we can fine tune these.

This last part here, I think it's going to be difficult at the nano scale, the FDA, I believe, needs to come up with a system when it comes to the regulation of looking at, how do you distinguish soluble polymer systems against colloidal systems. How do you distinguish nanoparticles versus micelles versus polymer-drug conjugates? Those are going to be key.

I'll skip over that one. So my boys and I went and saw "The Hulk" the other

day. Now, as a kid growing up, Lou Ferrigno was my idol and we already have some nanotechnology. I mean, Bruce Banner, he got some toxicity, he got gamma irradiated, so he has to use a pulse rate monitor here to keep his heart rate under 200, otherwise he turns into this guy which is what I look like when I get my reviews back. We have insulin pumps that began with a huge backpack. Now they're the size, essentially, of beepers on our belts.

We have ICDs that will track your cardiac rhythm and defibrillate if need be. We have MEMs for therapeutics. We have some great imaging agents, theragnostics that are coming into play, and this is a new one called a nanopump for diabetics. You can see it's smaller than your fingertip and what it does, it delivers nano liter quantities of insulin continuously throughout the day, disposable, their idea is, once a day, you replace it. And if you're a diabetic, that's

exactly the kind of treatment you need to have is a continuous dosing regimen compared to an acute subcue injection.

So my kids thought of this one because they want an iPod, but I was thinking iMed. Maybe someday we'll have something like this that some patients will wear around their arm or something that will track a number of different parameters -- your EKG, your heart rate, your respiratory rate -- and then have built into it some acute meds for disbursal.

We've cut a whole gamut of groups that are looking at the safety and efficacy and I want to go on record and say validation of nanotechnology when it comes to buckyballs and functionalize gold nanoparticles or dengimers or carbon nanotubes. We've got federal agencies, private groups, that are looking at this.

So when it comes to validation -- this is my last slide -- when it comes to

validation from the FDA perspective, it's going to be easy to enact new regulations, but it's going to be extremely difficult to enforce them. This is going to be further complicated without standards and with no established nanotools.

Now we do have some standard gold nanoparticles that we can -- and I think dengimers and I don't know if we have carbon nanotubes now or not, that we can use when it comes to comparisons for toxicity that we can get from this. But we need to establish metric benchmarks for stability, size distributions, in vitro and in vivo data. That's going to be extremely important so that everyone is playing on the same field, whether you're buying the carbon nanotubes in bulk from company X or you're borrowing them from investigator Y, that you can compare these head to head.

But there's always going to -- there's increasing political and economic

pressure to deliver these to the market right now when it comes to nanotechnology, and we already have them out with clothing and cosmetics, but nanomedicines are on the horizon and it requires substantial investment and the time to bring to market is extensive. But with FDA hesitance, it could run the risk of stifling commercialization and that's going to be the downfall of all of this. I think we all have the tools, we have the brain power, we have the motivation to get these interdisciplinary fields together and try to come up with a new toolkit design.

And finally I just want to thank Professor Ralph Albrecht at Wisconsin who helped. He's been invaluable with the gold nanoparticle work. My chair and a good friend, Dick Peterson, with the Zebrafish. My good friend Dave Grainger, who's the chair of pharmaceutical chemistry at University of Utah. And my graduate student who was working on this, Ofek Bar-Ilan. And thank

the Pharma Foundation and the Coulter Translational Research Award and also UW for their funding.

MR. MORRIS: Thanks, Darin.

MR. FURGESON: Sure.

MR. MORRIS: So, are there any questions for clarification before we transition to the discussion of the questions?

MR. COLLINS: Jerry Collins. Great talk, great overview, but just to clarify the one slide in the middle that I'm concerned people may have gotten the wrong message. You asked the question and we'll be debating it whether FDA requirements for preclinical assessment would be adequate to safely evaluate nanomedicines, and I think the context is important. I think that the context you were speaking about was in the development phase, the screening phase when you're trying to figure out what you have. I don't think -- I don't want to put words in

your mouth, but I'm just trying to clarify whether you were also extrapolating to the kinds of safety testing that we do before putting these products into humans, because I didn't see any evidence presented in your talk, but --

DR. FURGESON: No, not at all. I just think that this is another area that could be added and I know that, like the NCL, they've been looking at this. But right now, I mean, it's extremely stringent which is why it takes so long to get things through. You know, development costs so much money.

