UNITED STATES FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACEUTICAL SCIENCE AND CLINICAL PHARMACOLOGY

ADVISORY COMMITTEE MEETING

DAY 1

Rockville, Maryland

Tuesday, July 22, 2008

PARTICIPANTS:

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1 P R O C E E D I N G S

2 (8:36 a.m.)

3 DR. MORRIS: Well, good morning,

4 everybody. I believe we're good to go now.

5 We have our technical difficulties resolved

6 and I'd just like to welcome everybody. This

7 is the first meeting since 2006 of the

8 Committee and we have a lot of interesting

9 topics to discuss.

10 Before we get started there's a

11 brief statement that I'll read and then we'll

12 go around the table and have everybody make

13 brief introductions.

14 The statement is: For topics such

15 as those being discussed at today's meeting,

16 there are often a variety of opinions, some

17 of which are quite strongly held. Our goal

18 is that today's meeting will be a fair and

19 open forum for discussion of these issues and

20 that individuals can express their views

21 without interruption. Thus, a gentle

22 reminder, individuals will be allowed to

1 speak into the record only if recognized by
2 the Chair. We look forward to a productive
3 meeting.
4 And in the spirit of the Federal
5 Advisory Committee Act and the Government in
6 the Sunshine Act, we ask that the Advisory
7 Committee members take care that their
8 conversations about the topic at hand take
9 place in the open forum of the meeting. We
10 are aware that members of the media are
11 anxious to speak with the FDA about these
12 proceedings, however, FDA will refrain from
13 discussing the details of this meeting with
14 the media until its conclusion.
15 Also, the Committee is reminded to
16 please refrain from discussing the meeting
17 topics during breaks or during lunches.
18 Thank you very much.
19 And of course, in terms of the
20 topics, they are all general topics and we're
21 not talking about specific products anyway.
22 So with that, if we can go around

1 and do a brief introduction. Shall we start
2 with Keith?
3 MR. WEBBER: Keith Webber, deputy
4 directory of the Office of Pharmaceutical
5 Science, Center for Drug Evaluation Research.
6 MS. WINKLE: Helen Winkle, director
7 of the Office of Pharmaceutical Science,
8 CDER.
9 MS. NGO: Lieutenant Commander
10 Diem-Kieu Ngo, designated federal official.
11 MR. MORRIS: Ken Morris, University
12 of Hawaii Pharmaceutics.
13 MS. ROBINSON: Anne Robinson,
14 Chemical Engineering, University of Delaware.
15 MS. MORRIS: Marilyn Morris,
16 Pharmaceutical Sciences, University of
17 Buffalo.
18 MS. TOPP: Liz Topp, Pharmaceutical
19 Chemistry, University of Kansas.
20 MS. NEMBHARD: Harriet Nembhard,
21 Industrial Engineering, Penn State
22 University.

1 MR. KOCH: Mel Koch, the Center for
2 Process Analytical Chemistry, University of
3 Washington.
4 MR. MEYER: Marvin Meyer, emeritus
5 professor, University of Tennessee, College
6 of Pharmacy.
7 MR. KIBBE: Art Kibbe, chair,
8 Pharmaceutical Sciences, Wilkes University.
9 MR. GOOZNER: Merrill Goozner. I'm
10 with the Center for Science in the Public
11 Interest. I'm the consumer rep on the
12 committee.
13 MR. COLLINS: Jerry Collins,
14 National Cancer Institute at NIH.
15 MS. GLOFF: Carol Gloff, Boston
16 University and independent regulatory
17 consultant.
18 MS. TWAY: Pat Tway, Merck &
19 Company, representing Pharma.
20 MR. STEC: Rich Stec, Hospira,
21 Inc., representing generic industry.
22 MS. NGO: Before I read the meeting

1 statement, I would like to remind everyone to
2 silence your cell phones and pagers if you
3 have not already done so and also Mr.
4 Christopher Kelly from our press office is
5 here, if you can stand up.
6 The Food and Drug Administration
7 has convened today's meeting of the Advisory
8 Committee for Pharmaceutical Science and
9 Clinical Pharmacology of the Center for Drug
10 Evaluation Research under the authority of
11 the Federal Advisory Committee Act of 1972.
12 With the exception of the initial
13 representatives, the members and temporary
14 voting members of the Committee are Special
15 Government Employees or regular federal
16 employees from other agencies and are subject
17 to federal conflict of interest laws and
18 regulations.
19 The following information on the
20 status of this Committee's compliance with
21 federal ethics and conflict of interest laws
22 covered by but not limited to those found at

1 19 USC Section 208 and Section 712 of the
2 Federal Food, Drug, and Cosmetic Act, FD&C
3 Act, is being provided to participants in
4 today's meeting and to the public.
5 FDA has determined that the members
6 and temporary voting members of the Committee
7 are in compliance with federal ethics and
8 conflict of interest laws. Under 18 USC
9 Section 208, Congress has authorized FDA to
10 grant waivers to Special Government Employees
11 and regular federal employees who have
12 potential financial conflicts when it is
13 determined that the agency's need for a
14 particular individual's services outweighs
15 his or her potential financial conflict of
16 interest.
17 Under Section 712 of the FD&C Act,
18 Congress has authorized FDA to grant waivers
19 to Special Government Employees and regular
20 federal employees with potential financial
21 conflicts when necessary to afford the
22 Committee essential expertise.

1 Related to the discussions of
2 today's meeting, members and temporary voting
3 members of this Committee have been screened
4 for potential financial conflicts of interest
5 of their own as well as those imputed to them
6 including those of their spouses or minor
7 children and for purposes of 18 USC Section
8 208, their employers. These interests may
9 include investments, consulting, expert
10 witness, testimony, contracts, grants,
11 CRADAs, teaching, speaking, writing, patents,
12 royalties, and primary employment.
13 For today's agenda, the Committee
14 will one, receive presentations from the
15 Office of Pharmaceutical Science and discuss
16 current thinking on issues pertaining to the
17 use of nanotechnology in drug manufacturing,
18 drug delivery, or drug products, and two,
19 receive an update from OPS, discuss and make
20 comments on current strategies and directions
21 for the testing of lead in pharmaceutical
22 products. This is a particular matters

1 meeting during which general issues will be
2 discussed.
3 Based on the agenda and all
4 financial interests reported by the Committee
5 members and temporary voting members,
6 conflict of interest waivers have been issued
7 in accordance with 18 USC Section 208(b)(3)
8 and Section 712 of the FD&C Act to Dr. Marvin
9 Meyer for his stock ownership in two health
10 care sector mutual funds. The waivers allow
11 this individual to participate fully in
12 today's deliberations. FDA's reasons for
13 issuing the waivers are described in the
14 waiver documents which are posted on the
15 FDA's website at
16 www.fda.gov/ohrms/dockets/default.htm.
17 Copies of the waivers may also be obtained by
18 submitting a written request to the Agency's
19 Freedom of Information Office, Room 630 of
20 the Parklawn Building.
21 A copy of this statement will be
22 available for review at the registration

1 table during this meeting and will be
2 included as part of the official transcript.
3 Additionally, we would like to disclose that
4 Dr. Jessie Au is excluded from participating
5 in today's discussions on the use of
6 nanotechnology in drug manufacturing, drug
7 delivery, or drug products due to her related
8 interest in the topic.
9 We would also like to disclose that
10 Dr. Richard Stec and Dr. Patricia Tway are
11 serving as non-voting industry
12 representatives acting on behalf of all
13 regulated industry. Dr. Stec is an employee
14 of Hospira and Dr. Tway is an employee of
15 Merck & Company.
16 We would like to remind the members
17 and temporary voting members that if the
18 discussions involve any other products or
19 (off mike) not already on the agenda for
20 which an FDA participant has a personal or
21 imputed financial interest, the participants
22 need to exclude themselves from such

1 involvement and the exclusion will be noted
2 for the record.
3 FDA encourages all other
4 participants to advise the committee of any
5 financial relationships that they may have
6 with any firms at issue. Thank you.
7 MR. MORRIS: Thank you, Diem. So I
8 think at this point we'll start by turning
9 things over to Helen Winkle, the Director of
10 OPS, for an opening statement.
11 MS. WINKLE: Good morning everyone.
12 This is such a new configuration. It's
13 really different. It really is my pleasure
14 to be here with each of you this morning and
15 to welcome everyone to the Advisory
16 Committee. I especially want to welcome Ken
17 Morris back as Chair of the Committee. We've
18 enjoyed working with Ken in the past and we
19 look forward to continuing to work with him
20 in the future even though he's moved to
21 Hawaii, far away from us, we can still bring
22 him back that far.

1 A special welcome too to all of our
2 new members. We have a number of new members
3 and I hope that each of you as you
4 participate in various topics on this
5 committee over the next few years will really
6 find it extremely interesting but also I
7 think and hope that you'll find it rewarding
8 for many of your scientific endeavors now and
9 in the future.
10 I also want to thank all of OPS's
11 staff as well as other staff in CDER who have
12 worked together to make this meeting
13 possible. It takes a lot of work to put
14 these presentations together and I really
15 believe that the presentations that we have
16 put together for the next few days, that you
17 will find interesting and beneficial and I'm
18 really hoping that the discussions around the
19 topics that we have will be very helpful to
20 FDA in making regulatory decisions in the
21 directions we want to go as far as these
22 particular topics are concerned.

1 Last of all, I want to welcome all
2 the interested parties. We're glad to have
3 you with us.
4 I just want to talk a little bit
5 about FDA. I mean, I feel almost compelled
6 to talk a little bit about what's going on.
7 We haven't met since 2006, the Committee, and
8 we do have new members on the Committee, so I
9 want to just give a brief update. I don't
10 want to spend a lot of time talking, but I
11 thought I would talk a little bit about some
12 of our challenges that we've had over the
13 last few years and some of the skepticism
14 that now seems to be rising over our various
15 regulated products and about some of the
16 initiatives that we're working on really to
17 resolve any of the issues and skepticism that
18 exists out there.
19 I consider these really to be
20 exciting and challenging times and with the
21 challenges though come opportunities, so as I
22 go through a lot of what I'm going to talk

1 about this morning, I think you will see
2 where many of these opportunities exist and I
3 think these opportunities are things that
4 this Advisory Committee can really take
5 advantage of.
6 First of all, we've made a lot of
7 progress over the last few years on
8 implementing the concepts to improve quality,
9 our new CMC Review Paradigm. And I think
10 many of you have heard about this but
11 probably there are some of the new members
12 that haven't, and this is really where we've
13 been focusing a lot of our efforts to
14 implement what we're calling Quality by
15 Design. And all three of the offices in OPS
16 have been working very diligently at this
17 implementation.
18 Our Office of New Drug Quality
19 Assessment has really made a lot of progress.
20 They've had a pilot in which various
21 companies submitted applications that
22 contained information on pharmaceutical

1 development and on process and manufacturing
2 understanding. And basically this pilot has
3 been very useful in helping us to determine
4 what information is really relevant in
5 processing and application under the new
6 Review Paradigm, and where our scientific and
7 regulatory gaps exist so that we can begin to
8 fill those gaps.
9 The information in the pilot has
10 also helped us in looking ahead as to how we
11 want to continue to implement this paradigm
12 and some of the things that we need to
13 consider along that road.
14 The Office of Generic Drugs has
15 also implemented what it's calling it's
16 question-based review. And this review
17 basically provides a template of questions
18 that relate to the quality of design
19 principles and have been very useful in
20 helping companies to identify what
21 information they need to incorporate into
22 their applications. And I feel like in the

1 long run it's really going to expedite us
2 getting the applications through.
3 We've currently received, and
4 Lawrence can correct me when he gets up here,
5 but we have received over 400 applications
6 using this new template. Now we haven't had
7 a chance to review all 400 but many of them
8 are in our queue in Generic Drugs, but the
9 whole concept has been extremely helpful in
10 providing us with information and helped the
11 generic industry focus more on the concept of
12 quality by design.
13 The Office of Biotech Products has
14 just issued a federal registry notice. They
15 plan to do a similar pilot as has been done
16 in our office of OMDQA and they're looking to
17 see what kind of information is really
18 necessary in being able to do a biotech
19 application.
20 So a lot has been going on in this
21 area. We've talked about this many times at
22 previous advisory committees. We will not be

1 talking about Quality by Design at this one
2 but I'm hoping at the next meeting that we
3 have that we will have a better understanding
4 of where some of our scientific and
5 regulatory gaps are and that we can have
6 further discussion with the Committee as we
7 progress in our implementation.
8 We've also focused a lot over the
9 last couple of years on improving the science
10 base in the Office of Generic Drugs through
11 the implementation of Quality by Design, as I
12 mentioned, but through other activities as
13 well. And in strengthening our science base
14 in the Office of Generic Drugs, we've really
15 been better able to approve generic drugs in
16 a more expeditious timeframe.
17 There has been a really tremendous
18 demand for generic drug approvals and through
19 some of the more modern science spaces that
20 we've been able to implement, we've been able
21 to improve on getting generic drugs out on
22 the market. I think as you see from the

1 agenda, we have several topics tomorrow on
2 generic drugs and some of our scientific
3 challenges in the area of generic drug
4 regulation. And I think the discussions that
5 we will have tomorrow will be very helpful in
6 going that next step in sort of supporting
7 our scientific knowledge base for
8 bioequivalence.
9 I also wanted to mention as I'm
10 talking about progress is just international
11 harmonization. FDA has worked very hard with
12 other regulatory regions to harmonize on a
13 variety of issues having to do with quality
14 and have been very successful under the
15 International Conference for Harmonization in
16 implementing guidances, one Q8 on
17 pharmaceutical development, Q9 on risk
18 management, and Q10 on quality systems, and
19 all three of these guidances have been
20 incorporated into our thinking on regulating
21 CMC in OPS.
22 But, again, as I said, these are

1 challenging times and I just wanted to go
2 through some of the challenges that we have
3 been seeing and some of the issues, I think,
4 that are important as we talk and discuss
5 things at this Advisory Committee, that
6 you're aware of some of these things so that
7 we can build this into some of our
8 discussions.
9 All one really has to do is open
10 the newspapers, and I think every day you see
11 "FDA" and if it isn't the front page it's at
12 least the second page of the paper, a lot of
13 it having to do with drug safety and many of
14 the issues that we've had post-approval with
15 products. At least we aren't having to deal
16 with tomatoes, but we have had a number of
17 issues that have come up recently that have
18 provided us with a lot of action here in the
19 agency. I think most notable is Heparin, but
20 there have been a number of other issues as
21 well.
22 There are a lot of perceived

1 vulnerability on CDER's drug safety program
2 and we are really focused on trying to deal
3 with a lot of those issues. And as I talk
4 about some of the initiatives, you can see
5 some of the efforts that we're putting forth
6 in dealing with the drug safety.
7 Despite our improved scientific
8 base in OGD, we've also seen growing
9 skepticism regarding generic drugs and our
10 approval process. We've seen a number of
11 articles and in various newspapers, in
12 journals, and have received numerous letters
13 questioning, really, our regulatory process
14 and questioning the sameness of some of our
15 generic products.
16 Currently, it's a priority in the
17 center to determine how best to handle the
18 skepticism out there in the public and to get
19 better information out to both the public and
20 health care providers both on the safety and
21 quality of generic drugs so even though this
22 is a challenge, I think we're looking at ways

1 to resolve it.

2 Another thing I wanted to bring up

3 because I always get a lot of questions on it

4 is, where are we with follow-on biologics.

5 Although we've had a number of congressional

6 bills that have been proposed, we still do

7 not have any legislation on follow-on

8 biologics. We do continue though to keep up

9 with the science. We have had several

10 workshops to discuss scientific issues around

11 follow-on biologics and we will continue to

12 focus on that science both for chemistry and

13 immunogenicity until we do have a final

14 decision either to move ahead with follow-on

15 biologics or to take some other course.

16 Another challenge that we have and

17 it's a never ending challenge, is to

18 understand how to regulate new dosage forms

19 and new technologies. We will talk a little

20 bit about new technologies in our first

21 session this morning, on nanotechnologies.

22 It's always -- a lot of effort that has to go

1 in to determining how best we're going to
2 regulate if indeed we need to change any of
3 our processes in that regulatory arena in
4 order to handle these new technologies. So I
5 look forward to some good discussion on that
6 this morning.
7 And last of all, there's always a
8 big challenge to train our employees. It's
9 especially been a lot of necessity with the
10 changing paradigm to do a lot of training and
11 this is one of the things we've been focused
12 on quite a bit in the last year.
13 Okay, as I said, I wanted to talk a
14 little about initiative and other activities
15 that effect programs at OPS. I'm not going
16 to talk at length about any of these
17 initiatives or I would talk for the next few
18 days. Obviously, there's so many. But we
19 have continuing initiatives that we're
20 working on -- Pharmaceutical Quality for the
21 21st Century Initiative, the Critical Path
22 Initiative, PDUFA, which really handles a lot

1 of our resource issues, we have a number of
2 new initiatives and other activities that are
3 going on. Back in the fall of 2007, we
4 received a report from the Science Board.
5 The Science Board had been commissioned by
6 the commissioner to come in and look at the
7 science within the agency and we have
8 received their report. We received a report
9 early in 2007 from IOM talking about our
10 safety issues. We also have a new initiative
11 called the Safety First and Safe Use
12 initiative, and last of all, we just received
13 new legislation on FDAAA or the FDA
14 Amendment's Act.
15 I thought what would be best,
16 instead of going through all of these, is to
17 sort of give you an overall idea about the
18 general purpose of the initiatives and the
19 activities as they relate to CDER.
20 All of these initiatives basically
21 had some of the same principles and some of
22 the same concerns in them, and I think it's,

1 as we read through these or as I read through
2 them, I think you can see how beneficial they
3 will be to the FDA in making improvements.
4 And again, I think it's very good to keep all
5 of these principles in mind as we think about
6 the various topics that we're going to talk
7 about over the next two days.
8 The main thing that all of the
9 initiatives focus on was insuring adequate
10 scientific support, for insurance safety,
11 efficacy, and quality of marketed products.
12 Also the initiatives focus on providing
13 scientific and technical methods to improve
14 predictability and efficiency to better
15 develop and manufacture drug products. Also
16 to facilitate adoption of quality management
17 techniques in regulatory processes, not only
18 while we're looking at implementing quality
19 management techniques within the industry or
20 at least supporting that concept, we're also
21 looking at doing it in the agency to improve
22 upon our own internal processes. Implement

1 risk-based approaches to product regulation.
2 We have spent a lot of time both for our
3 inspection programs as well as our review
4 programs, at looking at the best (off mike)
5 risk based approaches that can facilitate us
6 getting our job done. Enhance post market
7 authorities to better insure product safety
8 -- this is basically to maintain focus on
9 drugs once they are on the market.
10 One of the things that came out of
11 the IOM report, and we're spending a lot of
12 time in at CDER, is to improve upon our
13 professional culture. There was a lot of
14 criticism of the fact that the disciplines
15 did not work well together within the agency
16 and we are very focused right now on that.
17 In fact, tomorrow I will be away from the
18 committee for a while during the middle of
19 the day to attend a work culture session with
20 all our directors and mid- level managers to
21 discuss some of our cultural problems.
22 Prepare scientific and regulatory