MS. TOPP: Yeah, I enjoyed your talk too. Thanks very much.

MR. FURGESON: Sure.

MS. TOPP: I just have a quick question about the toxicity studies both yours with Zebrafish and some of the other ones that involved cultured cell lines.

MR. FURGESON: Yes.

MS. TOPP: Do you know if in any of

these studies the particles actually agglomerate and then fall out of solution and are sort of either floating on top of -- sitting on top of the cells, or have, in your case dropped from the solution around the Zebrafish and are sitting on the bottom of the pools?

MR. FERGUSON: That's a great question. And I'm not going to tell you the answer. Yes, when we were doing our Zebrafish studies, the first thing I was worried about was that, okay, yeah, we can drop these nanoparticles on there, but if they just all precipitate down to the bottom, we're going to have some sort of concentration gradient and it's not going to be worthwhile.

No, with our Zebrafish studies, we do not have precipitation like that. With the cell culture studies, I can't say with any sort -- with confidence, if they saw that. It wouldn't surprise me because they

are incubating these with -- if they were using plasma or FBS in their cell culture medium, you could have some protein absorption and, yes, dragging them down. Exactly.

MR. MORRIS: So thank you. If there are no other clarification questions, thanks again to Mr. Furgeson and we're going to move to the discussion --

(Interruption)

MR. MORRIS: Okay, we're back online. In the interest of time, we thought what we would do is start the discussion now then break for lunch pretty much on time and then resume it after lunch and our open public hear speaker has graciously agreed to speak a little -- she hasn't agreed to speak a little later, but now we're certain that she would -- no, it's possible. Either that or they'll go first and then we'll continue, but one way or another, we will get fed.

At any rate, so we have the

discussion set portion of the first topic now on nanotechnology. The questions are going to be on the screen and once again if I could just ask the panel members to just raise their hand and let Diem capture us in the order in which we are going to be recognized and state your name as we start discussing.

So with that, the first question is, is specific CDER guidance needed for the development of nanotechnology derived drug applications? So I open the floor for comments.

I can start if nobody's -- this is Ken Morris. One of the things that I thought about reading the background material was that much of what we would be concerned with with nanotechnology, however different it may end up being, should be captured in part by -- I hate to go against what you'd said, but in the quality by design paradigm. Not that we're discussing the quality by design initiative, but the underlying precepts of

quality by design would dictate in part that scientific rationale and logic that was used to develop the materials would be one of the things that would be reported normally and researched normally, and that's just -- that was just my impression after reading the background materials, as I said.

Marilyn?

MS. MORRIS: Well, in listening to --

MR. MORRIS: If you could just state your name.

MS. MORRIS: Marilyn Morris. In listening to the presentations today with regards to nanotechnology and reading the background material, there seems to be somewhat two topics which are overlapping and yet somewhat distinct and these are the fact that there are chemicals that are in nanosize and changes in formulation of chemicals, and the second topic deals with really nanosize particles and more in the drug delivery area

and there's, I think, some differences that need to be recognized in the guidance.

Certainly, as an overview, there's certainly a need for looking at various characteristics of nanomolecules whether they're nanosized chemicals or whether these are drug delivery systems, and I think what all the speakers have characterized is it's important to look at physical characteristics of these. Certainly size, size distribution, charge, shape, aggregation -- these are going to be important for really all molecules, all nanomolecules.

Potential differences just due to the size of the chemicals themselves, changes in pharmacokinetics distribution of these -- does this change the therapeutics, does this change toxicity -- that will be important.