1 process for the future including
2 understanding new technologies and preparing
3 for different ways of developing drugs. This
4 includes novel dosage forms, and last to
5 ensure adequate resources. Almost every
6 particular activity that we had or report
7 that came in really focused on our lack of
8 resources in the FDA.
9 Again, I said it was really
10 necessary to keep some of these things in our
11 mind as we talk as an Advisory Committee. I
12 wanted to just speak a moment to the Advisory
13 Committee's role. I think that this
14 Committee is extremely valuable, when we look
15 back at the number of scientific issues that
16 do come before this Committee and the help
17 this Committee has been able to provide us.
18 The Advisory Committee along with
19 others in the Center basically promote a
20 better FDA and industry understanding of the
21 unique challenges in the present and in the
22 future health care environment. And there

1 has not really been a time in FDA that I can
2 remember in the recent future (sic) where our
3 science capabilities have been so questioned.
4 So it's really very useful for us to bring a
5 group of scientists such as yourself together
6 to help us really address these issues.
7 I took this quote out of the
8 Science Board Report of 2007 because I really
9 wanted you to get an essence of how FDA is
10 viewed from a science standpoint and why your
11 role is so extremely important and the quote
12 basically says, "Science at FDA is in a
13 precarious position. The Agency suffers from
14 serious scientific deficiencies and is not
15 positioned to meet current emerging
16 regulatory responsibilities." That's a
17 pretty negative quote but we really are
18 looking internally within our office as well
19 as in CDER to take advantage of as much
20 outside expertise to help support our science
21 and to really bring us in to the 21st century
22 as far as our knowledge and scientific

1 expertise is concerned.
2 I want to talk a little bit about
3 the agenda. I won't spend long on this. Day
4 one is basically on two areas where we have
5 had some concerns and questions. The first
6 is on nanotechnology. This particular topic
7 has been brought to the Committee before as
8 an awareness topic. In the fall of 2007, FDA
9 issued a report regarding nanotechnology and
10 how it should be regulated throughout FDA and
11 we're still in a position of figuring out how
12 we want to regulate and if we really do need
13 to spend any additional time our concern over
14 the safety of products which contain
15 nanoparticles. So we'd like to run that by
16 the Committee today and have some discussion
17 on that.
18 The second topic is lead in
19 pharmaceutical products. There has been a
20 national focus on all products containing
21 lead. We really want to talk a little bit
22 about pharmaceutical products that do contain

1 lead. We have done some studies. We'll
2 share some information with you. We have
3 looked at some other centers and how they
4 have regulated lead and we would like to
5 ensure that we have the appropriate
6 regulatory framework as we move forward in
7 this area and we look for your advice on
8 that.
9 I do want to say before I move on
10 to day two, is that as we go through these
11 various topics that are on the agenda, we
12 really are not talking about any specific
13 products. We really are looking at general
14 information on all of these topics and we
15 really feel that the decisions that come out
16 of these Advisory Committee Meetings will
17 really assist us in making decisions on
18 classes of products or on all of the products
19 we regulate, but again, nothing on a specific
20 product.
21 Agenda for day two is, we have
22 basically devoted this to generic drugs. The

1 first item on the agenda is bioequivalence
2 for locally acting drugs that treat
3 gastrointestinal conditions. We need to
4 ensure that we're using the most scientific
5 bioequivalence methodology. We will discuss
6 that. The second topic is drug
7 classification of orally disintegrating
8 tablets. This is basically a nomenclature
9 inconsistency issue which we will discuss
10 with the committee.
11 And the last topic is the use of
12 inhaled corticosteroid dose response as a
13 means to establish bioequivalence of
14 inhalation drug products. And again here,
15 we're looking at bioequivalence methodology.
16 So with that, again I want to
17 welcome each of you. I look forward to some
18 very interesting discussions over the next
19 two days and I want to thank you all again
20 for your attendance here.
21 MR. MORRIS: Thank you, Helen. I
22 noticed that that comment on the report

1 wasn't directed to OPS, right?

2 So that brings us to our first

3 topic, and the first topic, as Helen

4 introduced, is nanotechnology and drug

5 manufacturing, drug delivery, and drug

6 products. And our first speaker is Keith

7 Webber who is the deputy director of OPS.

8 Keith?

9 MR. WEBBER: Okay. Welcome to this

10 session on nanotechnology. I think that as

11 you know, I'm sure, nanotechnology is a

12 relatively new and quite exciting area of

13 materials and engineering that's moving

14 forward at quite a rate these days. Given

15 that it's new, there's a lot of uncertainty

16 involved with its applications. There is a

17 lot of promise. And I think the task that

18 the agency has ahead of it is to sort of

19 filter out the hype, the promise, into

20 reality and kind of use as best we can, and I

21 should say to the best we can, absolutely we

22 need to use the science base to -- and the

1 scientific knowledge to do that such that we
2 can be sure we move forward with the
3 appropriate regulatory policies.
4 Now, what I'd like to do first is
5 to introduce really the purpose of this
6 session, is to (off mike) had an earlier
7 session in which we introduced this as sort
8 of an informational topic at a previous
9 meeting. We would like to update the
10 Advisory Committee on the CDER's nanotech
11 related activities. We want to familiarize
12 the Committee with some pharmaceutically
13 relevant nanotechnology concerns as well as
14 some technologies that our presenters will
15 show you after my presentation. And then
16 receive advice from the Committee on the
17 scientifically sound basis for some of the
18 regulatory questions that we are faced with
19 related to nanotechnology.
20 Background, from my particular
21 talk, I really just want to introduce some of
22 the nanotechnology products that we have and

1 then some of the impacts that those have on
2 our evaluation system within CDER. We had a
3 task force at the FDA level that evaluated
4 this issue or these issues related to
5 nanotechnology and (off mike) provide some
6 summary recommendations that came out of that
7 committee as well as some public meetings we
8 had in relation to that as well as
9 subsequently, and then discuss briefly some
10 of our initiatives within CDER, which include
11 developing a database of products and some of
12 the research activities we have going on on
13 MAPP. Which if you're not familiar with what
14 MAPP means, it's essentially an internal
15 standard operating procedure basically of how
16 we handle or would handle an application that
17 proposed to introduce a nanotechnology drug
18 product into either human use, human studies
19 as an IND or to the market. And then the
20 question of whether we need guidance related
21 to development of nanotechnology products.
22 Now, this slide essentially goes

1 through and illustrates the wide variety of
2 nanoparticle products that are being
3 developed and these include essentially your
4 nanospheres which are either of consistent
5 structure or encapsulated. Again, another
6 sphere that is in a liposome-type format
7 where you encapsulate a drug or you have
8 targeting (off mike) outside and then
9 polymeric particles that can be used to
10 provide multivalent structure to a drug
11 product for targeting or delivery of a drug.
12 And then there are the inorganic
13 particles that are used for a variety of
14 applications, some for example in imaging
15 technologies.
16 So we're really dealing with quite
17 an array of products. It's not a simple
18 horizon that we're dealing with here.
19 Some of the potential
20 pharmaceutical applications of nanotechnology
21 include, as I mentioned, targeted therapies.
22 They hold the promise of being able to

1 increase the delivery of a drug to the site
2 of action which essentially increases the
3 concentration at the point where it's most
4 useful. That allows one to perhaps decrease
5 the systemic exposure of the product which
6 oftentimes, adverse events relating to
7 systemic exposure.
8 There are multifunctional particles
9 which could provide a drug which actually has
10 more than one activity, so it arrives at its
11 site of action and then it not only, for
12 example, binds to the site, (off mike) it
13 actually has another function which is
14 related to its therapeutic purpose.
15 There are a variety of novel dosage
16 forms that might be available, for example,
17 transdermal delivery of products, directly
18 through the skin. Carrier function which
19 again is to bring a drug product to a
20 particular site, and then folks are working
21 on how to develop novel forms of controlled
22 or sustained release products that could

1 provide a better therapeutic activity for
2 products that they are required to have a
3 long term steady state exposure. For (off
4 mike) products, if you can encapsulate them,
5 you might be able to protect them from
6 degradation until they reach their site of
7 activity, and then enhanced bioavailability
8 is a possibility as well for some of these
9 products.
10 Some of the challenges that we have
11 in terms of dealing with these, we have it as
12 well s the manufacturers do, is related to
13 product quality assessment. How do you
14 characterize what technologies are needed to
15 characterize nanotechnology products?
16 Initial to that is really what are the
17 relevant characteristics of a nanotech
18 product that one needs to be concerned with,
19 and then do you have the technologies
20 available to evaluate those? During
21 manufacturing questions come up of how are
22 you going to ensure the quality of those

1 products such that you have consistent lot to
2 lot quality of a product that's going to go
3 to market or into patients? And then what
4 are the best ways to manufacture these
5 products? These are all things that
6 certainly our office is concerned about
7 specifically in the product quality area.
8 And then from a safety assessment
9 side one needs to be concerned with
10 biodistribution of the products. Do they go
11 where they belong? Do they stay where they
12 are or do they get cleared? Some people have
13 concern that some of these particles may
14 reside in the body for a long term so
15 clearance is certainly a consideration. How
16 are they metabolized? What are their
17 metabolite products that are produced and are
18 those a concern from a toxicological
19 perspective?
20 Now, some of the products that we
21 have so far dealt with in our center are
22 sunscreens, where there are titanium oxide

1 and zinc oxide nanoparticles present which
2 are essentially to smaller size for -- the UV
3 absorbent material provides a better
4 presentation of the product, basically. It's
5 clear on the skin, doesn't give you that
6 white, unsightly stuff on your nose.
7 So other areas are in
8 reformulations of previously approved
9 products, so you have nanoemulsions of
10 products that can hopefully have better
11 transport through membranes and then
12 nanocrystal colloid dispersions.
13 In preparation for dealing with
14 nanotechnology products throughout the
15 agency, the commissioner's office convened a
16 nanotechnology task force a couple of years
17 ago. And the focus of this group was really
18 -- it was an intercenter task force that was
19 to look at ways that we could enable the
20 development of safe and effective products in
21 this technological area and evaluate what we
22 currently have in our regulatory repertoire

1 to find policy gaps that exist. And then
2 also, because science is really critical to
3 how we regulate products at the agency, to
4 identify what science and technology needs we
5 have. And then because it was an intercenter
6 group, they were also looking at how we can
7 strengthen our collaborations with other
8 agencies -- EPA, USDA, NCI, Nanotechnology
9 Laboratories, National Institute for Science
10 and Technology. So that, I think, is another
11 important area that we really develop our
12 abilities to leverage with other agencies.
13 So what were the bottom lines of
14 this task force? What came out of it?
15 Really they said that these types of
16 materials can be found or could be used in
17 almost all products regulated by the agency,
18 and that the challenges that they present are
19 really similar to other emerging
20 technologies, not necessarily the same as but
21 that we have other emerging technologies that
22 have challenges as well.

1 With nanotechnology, the fact that
2 the safety and efficacy potentially can vary
3 with the size of the material adds an
4 additional level of complexity in terms of
5 having to deal with a physical characteristic
6 such as size as opposed to just a chemical
7 characteristic.
8 They didn't find any evidence that
9 nano scale materials as a group have inherent
10 hazards above and beyond other materials of
11 similar nature and that we need to take steps
12 to better inform our reviewers as well as the
13 industry, about what's know, what is needed
14 in this area, and what we should be expecting
15 from manufacturers.
16 Some of the specific
17 recommendations that the taskforce came with
18 was that we should issue guidance
19 recommending that sponsors identify particle
20 size of small particle materials in FDA
21 regulated products. That's essentially an
22 identification requirement that if we don't

1 know the size of products in general, we
2 won't necessarily recognize nanotech unless
3 someone specifically identifies it in their
4 application and they may or may not do that
5 for various reasons.
6 From a safety and efficacy
7 perspective, they recommend that we issue a
8 call for safety and effectiveness data. This
9 again is for all FDA regulated products, but
10 for CDER it would be specifically for the
11 pharmaceuticals of course. And then a number
12 of issues -- they recommended that we issue
13 guidance in a variety of areas, the main one
14 of importance for CDER would be in
15 manufacturing areas since these others are
16 primarily focused on other centers.
17 With regard to labeling, that's a
18 very complex issue because as I said, some
19 people would like to say new and improved, we
20 have nanotechnology in our product. Other
21 people may not want it to be there because
22 there's fear of nanotechnology. So the

1 agency is pretty much required to come up
2 with, on a product by product basis, whether
3 or not a label should contain information
4 related to nanotechnology or whether it
5 shouldn't depending upon the relevance,
6 basically, scientific relevance of the fact
7 that the product is a nanotech product to its
8 safety and efficacy activity.
9 We did have a number of public
10 meetings. In association with the taskforce,
11 they held a public meeting on nanomaterials
12 in October. Part of the follow up to that
13 from a scientific perspective was that we
14 were working with the Alliance for
15 NanoHealth, which is a consortium of
16 universities in Texas to hold a meeting in
17 March to really look at the scientific needs,
18 scientific potential, for nanotechnology in
19 the health care related field. And then in
20 September, we are planning to have an
21 FDA-wide meeting which would be another open
22 meeting to get comment from the public. Each

1 center will be participating. We'll have
2 centers -- so there will be center specific
3 issues presented and our main focus, I
4 believe at this point, will be on
5 characterization, instrumentation, and
6 manufacturing concerns for this particular
7 meeting.
8 Now, some of the initiatives that
9 we have going on now or will shortly in the
10 future, from a policy perspective, as I
11 mentioned, we're developing a database of
12 drug products so that we can identify what
13 data gaps there might be in the applications
14 that we have for these products, for example,
15 particle size information, and then the
16 ability to track these files. So that if we
17 need to consolidate information or fish out
18 specific generalities based on the
19 information we have, that we'll be able to
20 pull those files easily out of our database
21 to look at, so we need to have a good system
22 for tracking.

1 And then as I mentioned, developing
2 a MAPP, internal procedures for how to
3 capture the data that's necessary as well as
4 how to be sure that we're looking at the
5 right information, relevant information from
6 a scientific perspective for this type of
7 product.
8 There are a number of research
9 activities going on in the office, or in the
10 center. We're collaborating with NIST, the
11 Nanotech Characterization Laboratories, NCI,
12 as well as CDRH. Some of the projects that
13 are ongoing are evaluating dermal penetration
14 of nanoparticles that are found in
15 sunscreens, characterizing nanoparticles in
16 these sunscreens, that's to get data to
17 respond to a Citizen Petition, concerned with
18 that, and then also looking at the potential
19 for toxicity of selected nanoparticles that
20 see if we can correlate in vitro findings of
21 size and composition with in vivo results.
22 In the future, we are considering

1 developing a definition for drug related
2 purposes if that's necessary. As I
3 mentioned, nanotechnology is not just
4 nanoparticles. It's a very broad field. So
5 that is a huge challenge that we've been
6 faced with and are still considering. One of
7 the questions that we'll ask you is what sort
8 of characteristics or issues we should
9 consider if we're going to develop a
10 definition for these products over this
11 product area.
12 We need to identify areas that will
13 require guidance for industry and then
14 finally, if we do identify those areas, to
15 develop guidance as needed.
16 Now, for today's presentations to
17 really give you a better feel for the
18 industry are as well as some of the concerns
19 with nanotechnology products, we've invited
20 three presenters: Dr. Tamarkin from
21 CytImmune Sciences who will talk about some
22 products that his company is developing, Dr.

1 Ruddy from Elan along those lines, and then
2 Dr. Furgeson from the University of Wisconsin
3 who will give some presentations as well.
4 As you're listening to those
5 presentations, I put the questions up here
6 that we have for the committee, to keep those
7 in mind as you're listening because really
8 this is where we need the scientific guidance
9 from you and that is really to give us advice
10 on whether guidance is needed for the
11 development of these products at this point
12 for drug applications and if the guidance is
13 needed, as I mentioned just a moment ago,
14 what areas of these guidances should they
15 focus on. And then, for regulatory purposes,
16 what elements or factors should we consider
17 if we're going to develop a definition for
18 nanotechnology.
19 And with that, I think we'll move
20 on to the first speaker who is Dr. Tamarkin
21 from CytImmune.
22 MR. MORRIS: And as Dr. Tamarkin

1 comes up, what is typical is we would take
2 any -- if there are any clarifying questions
3 that the Committee has for Keith or for any
4 of the speakers, but we'll hold the
5 discussion of the full questions until after
6 everyone has presented. So if anybody has
7 nay clarifying questions, this is the time.
8 Otherwise we'll do it after each speaker.
9 DR. TAMARKIN: Thank you. Thank
10 you, Keith for the introduction. What I'd
11 like to do this morning is I've been asked to
12 comment on the issues and challenges
13 associated with creating, developing, and
14 testing nanoparticle-based therapy and then
15 specifically I'd like to focus my comments on
16 our cancer therapy when we started with
17 nanoparticles, now it's become a term called
18 nanomedicines. And the best way I felt I
19 could share my views of this is to draw upon
20 our own experience from developing our own
21 cancer therapy which we call internally
22 CYT-6091 and we've given it the trade name

1 Aurimune. This work traces its roots back
2 now over 20 years to when Giulio Paciotti and
3 I first used colloidal gold nanoparticles to
4 bind cytokines as a way of creating an
5 immunogenic construct to develop antibodies
6 for enzyme immunoassays that we were
7 developing as research products.
8 In 1996, we basically turned our
9 full attention to developing our first
10 nanomedicine and that's what I'd like to
11 share with you this morning.
12 So in cancer what's basically the
13 issue and the opportunity? The problem for
14 most cancer therapeutics is that they
15 inherently are toxic and they are toxic to
16 rapidly dividing cells and those cells could
17 either be cancer cells or sometimes,
18 oftentimes, healthy rapidly growing cells as
19 well. So the best way that we thought that
20 you could -- and again, this is sort of the
21 promise that Keith alluded to, the promise of
22 nanomedicines is that you can, by limiting

1 the biodistribution, you can -- and then
2 targeting the tumor, we are not just looking
3 for an improved or extended pharmacokinetics
4 but we're basically looking for time to
5 tumor. So if we get the time to tumor to be
6 reduced, that would limit the exposure of
7 healthy tissues and organs to cytotoxics.
8 And the solution of nanomedicines
9 is basically to engineer these new
10 formulations to harness the therapeutic
11 potential of therapeutics, and basically in
12 our mind's eye, the ideal way is there are
13 plenty of cancer therapeutics that already
14 exist that we can try to capitalize and using
15 the nanomedicines or nanotechnology,
16 nanoparticle based technology, we should be
17 able to elevate the dose, limiting the
18 toxicity, and that should lead to an improved
19 response which in cancer then is tumor
20 regression with reduced side effects.
21 Now in my mind's eye, there are
22 three legs to the stool that we need to be

1 considering when we develop a nanomedicine
2 and they need to be thought about in the very
3 early planning stages. Basically the first
4 thing we need to do is to create a structure,
5 a construct, that will avoid uptake by the
6 reticulum endothelial system, otherwise known
7 as the RES, primarily liver and spleen.
8 Secondly, there needs to be a
9 strategy to target the tumors and that not
10 only has to be a passive strategy but an
11 active strategy and the corollary to that, if
12 it's well constructed and well designed, that
13 should lead us to less severity or frequency
14 of side effects compared to the unformulated
15 active pharmaceutical ingredient.
16 And thirdly, and just as equally
17 important in the designing and
18 conceptualization of a nanomedicine is that
19 the product needs to be manufactured to
20 defined specifications and those
21 specifications need to be robust and I mean
22 the design manufacturing needs to be robust