With regards to nanotechnology and drug delivery systems, again, this is going to be (off mike) important with regards to all the physical characterization and also

the biological characterization, the pharmacokinetics, different biological interactions, possibly, discrimination between the chemical and the drug delivery system, does the drug delivery system itself have toxicity, the fate of the drug delivery system, the release characteristics, the mechanisms of interaction, so there's a number of differences when we're talking about drug delivery systems, and so I think in looking at all of this, it's important to think about, first, the chemical, in a nanosize, plus the use of nanotechnology as it relates to drug delivery systems.

MR. MORRIS: And I guess just to follow up, so do you think that that needs to be captured in a guidance as opposed to being covered by existing guidance?

MS. MORRIS: I think it needs to be captured in a guidance.

MS. TOPP: This is Liz Topp. And I just have a little follow up. Is that okay?

Am I okay, Diem? So I just had a little follow up comment and I think Ken and Marilyn, you both raised really good points and I think one of the questions we have to ask is, are there unique properties of these nanosized materials that don't fall under existing regulatory considerations? Are there unique characteristics that somehow would not be captured if we just submitted these to the normal regulatory pathways? And I don't know the answer to that question, but one of the concerns that I have is that at the nanosize, particularly engineered nanosize materials, start to be flags for the immune system and so the body responds to viruses as nanosized materials and says, oh, my gosh, we've got to do something about this, whereas the array of materials, chemicals, in that nanosized particulate might not, by themselves, cause the same kinds of immune response.

So that's an example of one area

that I think considerations for molecular sized materials, molecular sized drug products, or more macro scale drug delivery systems like tablets that somehow that the information -- things that are happening at the nanoscale may not be captured by a regulatory process that is used to dealing with either molecular scale materials or macro scale.

MR. COLLINS: Jerry Collins. I don't think that any specific guidance is needed for clinical evaluation. My impression is that the tools that we have for doing, first in human and IND guided studies are perfectly adequate. For toxicology studies or for IND directed studies in general, I'm not personally aware of any evidence that the current testing paradigm. It may be just as clunky for nanotech products as it is for synthetics and natural products and everything else, but I don't see anything that makes me worry that it's going

to be worse for them. There are a number of factors that (off mike) that anyway and that are very important, like the immunological ones, but that's sort of the routine thing.

I think there needs to be a tighter integration between the manufacturing process and the preclinical studies. With small synthetic molecules the nature of characterization isn't nearly as important as it is for biologicals and I would say nanotechs are more like those.

In terms of whether FDA has anything to offer in terms of advice, we haven't really heard that this morning. What would be really useful in terms of guidance is to say, FDA has received 250 INDs. As a result of that review we found that many preconceptions of problems didn't exist. Certain trends are existing that should be done. I don't think collecting a bunch of people around in a room and saying, I wonder if we should do this and I wonder if we

should do that, is nearly as important and as helpful as making it an experience-based guidance document.

MR. MORRIS: Ken Morris. Just one question. I guess my only question, Jerry, to your comment is that one might argue that by the time you've accrued that much data, if a problem is showing up, you might be queried on why he didn't anticipate it. And so I guess if we were looking at the transitioning of current compounds or increment dosage forms that obviously don't have any problem because they're on the market, that with some of what you were talking about, Liz, that new problems show up, whether or not there's need to discriminate between nanofication of existing products versus development of new products where they would have gone through the full rigor of first in human, IND process.

MR. COLLINS: Jerry Collins. Well, I thought that was more the second and third

question in terms of prioritizing the areas of greatest need, so maybe I should modify what I say that there should be some early warning system that comes out of the IND review process. I mean, there is an agency-wide task force to look at nanotechnology and I just -- again, you don't have some magic number at the beginning saying, I won't look at the data until I've got 200 INDs. If something starts showing up then you want to feed that forward into the process right away. So that would be a good amendment.

MR. MORRIS: Any other comments before we -- is this the voting question? Is that correct? So at this point, if there are no other questions or comments, we should call for a vote and so this is the new system, so the voting -- I'll read the question in a moment -- but the voting is on your mic base and it has a yes, no, and abstain, if you notice there. You only get

to vote once. It's not like Chicago.

MR. GOOZNER: This is Merrill Goozner. We're going to vote before the public comment?