1 and what I mean by that in my mind's eye,
2 again, is it needs to be simple. It needs to
3 be reproducible and that again -- in other
4 words, we have to be able to characterize it
5 very well and reproducibly. And lastly, and
6 not of directly relevance to this committee,
7 but to anyone in the industry that's trying
8 to make a drug, it needs to be developed in a
9 manufacturing strategy that is in fact cost
10 effective.
11 So, let me run through this video.
12 Basically when we manufacture these
13 nanomedicines, we basically each particle has
14 to be constructed the same way so that when
15 it's injected systemically into the body, the
16 particles need to be small enough to safely
17 traverse through the body again avoiding
18 immune detection, big enough so they don't
19 exit the circulation through healthy, normal
20 blood vessels, but then go to the tumor and
21 exit the circulation through the inherent
22 leakiness of the neovasculature that supports

1 every growing tumor. And by allowing this to
2 happen you would sequester more drug at the
3 site of disease.
4 Let me just -- this is the core of
5 what the promise of nanomedicine is about.
6 So again, let me just run through this one
7 more time. Again, the manufacturing process
8 has to ensure that we have -- each
9 nanoparticle is uniformly coated so that when
10 it's then rehydrated or put into the body.
11 It's masked from detection from the immune
12 system. It's small enough, again, to safely
13 go through the body not being picked up. So
14 we work with the NNI definition of about 100
15 nanometers, 1 to 100 nanometers in size, the
16 fenestrations, the holes of the gaps in the
17 neovasculature about 200 nanometers in size,
18 so the particles of anywhere from 50 to 100
19 nanometers, again, should exit the
20 circulation bringing more drug to the site of
21 disease.
22 Let me share with you our blueprint

1 of our nanomedicine and this is simple,
2 again, the way I think I can share with you
3 the challenges that we thought of as we
4 designed this nanoparticle based
5 nanomedicine.
6 Firstly, the core of our
7 nanomedicine is a nanometer particle of gold
8 and on the surface of that gold particle we
9 bind two other molecules, polyethylene
10 glycol, to which a distal thiol group has
11 been added and TNF. And TNF serves two
12 purposes on this molecule: One is a
13 targeting molecule and one is a therapeutic
14 payload.
15 The polyethylene glycol serves to
16 hydrate the nanoparticle and you can see that
17 this blue circle around the nanoparticle
18 essentially is a water shield. And what
19 we've learned is that prevents the
20 nanoparticle from being (off mike) or
21 recognized by the immune system allowing it
22 to traffic freely through the body.

1 So why gold in the first place?
2 Gold has been used since the 1930s to treat
3 rheumatoid arthritis. So we knew that
4 colloidal gold had a long history of safety
5 in medicine, so that seemed to be a good idea
6 to start with.
7 Also, it's been used in in vitro
8 diagnostics for years. And we knew that the
9 surface of gold binds protein very avidly and
10 the chemistry of that was through dative
11 covalent bonds and dative covalent bonds are
12 unique bonds that form between thiol groups
13 and gold Au Zero (Au-0). Also interestingly,
14 gold nanoparticles can be seen in
15 electromicroscopy and we'll use that benefit
16 later on.
17 But so that we're all on the same
18 page, why did we choose Tumor Necrosis Factor
19 Alpha otherwise known as TNF? The promise of
20 nanomedicines as I see it is to take not only
21 molecules that are approved by the FDA and
22 improve their therapeutic index, but also to

1 take potentially molecules whose safety
2 profile has been unacceptable and to
3 repackage them onto a nano platform and
4 potentially capture the therapeutic potential
5 of many therapeutics that have not been
6 successful thus far. So this TNF is an
7 example of just such a molecule.
8 In 1975, it was discovered and it's
9 actually part of our own immune system and in
10 animals it was shown to have significant
11 anti-cancer activity. In 1985, Genentech
12 made the first recombinant form of TNF. And
13 then over the next decade more than 100
14 clinical trials tried to harness the
15 therapeutic potential of systemically
16 administering TNF.
17 The maximum dose given in a single
18 dose was 400 micrograms and at that dose, no
19 clinical benefit was seen. At doses of 1
20 milligram, patients with one dose experienced
21 severe hypertension which led to a
22 catastrophic series of organ failures,

1 otherwise known as complete organ failure.
2 In 1992, two French surgical
3 oncologists recognized that they could limit
4 the biodistribution of TNF in patients who
5 have tumors on their arms or legs, basically
6 surgically isolating the major blood supply
7 to an effected limb, putting that blood
8 vessel on a heart-lung machine, and then
9 regionally profusing a high dose of TNF into
10 that limb, basically in this case, now today
11 it's being done. It's approved by the EMEA
12 in Europe and Boering-Ingelheim is the
13 supplier of that TNF.
14 If one milligram currently is being
15 used, then followed 30 minutes later by a
16 chemotherapy that's either doxorubicin or
17 melphalan, with one milligram and then what
18 you basically have to do is then allow either
19 through washing out or through just general
20 metabolism where the patients in the early
21 days were hooked up to the heart-lung machine
22 for actually 12 hours of the TNF degraded

1 over time, then reconnect the blood supply.
2 At that dose, the local response rates, the
3 published local response rates, ranged from
4 60 to 85 percent.
5 So what we learned from that
6 clinical experience is that if we can limit
7 the biodistribution of this potent cancer
8 therapy and combine it with another
9 chemotherapy, you'd have a very dramatic
10 response rate, and that is the promise of
11 nanomedicines.
12 So let me share with you a summary
13 of our preclinical data, again, to highlight
14 some of the issues that I think are germane
15 to any nanomedicine. First of all, the
16 PEG-Thiol binding to the surface of gold did
17 prevent the nanoparticle from being picked up
18 by the RES and I'm going to show you some
19 information on that in a minute.
20 Secondly, 6091, we have shown,
21 delivers TNF to solid tumors through two
22 independent mechanisms -- passively, by

1 extravagating from the tumor neovasculature,
2 and actively, by binding to TNF receptors in
3 and around the solid tumor, and what we've
4 found is, that the binding of TNF is actually
5 independent of whether the cells, the cancer
6 cells themselves, have TNF receptors, because
7 it actually accumulates whether the cancer
8 cells in a xenograph model has receptors for
9 TNF or it doesn't. If it's a TNF sensitive
10 model, one -- just singly -- one injection of
11 6091 induces a potent anti-tumor response.
12 But in most circumstances, TNF receptors are
13 not present on cancer cells. So in a TNF
14 insensitive tumor, we've learned a very
15 interesting number of things. Number one, a
16 single treatment only induces a very
17 transient response and it's not a very strong
18 response at all, but interestingly, multiple
19 doses cause cytostasis where the tumor
20 remains about the same size and lastly, in
21 combination just like we saw in the isolated
22 limb profusion, the combination to a

1 chemotherapy, doxorubicin, for example, is
2 additive.
3 Here is a very early study that we
4 did and this shows you a couple of things.
5 This is the liver and spleen from a mouse on
6 our extreme right.
7 And that's a healthy, untreated
8 mouse. You see the color of the tissue is
9 still nice and pink, and the middle is our
10 first formulation. Basically, we just simply
11 coated TNF onto surface of gold, inject it
12 into tumor bearing mice and what looked for
13 clinical signs of toxicity, there were none.
14 The mice look fine. The tumors didn't seem
15 to respond very much but then we opened up
16 the animals and lo and behold, the livers and
17 spleen were black. Why are they black?
18 They're black with aggregated particles of
19 gold. In other words, this drug was safe
20 because it trafficked almost exclusively to
21 the liver and spleen. It (off mike) to the
22 site of disease.

1 What you see on the extreme left
2 now is our current formulation and the color
3 of the tissue is much like it is in the
4 untreated animal. This was the effort of
5 approximately 200 or more different
6 formulations to get to this result. In other
7 words, trying to avoid immune detection is a
8 challenge and it's not necessarily easily
9 done. It took us lots and lots of trial and
10 error to find that.
11 Secondly, the question is, what
12 happens to the two part -- does the TNF and
13 the gold traffic together? As I shared with
14 you, TNF is a very toxic molecule, so we're
15 very concerned about whether the nanoparticle
16 construct actually stays together once it's
17 injected in vivo. In vitro studies only
18 share some insight into what's going on but
19 really the critical element is whether or not
20 these two elements stay together in vivo.
21 And what you're seeing here is a study that
22 was done in collaboration with the

1 Nanotechnology Characterization Laboratory,
2 part of the National Cancer Institute, in
3 which they use a rat model, a cannulated rat
4 model, and injected 6091 into the rat and
5 then samples were taken over time in the
6 upper panel. In the bottom panel is the
7 analysis of these data and let me direct your
8 attention to the lower line which is the
9 terminal half life.
10 The terminal half life of TNF just
11 like many other protein drugs, is very short,
12 to about 26 minutes. In contrast, the half
13 life of TNF when it's bound to the gold
14 nanoparticle is almost nine times -- eight
15 times longer. Interestingly, the half life
16 of the gold and the TNF are similar in amount
17 of time. So what that suggests is that the
18 two components are trafficking together,
19 they're staying together in vivo, and this is
20 critical if we're going to think about safety
21 and biodistribution.
22 The next question one would have to

1 ask and that was proposed again in Keith in
2 his -- where does this all go and how long
3 does it stay there? Okay, what happens to
4 it? And this is a study done by Dr. John
5 Bischof, another collaborator at the
6 University of Minnesota and what he did is
7 injected 6091 and looked at the concentration
8 of gold by ICPS atomic emissions spectroscopy
9 and in this case what he did is to follow the
10 gold in a number of different tissues over a
11 period of time. And again, looking at blood
12 in the red and then various tissues in the
13 lung, liver, spleen, and a summary of these
14 data are here on the next slide, and as you
15 can see, over the course of 60 days, most of
16 the gold particles actually gets to the liver
17 and then it starts to decrease. In fact, if
18 we look at the total recovery, if we look at
19 the column on our extreme left, we see that
20 at the end of a 120 days, we can only recover
21 from these major -- these are the major
22 organs which we thought would take up the

1 gold nanoparticles, again, the liver and
2 spleen are the obvious candidates, kidney,
3 because if the size of the nanoparticle is
4 under 10 nanometers or 10 nanometers or
5 under, then it has the possibility of being
6 filtered out by the kidney.
7 Particles that exceed 10 nanometers
8 will be excluded from kidney filtration.
9 This is something that's also important as we
10 go forward in designing the nanoparticle.
11 So as you can see in the extreme
12 left hand column that after 120 days,
13 actually only 35 percent of all the gold that
14 was administered was actually recovered. We
15 believe that 63 percent was excreted. We
16 don't have evidence for that, but these are
17 the major organs that we would expect to see
18 gold, and as you can see, the kidney took up
19 very little, the spleen, somewhat more, but
20 the bulk goes into the liver.
21 Now last (off mike) question is
22 targeting what we talked about. Does a

1 nanoparticle actually get to the site of
2 tumor and what you're looking at here is an
3 electron micrograph of a split from an animal
4 that had a xeno-transplant, in other words,
5 it had a tumor injected on its belly, and we
6 looked at the spleen, the tumor, and the
7 liver, and what you're seeing is just one
8 micrograph. And the center, you can see it
9 where it says tumor, you can see a number of
10 black dots.
11 We know that gold nanoparticles are
12 electron dense. We believe that those black
13 dots that were primarily present in the tumor
14 were in fact gold nanoparticles, but again,
15 proving this is somewhat more challenging.
16 And again, in collaboration with the
17 Nanotechnology Characterization Lab, we did
18 energy dispersive X-ray analysis of a single
19 micrograph, what you're looking at is a
20 single micrograph taken from a mouse that had
21 a tumor. Now, you have to do this -- this is
22 a little complex, so let me walk you through

1 this. This is a TEM of that, and you can
2 see, these are the black particles that were
3 focused on. You do it under scanning
4 electron microscopy and this is what we have
5 to look at. What the X-ray beam is actually
6 shining on is either this section of the SEM
7 compared to the background here and then
8 we're looking at the spectral analysis and
9 asking the question, does the spectrum, which
10 is a fingerprint of a particular element,
11 actually going to be gold. And what you see
12 here in this spectral analysis is that this
13 is in fact a gold nanoparticle, but this here
14 is not and so what we have here is
15 qualitative evidence now that those black
16 dots, by EDX are indeed nanoparticles of
17 gold.
18 Let me walk you through a little
19 bit, again, more of the pre-clinical data.
20 This is in a TNF sensitive model. A single
21 injection -- this is the promise of
22 nanomedicines. A single injection of TNF

1 alone, 15 micrograms, causes complete -- as
2 you can see in the open circles in the bottom
3 there -- complete suppression of the tumor
4 growth in this xeno-transplant. These are
5 MC-38, these are colon carcinoma cells that
6 have TNF receptors on them.
7 The problem here, with one
8 injection, 40 percent of the animals died. A
9 typical chemotherapy protocol requires at
10 least -- well, usually four to six
11 treatments, so clearly this is unsafe.
12 If you lower the dose only by half,
13 you have a much better survival profile, only
14 10 percent of the animals die, but again, as
15 represented by the triangles you see that you
16 get much less efficacy.
17 In contrast, in 6091 -- again,
18 represented here as the trade name Aurimune
19 -- 15 micrograms of Aurimune was 100 percent
20 safe, none of the animals died, and it had
21 exactly the same efficacy as native TNF. But
22 more interestingly, because of the targeting,

1 one half of the dose -- of course it's safe,
2 but it's equally effective.
3 So this again is the promise of
4 nanomedicines. Theoretically and
5 practically, we may be able to -- for very
6 toxic agents, we may be able to actually use
7 less of a dose and get a therapeutic
8 response.
9 Now let's turn our attention to a
10 TNF insensitive model. This is a model --
11 B16/F10 melanoma cells do not respond to TNF
12 in vitro. They simply do not have TNF
13 receptors on them. If you put these tumors
14 into mice, what they're going to do is
15 they're going to grow and then we're going to
16 treat with a chemotherapy, doxorubicin, but a
17 suboptimal dose, a dose that we knew wouldn't
18 be terribly efficacious. Then we're going to
19 give 6091 multiple treatments and then we're
20 going to give a combination. The combination
21 is designed much like the isolated limb
22 protocol is to give 6091 first followed two

1 hours later by the doxorubicin and then we're
2 going to look at the response over time.
3 You can see in this figure here, is
4 that what you see is that doxorubicin at 50
5 micrograms doesn't slow down tumor growth and
6 in fact the animals had to be terminated
7 because of the size of the tumor. But
8 multiple injections of 6091 by itself
9 surprising to us actually caused cytostasis.
10 The tumor stopped growing for the
11 most part. And when we added doxorubicin, we
12 got somewhat of an additive effect.
13 The question we asked ourselves,
14 why is this happening and in fact, similar to
15 the isolated limb perfusion, when we looked
16 -- this is the vascular bed of a B16/F10, the
17 slide on your right is the untreated animal
18 and you can see these holes -- this is a
19 cross section of a blood vessel, basically,
20 and surrounding it are the endothelial cells,
21 that's what you're seeing, and the
22 immunohistochemistry, the staining, the

1 endothelial cell supporting that blood
2 vessel.
3 In contrast, our slide on the left
4 is a completely disrupted vascular bed. In
5 fact, what has been shown and published with
6 the isolated limb profusion, pretreatment
7 with TNF causes vascular disruption of the
8 tumor allowing the subsequent chemotherapy to
9 penetrate more deeply to get to the site of
10 disease and this is exactly the same response
11 that we have now giving it a dose of 6091,
12 giving a sense of TMF systemically, we're
13 also getting vascular disruption.
14 Now, one can argue, and this is,
15 again, the challenge in nanomedicine,
16 particularly as we rely on the vascular bed
17 as a way, a targeting site, to deliver these
18 nanosized materials. The question is, does
19 the xenographs, in these murine tumor models,
20 truly represent a vascular bed that's going
21 to happen in naturally occurring cancers?
22 And that is a topic of discussion.

1 But nonetheless, let's take a look
2 at -- we did have a chance back in '01 to
3 treat in a compassionate way -- to treat two
4 dogs, and we've treated a number of dogs
5 since then, but we treated two dogs -- these
6 are the first two dogs we treated with our
7 drug, with 6091, and we gave a dose that
8 exceeded the MTD for TNF alone in these tumor
9 burdened animals.
10 Elsa, the dog on our left, had a
11 soft tissue sarcoma about the size of a
12 cantaloupe that was impinging on major renal
13 artery and she was given about two weeks to
14 live because it was crushing that renal
15 artery. Callie, the dog on our right, had
16 transitional cell carcinoma of the bladder
17 and the tumor had migrated into her urethra
18 so she couldn't urinate, so clearly this dog
19 was in trouble as well.
20 The owner of both of these dogs is
21 a veterinarian and a Ph.D. and she asked us
22 to do this on a compassion use basis. We

1 obviously were quite reluctant to do this
2 initially, but she said that the dogs were
3 probably going to expire within two weeks and
4 maybe we could learn something, and we
5 learned an incredible amount.
6 What we learned is -- we gave four
7 times a dose that had ever been given to a
8 dog before. And interestingly, the tumors
9 were still present. We could see that on
10 sonography but Elsa actually lived for six
11 months. Eventually the tumor crushed her
12 renal artery and she did expire, whereas
13 Callie was able to urinate freely 24 hours
14 after treatment, was able to urinate freely
15 for the rest of her life, lived for a year,
16 and ultimately died of cardiovascular
17 disease.
18 What did we learn from the very
19 first injection? From the very first
20 injection you should know the biologic
21 response of TNF -- one of the biologic
22 responses of TNF is to cause you to have

1 fever. It's a pyrogen. It causes us to have
2 fever. And sure enough, Elsa, our first
3 treatment, we monitor the TNF levels by
4 taking blood samples periodically, but we
5 also monitored basal body temperature, and
6 you can see, she developed a very robust
7 fever for a dog. Basal body temperature in a
8 dog in Fahrenheit is about 101 degrees
9 Fahrenheit. The dog got to -- the maximum
10 fever was about 104 degrees Fahrenheit.
11 And this resolved itself over about
12 six to eight hours. But fever is a clinical
13 response that we can manage, and in a dog,
14 subsequent doses, we pretreated with
15 Ketoprofen so we basically eliminated the
16 fever response. But the bigger problem for
17 us was hypotension because I already shared
18 with you, hypotension leads to renal failure,
19 organ failure, complete organ failure, and
20 this is not good.
21 So one of the things we did is to
22 -- we had a blood pressure cuff at the same

1 time that we were measuring basal body
2 temperature, and as you can see, blood
3 pressure never dipped below 80 mm of mercury,
4 so basically she did not experience
5 hypotension, so we were able to separate the
6 clinically manageable side effect of fever
7 from the clinically -- the harbinger of bad
8 things (off mike) hypotension. And again,
9 this is again the promise of nanomedicine.
10 Another question we had -- this is
11 a completely different dog with bladder
12 cancer that we treated, and as you can see on
13 the sonogram on our right that this ring of
14 tissue where the black arrow is pointing,
15 what you're looking at is the lumen of the
16 kidney, is the black center there, and the
17 ring of tissue is a combination of
18 inflammatory tissue and cancerous tissue.
19 And this dog was incontinent and after six
20 treatments, over a period of about five
21 months, you can see that the bladder resolved
22 itself and this dog also lived for about a