MS. NGO: There's no open public hearing speaker for this topic.

MR. MORRIS: I knew that, but I wasn't allowed to say it. I would have been audited, I think.

So what we'll do is after we vote -- I'm sorry, did somebody else have a comment? So I'll read the question. We vote on the electronic version, and then we'll go around had have everybody verbally describe their vote for reasons we can discuss later. For the record. Well that's for the record. The reason we do it in this order is more interesting, so with that, let us go ahead and read the question here.

So the question is, is specific CDER guidance needed for the development of nanotechnology derived drug applications?

And it's yes, no, or abstain. So you can vote at your leisure here.

(Voting)

MR. MORRIS: Okay, we have it on good authority that everyone is in. So if we could, do you mind if -- Carol, if I pick on you and we start and go around?

MS. GLOFF: My name is Carol Gloff and I did vote yes. However, I want to explain that briefly. I didn't feel the need to express comments during the comments by others because I think they expressed pretty well many of my feelings.

I think specific CDER guidance is needed. I'm not convinced it's a new guideline though. I think people need feedback as to the types of things that might be appropriate for them to emphasize. And again, I'm not convinced that's a specific guideline, so it's feedback with pre-IND meetings or feedback in other ways that might be more appropriate than a formal guideline.

MR. COLLINS: Jerry Collins. I just voted along the lines of my comments earlier as I think it's premature to give recommendations until the experience is evaluated at the transition from manufacturing to preclinical studies and the other areas, I think are, as far as I can tell, there's no evidence that there are problems there.

After experience is gained I would change my vote and say, yes, when we have something to offer, we definitely should share it as widely as possible.

MR. MORRIS: And also, if everybody could say how they voted. The camera is on the record when you start.

MR. GOOZNER: This is Merrill Goozner. I voted yes, along the lines, I think of what you were talking about which is, I think there's enough -- they must have enough experience to know as they go through a process of writing a guideline, what

anticipating what some of the data needs will be, and I'm not sure that that's all out there currently when it comes to evaluating not just the drug, but also the material, the (off mike) drug.

MR. KIBBE: Art Kibbe. I voted no for the same reasons that Carol voted yes. At the end when she said that there really isn't anything dramatically unique in my mind about the kinds of things that we do in terms of good manufacturing practice, good laboratory practice, and testing, and evaluation, that aren't already well codified and if you follow good scientific process, I think that what we have will cover it although I think it would be useful for these companies to do what we suggest all companies do when they have a unique or new product coming out, and that's to get to the FDA before they go too far and have those discussions with FDA so that everybody's on the same page.

Often the case is, that a company with a unique or novel approach or a new chemical entity, will know far more about that approach or chemical entity than any of the regulators do -- and I'm not trying to insult regulators -- but they just aren't doing the research in that area and those discussions go a long way to making the regulation reasonable. And I don't think you need a new guidance to get people to come in and do that.

MR. MEYER: Well, I could have been the tie breaker, so for suitable remuneration I could swing the vote here. No, I do have a conflict. You're right.

I try not to vote on this that I don't have enough information on, and while we heard three excellent presentations, to me there were -- I would have liked to have seen like a side-by-side of what are the issues, and what does FDA already do, not being intimately involved with the review process,

so I don't know how many of new problems are already covered by FDA and if so, then we don't need a guidance. I could certainly, in my opinion, the second presentation by Steve Ruddy, sounded like a dosage form that is pretty well already covered. We pretty well understand it's smaller, there may be some tox issues, but it's a more conventional than the first presentation by Tamarkin. That sounded like a much more complex dosage form that probably would take maybe at least some new things to look at, new things for the FDA to request.

Somewhere I read one of the issues is FDA shouldn't drag their feet or begin to invent the wheel after somebody comes in with a three wheel cart. You need to have these anticipated to the extent then you can, in a timely way, anticipate and process an application. So I think it would be good to have some type of guidance that would anticipate problems that are not covered. I

didn't vote for that because I'm not sure there are any although there probably are. So that's kind of why I was in limbo.