1 year not dying of bladder cancer.
2 So if you're going -- and I might
3 mention at this point, Boehringer Ingelheim
4 Vetmedica is actually taking this drug and is
5 going to be manufacturing it for use in
6 veterinary oncology to treat dogs. And
7 CytImmune is going forward using this in
8 clinical oncology.
9 But we all say we need to go from
10 the bench to the bedside. To go from the
11 bench to the bedside, you've got to climb
12 this mountain that's called manufacturing and
13 manufacturing in our world of nanomedicines,
14 is not simple because it is a complex
15 product. And in our case, we not only have
16 to use standard techniques to evaluate the
17 purity and quality of our drug, but we have
18 to use special techniques and each nano
19 construct is going to require somewhat
20 different techniques to analyze what they're
21 doing.
22 In our case, we need to understand

1 the amount of gold because the ratio of gold
2 to PEG- Thiol and TNF is absolutely critical
3 to ensure that we have a properly
4 manufactured product. We need to evaluate
5 the active pharmaceutical ingredient, in this
6 case TNF and how are we going to do that.
7 Thirdly, we need to make sure that
8 we understand our immune avoiding molecule,
9 in this case, we use polyethylene glycol, and
10 what's happening with that, does it stay
11 associated with the nanoparticle?
12 And lastly, we also have to
13 understand the surface charge of our result
14 and product because basically this is
15 important on a toxicity issue. For those of
16 you not familiar, basically, surface charges
17 of negative charge tend to be toxic, whereas
18 neutral or negatively charged particles are
19 safer if not safe.
20 So although the ideal way to
21 characterize a nanoparticle of gold is
22 electron microscopy, that doesn't lend itself

1 to manufacturing very easily so we had to
2 find ways to correlate an accepted procedure
3 with those that would be applicable to the
4 manufacturing process. Believe it or not,
5 the simplest manufacturing process to
6 evaluate gold is simple UV absorption,
7 spectroscopy. Also, to evaluate size, and
8 size does matter as I shared with you. Size
9 does matter. We use differential
10 sedimentation by centrifugation otherwise
11 known as discentrifugation as a way of
12 separating and qualifying the size of the
13 nanoparticles and the distribution of the
14 nanoparticles. How wide is your distribution
15 of particles that you make? Is it very
16 narrow? Is it very large? And what is the
17 tolerance there? You're going to have to
18 define those.
19 And lastly, you'll have to find
20 quantitatively how much gold we started with
21 and how much gold we ended with in the
22 process because we have to know exactly what

1 we do in the process.

2 The TNF analysis is also

3 interesting. Now, because our nanoparticle

4 -- if we go back, if you remember, the

5 initial formulation, that initial construct

6 of that blueprint that I showed you way at

7 the beginning of my presentation, the

8 nanoparticles of gold give us a unique

9 opportunity which again may or may not be

10 applicable to all nano constructs.

11 We can actually, because the gold

12 has a significant weight, we can centrifuge

13 the result when we re-suspend the final drug

14 product, we can centrifuge the drug and the

15 TNF should actually stay -- if it's going to

16 be bound to the gold, it should be

17 precipitatable and we can measure what's in

18 the supernatant, and we call that what is

19 free or unbound.

20 So we can measure, because the TNF

21 is on the surface of the gold, we (off mike)

22 we can quantitatively measure the TNF on the

1 surface of this nanoparticle.

2 I didn't share with you that we

3 also know from in vitro analysis, that every

4 molecule of TNF retains its biological

5 activity and basically that we can also use

6 that to define our final drug product and

7 define the potency.

8 Also what I didn't share with you

9 is that not only can we construct the

10 nanoparticle using this data covalent bond,

11 but we can actually strip off each of the

12 components, the PEG-Thiol and the TNF using a

13 strong reducing agent, dithiothreitol.

14 Dithiothreitol doesn't exist in nature, so it

15 doesn't necessarily, as I showed you in the

16 earlier studies, doesn't fall apart in vivo.

17 But we can use that DTT,

18 dithiothreitol, to strip off the TNF and then

19 analyze it for purity by high performance

20 liquid chromatography. Finally as I shared

21 with you, we can evaluate and define the

22 potency of our drug using a bioassay to

1 measure the final drug product in its intact
2 form. We do not have to break it apart to
3 evaluate how much active pharmaceutical
4 ingredient is in the final drug product.
5 This may be different -- I hate to use the
6 word unique -- but it may be different than
7 other nano constructs where you package that
8 API inside the nanoparticle and that makes
9 analysis like this somewhat -- much more
10 difficult.
11 Lastly, we by -- again, we can
12 determine how much of our immune avoiding
13 molecule, in this case, PEG, polyethylene
14 glycol, is actually bound to the nano
15 construct versus how much is unbound, and
16 again we use the ability of the
17 centrifugation to measure total PEG in the
18 construct and then when we precipitate the
19 gold particles, we measure that and then
20 strip it off with DTT, we know exactly what's
21 bound, so we know the relative ratios. And
22 lastly, we can measure surface charge by zeta

1 potential.

2 So let me just share with you how

3 do we make gold. And again, this is, again,

4 what I like about what we do is we've sort of

5 taken the history of science and we've

6 brought it back to a new and -- new

7 therapeutic.

8 This chemical strategy of making

9 gold nanoparticles dates back -- actually,

10 the first publication of this is by Michael

11 Faraday in 1857, and this chemistry dates

12 from that time and the equipment almost dates

13 from that time. As you can see, what you're

14 seeing there is a reflux apparatus and the

15 resultant particles are actually

16 nanoparticles of gold as you'd see them under

17 their monodisbursed nanoparticles with gold

18 nanoparticles.

19 What I'm showing you now is

20 actually how to make a gold nanoparticle.

21 Basically what we need to do is -- basically

22 what we're doing is boiling water, adding

1 gold chloride, and then you're going to add
2 sodium citrate. Three reactions will take
3 place very quickly. The solution will turn
4 clear as the particles become -- nucleates.
5 Then it will turn black as they aggregate,
6 and then turn red as the excess gold layers
7 on. In real time, that is actually 27
8 nanometer particles of gold.
9   And you can see the distribution of
10 that is very reproducible. Eighty-five
11 percent of the particles, basically, are in
12 size between 15 and 35 nanometers.
13   We now make this at a larger scale,
14 150 liters of gold, and you can see this is
15 the procedure here and now how do we make the
16 actual nano construct. How do we ensure that
17 every nanoparticle of gold is uniformly
18 coated? In this video, a bench scale, we
19 take two reservoirs and are drawn by a single
20 peristaltic pump into a T-connector. That
21 T-connector is actually where the gold
22 nanoparticles meet the solution of TNF and

1 PEG- Thiol and that's the formation of your
2 colloidal gold based product, 6091. That
3 simple.
4 And again, this is on a larger
5 scale now. You can see the Y-connector in
6 the middle and that's where the drug is
7 actually made. The bind TNF and PEG-Thiol
8 bind virtually instantaneously to the gold
9 nanoparticles.
10 The lyophilized product is then
11 ready for clinical study and in fact this is
12 a study that we did at the National Cancer
13 Institute, and I'll go through this rather
14 quickly because time is running out, and
15 basically these are patients with advanced --
16 we did a phase I clinical trial in advanced
17 stage cancer (off mike) patients. Each
18 patient received only two doses and there
19 were three patients per group. And we
20 primarily wanted to establish an MTD, and
21 then we also want to see if the tumors
22 actually traffic to the site of -- that the

1 gold particles traffic to the site of the
2 tumor. Sorry.
3 The trial is now complete and we've
4 seen that it is well tolerated. Our target
5 dose was 1mg, we've now exceeded 1mg and
6 we've actually given patients 1.2mg of TNF
7 with no clinical -- a significant dose (off
8 mike) hypotension, and so no serious adverse
9 events that were unexpected or related to
10 treatment. And we did see gold nanoparticles
11 in the site of tumors.
12 This is the number of patients.
13 You can see the different histologies and we
14 (off mike) as per the protocol from a very
15 low dose, and the red 200 is the previous
16 maximum tolerated dose of TNF alone and we
17 exceeded that in green, up to 600 micrograms
18 per meter squared, which is about 1.2mg per
19 dose.
20 This is the first patient, first
21 response in patient 01 the lowest dose, this
22 patient developed a similar, just like the

1 dog, a very robust fever that was completely
2 abrogated in the second treatment by
3 pretreatment with acetaminophen and
4 endamephosine. Everybody was then pretreated
5 like that, and again, looking at hypotension
6 in the whole of patients, none of the
7 patients developed clinically significant
8 hypotension again, systolic blood pressure
9 never dipped below 80mm of mercury.
10 The pharmacokinetics, again, very
11 interesting. (off mike) just to show you
12 that the half life and that the analysis here
13 compared to historical data. Interestingly
14 enough, the half life of TNF historically,
15 native TNF, is about 27 minutes which is
16 similar to what we saw in the rat which was
17 26 minutes and if you look at our drug, the
18 6091, the half life on average was about 191
19 minutes which was similar to that which we
20 saw in the rat.
21 Again, the most significant thing,
22 again, the promise of nanomedicines, is that

1 the exposure -- the exposure, which is
2 represented by area under the curve at
3 600mg/m2 is some 30 times higher -- 30 times
4 higher -- that that which was achieved with
5 TNF alone with no significant toxicity.
6 And again, this is a patient with
7 inoperable breast cancer. As you can see on
8 the tumor, the nanoparticles traffic to the
9 site of disease but not to the healthy breast
10 tissue.
11 Again, we're making -- not only are
12 we going to make this nano construct, but
13 we're also making a combination nano
14 construct of an analog of taxol and TNF bound
15 to the same nanoparticle of PEG-olated gold
16 and we believe that this is, again, an
17 opportunity.
18 So let me lastly thank all the
19 people, these are the folks in our
20 laboratory, and Dr. Steven Libutti from the
21 NCI, and our medical staff, Dr. Gannon, Dr.
22 Price, and our statistician Ena Bromley.