MR. KOCH: Mel Koch. I voted for it largely based on background understanding and also to build on some of the points that Marilyn made earlier in terms of some of the discrepancies between the chemical and the dosage form.

I also think that the guidance puts a little bit more -- pressure may not be the right word, but a little more appreciation for the concern as it goes to the pharmaceutical companies. There's certainly -- we don't want to get into the "well after the fact" type concerns we had with say, asbestos, when we see nominally a lot of good uses for it, but there's a bad actor in the bunch that we should probably have understood earlier. So for that reason I would like to see a guidance.

MS. NEMBHARD: I'm Harriot

Nembhard. I voted in favor of a guidance. I think that what we have seen with nanotechnology in general is a higher burden in terms of integrating knowledge, particularly statistical knowledge, across manufacturing, clinical, and even environmental impact of, in this case, pharmaceuticals. So for that reason, I voted in favor of having a guidance and particularly would be interested in seeing this sort of lifecycle approach taken and integrated into such recommendations.

MS. TOPP: I'm Liz Topp. And based on my comments this morning, many of you might be surprised that I voted against having a guidance. I feel like I really need to explain myself.

I look at the issue with regard to nanomedicines as being a question of safety and efficacy. And with regard to the presentations we've heard this morning, we've heard a lot of really fascinating and

compelling information -- I've heard a lot of really interesting data and read a lot of interesting data that suggests that these materials can be uniquely efficacious. They can be fabulously efficacious, targeted delivery to tumors, and also really some interesting solubalization phenomena. We've heard about that this morning. So I think with regard to efficacy, we're going to cover the efficacy of these materials and there's compelling scientific data to say that the efficacy -- we'll have data to see the efficacy.

My questions really come down on the safety side. Will these nanomaterials turn out to be safe and efficacious materials? And I think in the last presentation, Darin's presentation this morning, what I heard from that presentation and other things that we've read, is that we really don't have a good idea about whether nanomaterials are going to be toxic in the

long run and we don't really have good assays for figuring out how particulates interact with the body, so even in the area of vaccine adjuvants, for example, we don't really understand how vaccine adjuvants do what they do, how they stimulate or interact with the immune system.

So on the efficacy side, I think we've got it covered. On the safety side, I don't think we have the tools, really, to tell us whether they're going to be safe or not. We simply don't have enough of a track record.

So for that reason, I think the efficacy issues will be covered by existing FDA policies and procedures, and the safety issues, we simply don't have the tools. So right now, I don't think a guidance is appropriate.

MS. MORRIS: Marilyn Morris. Well, I voted in favor mainly due to what I see as the complexities and a number of the

differences from natural -- from other therapeutic agents. However, I had difficulty in coming to that decision because I felt maybe I should abstain because I'm not aware of whether or not all the formulation issues, the safety and efficacy issues, are covered by other guidances, and so although I voted for it, again I was sort of on the line for doing so.

MS. ROBINSON: Anne Robinson. My vote was no for the same reasons, really, that some other people have discussed, for the "no" reasons although I do agree, particularly with the drug delivery and other things, using new materials or old materials in a new way, that there could be some concerns about the safety, again, as Liz Topp suggested, it's not clear what those should be and so I think right now, based on that and the background material, it's not appropriate to have guidance.

MR. MORRIS: Ken Morris. I voted

no. I really wanted the "nes" category, the no/yes category, for the same reasons. Basically there were a couple -- to Harriet's point, the idea that we should be integrating and coupling development and manufacturing, I agree. That is something that needs to be done. But it needs to be done and I think that's what we're trying to push with the larger guidance and initiatives that we're trying to push now, and the other reason was more a combination, actually, of what Liz and Marilyn and somebody else had said, I guess maybe Jerry is that with respect to guidance, a premature guidance probably does more harm than good even if there eventually will be enough information on some of the topics discussed, so that was my rationale.

One thing that I neglected to do that we have to do before we do what we just did is raise your hand and swear to turn your money over to me. No, no, raise your hand as we call for yes and no votes. Is that

correct? So everyone who voted yes, please raise your hand. Good enough. And for everyone who voted no, please raise your hand. And for everyone who voted "nes" or abstained, please raise your hand.

MS. NGO: Okay, for the record, that's five yes, five nos and one abstention.

MR. MORRIS: So are we ready to break at this point? Okay, so we can either go to 12:30 and do one more question then break or we can break now and return to discuss. Does it push your buttons -- no, no, so we would like to continue? So let's continue.

So we're going to go on to question two. And question two, if a guidance is needed -- so let's take that as the hypothetical -- given our last vote, we haven't decided exactly, what areas should these guidelines focus on? And I sort of struggle with whether this should have been first, but it's the same problem. If we put

it first then we presume that the answer to the next question would be yes. So again, if guidance is needed from CDER, what areas should these guidelines focus on? So can we start discussion?

MS. TOPP: Yes, I'll jump in and try to get my microphone to work this time. So I think everyone who voted no, is really recused from -- no, so that only five people really get to talk now.

I think really one of the issues is the safety issue. You know, how do you assess the safety long term, short term, safety toxicity issues of these materials? And I had an interesting conversation with Harriet earlier and she can weigh in on this if she would like, as someone -- she's someone who's interested in manufacturing of nanomaterials and apparently when she submits NSF proposals, the NSF is quite concerned about the environmental burden of any nanoparticulate materials. Well, if the NSF

is concerned about the environmental burden, perhaps we should be concerned because ultimately we're concerned about the human effects and the effects on things like Zebrafish, so you know, we should be concerned about those issues at this level as well.

MR. GOOZNER: Merrill Goozner. Let me just underscore that. When the lifecycle approach was raised earlier, I know that it talked to a lot of the concern, what I was thinking about a lot that was raised in the taskforce report and I was surprised that nobody addressed it this morning but that is, what happens to these things when they go out in the environment? One of the slides that stuck in my mind this morning was, you know, only 35 percent got captured by the body. That meant it was a great thing, 65 percent was excreted. Well, where did it go? What is it? What does it do? And the FDA -- he held up the drinking water. Exactly right.

The FDA historically, I think has not -- you know, I'm not an expert in this, but I think it hasn't really concerned itself with that question. But maybe it's time that it begin dealing with some of those kinds of questions.

MR. MORRIS: Liz? No. Meyer? Oh, no Marv.

MR. KIBBE: Dr. Kibbe here. Just a quick statement about the -- there's been a lot of work through EPA on drugs, residual and groundwater. There's a lot of international -- look at that, and I don't think that necessarily is something that ought to be part of a submission per se and I don't know why the FDA wants to get into that, but that is a concern in general because, especially cytotoxic materials that are not easily biodegradable going into the water system because we do a lot about recapturing out of date toxic drugs and how carefully we take care of it and then we give

it to a person and then they excrete it and it goes into the standard sewer system and then you find it in groundwater, but whether that's something that we should be addressing is, I think, it's beyond where we need to go and I voted no because I think a lot of the standard questions we ask on every compound that comes before us, is it going to be in the body a long time? Are we going to use it chronically? Are we going to use it acutely? What kind of toxicity studies do we need? Do we need three- generation teratological studies? Those things are already in the literature and in the guidances and that's why we don't need them.

MR. KOCH: Mel Koch. I guess my concern would be around the safety issue primarily but then afterwards I've got some concerns that bridge on toxicity but have more to do with mechanism of action, and that is the particles get smaller is indeed the mechanism of action, absorption, et cetera,

were they following the same track as we would expect from the macro on its way down.

And then another concern, really, is in the environmental area and I go back to the early days when biopolymers were quite popular. We found that until they were dramatically modified, there were some problems because of a biopolymer degrading to a monomer ended up as something that was actually more toxic than the polymer and I think as progress has shown, much more attention has shown that the biodegradable material is what's safer.

And then we go into some of the disposal issues in terms of where is the ultimate fate, and you look at some of the disposal concerns now with electronics and LCDs and other things in terms of how does one handle it ultimately. So I think a lot of these are reasons for at least addressing a guidance.