1 So let me leave in closing then,
2 what is the ideal nanomedicine? The ideal
3 nanomedicine conceptually needs to avoid
4 uptake by the reticular endothelial system,
5 you need to come up with an idea how to do
6 that. It should target the tumor in two
7 independent ways -- passively and actively --
8 by binding to some receptors. And again,
9 equally as important, it has to be
10 manufactured to defined specifications.
11 Thank you for your attention.
12 MR. MORRIS: Thanks, Dr. Tamarkin.
13 That's very interesting. Does anybody have
14 clarifying questions? I actually have one,
15 but are there any questions before we go to
16 break?
17 MS. ROBINSON: Yes, this is Anne
18 Robinson speaking. I was just curious, in
19 the clinical trials that you showed, did you
20 look at (off mike) targeting of the colloidal
21 gold? Did it go anywhere else? Liver?
22 Spleen?

1 DR. TAMARKIN: We looked at -- yes,
2 we did look -- we didn't look at liver -- I
3 mean, these are patients, so you're doing
4 core biopsies. A significant number of these
5 patients were very ill, so a lot of the core
6 biopsies are actually done of the liver. So
7 we did a lot of liver biopsies and in fact
8 you do find -- now, just you need to know,
9 that the samples were taken 24 hours after
10 administration, obviously, again, for
11 logistical purposes. And so we do see the
12 nanoparticles in the liver.
13 In most of the patients there were
14 more nanoparticles quantitatively, just
15 counting dots, quantitatively in the tumor,
16 even in the liver, than there was in adjacent
17 healthy liver tissue.
18 MS. TOPP: Hi, this is Elizabeth
19 Topp speaking. I have two questions for the
20 speaker. The first one is a kind of general
21 one because I want to make sure I understand
22 your data. So you show a particle size

1 distribution. This is the particle size of
2 the gold core or the hydrated particles?
3 DR. TAMARKIN: This is the particle
4 size of the gold core.
5 MS. TOPP: Okay, do you have an
6 idea of the effective particle size of the
7 hydrated particles that are actually
8 administered?
9 DR. TAMARKIN: That's a very good
10 question. Thank you for asking. I think you
11 raise a very critical point because what is
12 the apparent size versus the actual size, and
13 the apparent size, using DSL as a way of
14 doing that, is 70 nanometers.
15 So, I think what we're saying here
16 is that you need to pay attention to the
17 fenestration sizes that you're thinking
18 about. If they're between 200 and 400, a
19 particle that's 100 or more that may double
20 in size by its height by, let's say, it's
21 immune shielding, that could be -- it may not
22 end up trafficking to the site of tumor.

1 MS. TOPP: Or may traffic
2 differently.
3 DR. TAMARKIN: It may traffic
4 differently.
5 MS. TOPP: I have one more
6 question.
7 DR. TAMARKIN: Sure, please.
8 MS. TOPP: I'm quite interested in
9 your immobilized TNF on these particles which
10 is essentially what you're doing, you're
11 binding these to the gold nanoparticles --
12 DR. TAMARKIN: That is correct.
13 MS. TOPP: -- and you mentioned
14 that you assay for stability of the TNF by
15 HPLC?
16 DR. TAMARKIN: Well, we strip it
17 off.
18 MS. TOPP: Right. Do you have any
19 more high resolution types of assays? So do
20 you do any, for example, triptych mapping?
21 So HPLC may not be able to tell you about
22 local sites of changes, so oxidation at

1 particular groups, for example, or specific
2 amino acid changes, so have you kind of fine
3 tuned the assays to have that higher focus or
4 not so much so?
5 DR. TAMARKIN: No. First of all,
6 you need to know that the API is actually
7 unmodified from the material that is approved
8 in Europe for this isolated lymph profusion.
9 It's prepared by Boehringer Ingelheim. It
10 binds to the surface of the gold because we
11 were taking advantage of this available
12 Sistine binding. And it maintains its shape
13 and it maintains its bioactivity on a
14 quantitative basis. I mean, it's a good
15 question, but again, there is -- from the
16 data that we have, there's nothing to believe
17 that anything has radically changed in either
18 the shape or the metabolism of the drug.
19 MS. TOPP: Thank you.
20 MR. MORRIS: Are there any other
21 questions? If not, we'll take a short 15
22 minute break and again, panel members,

1 please, there should be no discussion of the
2 issue at hand during the break amongst
3 yourselves or with any member of the audience
4 and we'll resume at 10:25. Thank you.
5 (Recess)
6 MR. MORRIS: If we could resume our
7 seats and get going with the next session of
8 the meeting.
9 So our next speaker is Stephen
10 Ruddy from Elan NanoSystems. He's the senior
11 director of Pharmaceutical Development and we
12 have his talk. Here we go. He'll be
13 speaking on Leveraging Rapid Dissolution to
14 Improve Performance of Poorly Water- Soluble
15 Drugs.
16 MR. RUDDY: Good morning, everyone.
17 It's a pleasure to participate in this event
18 this morning. I think the technology
19 involving nanomedicines is very significant
20 in today's world.
21 The science underpinning a lot of
22 technologies is very fascinating and a lot of

1 the benefits, truly compelling.
2 I was very pleased that Dr. Webber,
3 in one of his earlier slides, showed the
4 spectrum of nanotechnologies currently in
5 research and development because it helps me
6 to start off with the basic point, that we
7 have a very broad spectrum of technologies in
8 nanomedicine ranging on one end of the
9 spectrum from technologies that involve
10 highly complex structural particles. In many
11 cases these particles are truly insoluble,
12 and in many cases these particles have
13 multi-functionality such as passive or active
14 drug targeting and the ability to actually
15 penetrate into the cell body itself.
16 On the other end of the spectrum,
17 we have technologies that are comparatively
18 simplistic in their design and functionality
19 and these are the particle systems I'd like
20 to describe today.
21 We talk about these particles as
22 being poorly water-soluble, but in reality

1 they actually are soluble particles if we
2 consider a larger volume of aqueous medium.
3 From a formulator's perspective, they're
4 considered poorly water soluble.
5 So I thought I'd begin with a
6 definition of the types of systems that I
7 wish to address this morning and I'll refer
8 to these as engineered drug particles,
9 engineered particles, or just nanoparticles,
10 for brevity. But in essence, these are
11 nano-scale particles of API characterized by
12 extremely high surface are to mass ratios and
13 these systems have extremely high surface
14 re-energy and to prevent them from
15 agglomerating, they must be stabilized by
16 surface modifiers.
17 In addition, these materials are
18 not naturally occurring, they're produced by
19 two fundamentally basic processes, one,
20 through molecular deposition or complexation,
21 which we call a "bottom up" approach to (off
22 mike) the particles. The other approach,

1 through attrition of larger non- nano-scale
2 material, sometimes micronized materials,
3 sometimes much larger than that, which we
4 refer to as a "top down" approach and in
5 general, the size range for these
6 applications is in the order of slightly less
7 than 100 nanometers up to about a micron in
8 mean particle size for many pharmaceutical
9 applications.
10 Now for many of these technologies,
11 the manufacturing process itself has the drug
12 particle suspended in an aqueous environment.
13 In the case where that is not true, we may
14 have a final pharmaceutical product that is a
15 aqueous nano- suspension and if that isn't
16 the case, we certainly have ultimately
17 contact with aqueous fluids in the body when
18 the nanoparticles are ultimately delivered to
19 humans.
20 And this schematic basically shows
21 what these particulate systems look like. We
22 have a drug particle and they're not really

1 cubic, but for the purpose of illustration it
2 makes it easier, and these particles, again,
3 have a very high surface re-energy owing to
4 their large surface area. As a consequence
5 of Van der Waals attractive forces that seek
6 to reduce the free energy of the system and
7 pull these articles together, we must
8 stabilize them by opposing forces.
9 Typically this is done through a primary
10 stabilizer which sometimes is polymeric, but
11 acts to sterically stabilize the particles
12 against agglomeration, and optionally, we can
13 employ a charged stabilizer, frequently a
14 surfactant, that imparts a net charge to the
15 particle and through electro-static forces,
16 helps to stabilize the particles against
17 agglomeration.
18 The stabilizers themselves are not
19 firmly bound but are absorbed onto the
20 surface of the particles.
21 Now in a presentation like this, I
22 hate to jump into math. I promise this is

1 the only slide like this and I'll try to make
2 it as exciting as possible, but it is a very
3 important slide nonetheless.
4 The rationale for engineered
5 nanoparticles of this type in drug delivery
6 is based upon the fact that drugs that have
7 very poor solubility, also tend to have
8 characteristically slow rates of dissolution
9 and the only way that we can readily
10 counteract that is to dramatically change the
11 exposed surface area of the drug particles.
12 Now if you look at the schematic to
13 the right, we see the surface of an
14 undissolved particle suspended in a bulk
15 aqueous environment and we see that the
16 concentration of the dissolved drug, C-S,is
17 highest at the interface of the solution and
18 the particle and that that concentration
19 decreases at some distance from the particle
20 surface which we call the aqueous diffusion
21 layer. It's also represented by the term "H"
22 in equation 1, the Noyes-Whitney equation.

1 And the difference between the saturation
2 solubility of the drug at the surface and the
3 concentration in bulk is the thermodemic
4 driving force for the solution process which
5 we also express as C-S.
6 If we include the diffusion
7 coefficient for dissolved solute, the exposed
8 surface area, S, of the drug and V, the
9 volume available for dissolution, we have an
10 expression for the dissolution rate dC/dt,
11 which again, is familiar to many as the
12 Noyes-Whitney equation.
13 And we can simplify this in
14 equation 2 by making the basic assumption
15 that we have a synch, that is that the
16 concentration at saturation is much, much
17 higher than the concentration in the
18 surrounding bulk and so we collapse to
19 equation 2. We can further simplify this
20 term by combining the diffusion coefficient,
21 the volume term the aqueous diffusion term,
22 and the concentration term, into an effective