MS. NGO: Dr. Nembhard.

MS. NEMBHARD: Again, I would like to reiterate that I think that it's very important that guidance for emerging nanotechnologies really focus on a collaboration with the other agencies. For example, Dr. Furgeson's last slide indicated the number of agencies that have an interest in developing and overseeing nanotechnologies including OSHA and EPA.

Again, if we're looking at lifecycle and end of lifecycle issues for potential new drugs, I think it's important to understand safety issues for people who are actually doing the manufacturing. It's important to understand how transfers and processing and tooling of nanomanufacturing impact the drug in terms of both its mechanism, how it's made, and how those materials are recaptured at the end, again, of the lifecycle of the drug whether that be through excretion or even just waste in the manufacturing process. I think that all of

these are issues that I can certainly be educated on how far the FDA's oversight would go on this issue, but I think it does point to a need for collaboration particularly for nanotechnologies in this area.

MS. ROBINSON: Just to offer the maybe contrasting opinion, although not to belittle the importance of the impact on the environment, I think I agree that the connecting the different agencies is important. I don't think that -- let me take a step back and say, with any pharmaceutical I think what Dr. Ruddy pointed out was that making things in nanoparticles actually enhance the absorption into the body and decreased the dosage that was required.

What that means is, if you think of the mirror of that means that in the normal dosage, more is excreted and that's an environmental concern. So it's an environmental concern for any pharmaceutical what happens when it leaves the body and is

excreted. And I don't think that this issue, although it's very critically important, falls under CDER's purview.

MR. MORRIS: Keith?

MR. WEBBER: Just a point of clarification for the committee as well as a question I had. FDA -- or CDER, FDA in general, is required under the National Environmental Policy Act, to address environmental issues related to the approval of drugs so we do take that into consideration when we evaluate applications. Just so everyone knows we do do that. Regarding the question of safety, are there unique aspects of nanotechnology of products that we should consider from a safety perspective that wouldn't be evaluated under our normal safety evaluations and the question of what should go into a guidance if we had one, what factors should we consider in that regard?

MR. MORRIS: Yes. I just have a

comment and then Carol and then Liz.

Yes, that actually, Keith, that's sort of the point I was going to raise. To me, I think the issues are -- in terms of what the guidance -- what areas the guidelines should focus on, in a sense it is. It's what is it that's unique about a nano either technology or whether it's just a technology in the sense that it's the technology used to produce it that gives you the size characteristics, or that it's actually a -- we haven't talked much about device issues but there are issues with devices whether they be external devices or internal devices that really do create unique manufacturing processes as well as the mode of action might be different, so in a sense I was sort of thinking that it should focus on identifying what it is that's truly unique about a given nanotechnology and maybe at that line even categorize what is and isn't unique in the broad brushstroke sense of the

word. So uniqueness if you will.

And Carol, I think you're next.

MS. GLOFF: Carol Gloff. Yes, I was going to make the point as well, we need to focus on what is unique about nanotechnology relative to the types of products that are widely being developed or on the market at this point in time, and I look at that both from the manufacturing perspective but also from the safety perspective and perhaps a bit to answer Keith's question, one of the things that goes through my mind, maybe because I'm a pharmacokineticist at heart is, looking at clearance and looking at where these nanoparticles are going.

I think for at least many traditional drugs that are developed and have been developed over the years, there certainly is some pharmacokinetics that are done in animals in advance, probably some biodistribution, but there's not a major

emphasis on that and I think there may need to be an additional emphasis on that for these types of products -- nanotechnology products, that could then help us to predict and to investigate further what sort of safety and toxicity issues we might run into.

MS. TOPP: Yes, Keith. I would like to give my little answer to your question. So you asked the question, are there unique safety issues with regard to nanoparticles? And I think the answer is, well there might be because of their size. They might have unique safety toxicity concerns specifically because of their size, not because of their chemical composition, but because they lay between this macro issue and these molecular scale issues.

And then the second part of your question was -- so the answer to the first part of your question was maybe. And then the second part of your question is, what specific guidance should be given? And the