the beginning, and then end-of-life care.

I work with Daniel Brinkley, who brings end-of-life care, particularly to veterans in the VA hospitals, which I think is so important in our country, to really change the practice of medicine. He called me before I came today and he is going to be here December 5th and 6th and would like to have dialogue with all of you.

The other point I have to make is that surgery is one of the great places to study CAM treatments, and this book, if you don't know it, Dr. Oz's book from Columbia, he has been doing before-and-after treatment of his surgical heart transplant patients and bypass patients. It is a pretty exciting book, called "Healing from the Heart."

That is a very limited sphere. So, it makes research really possible. Finally, I just want to say that one of the phrases I liked that you used so much, Jim, is that outside the measures of current science, like you were saying, if we are going to look at the body, you can have all your body parts and not be alive. This idea of electrical medicine is so important to us.

My twin brother is a neurosurgeon who is very

suspicious of complementary therapy. He hated the movie "Patch Adams," because it made him feel bad. So I would like to end on that, and say that I really agree that some kind of conflict resolution where we can present these things, perhaps inviting Victor Frankel to the next conference on medical education.

Thank you.

DR. GORDON: Thank you.

Any questions or comments?

[No response.]

DR. GORDON: Thank you very much.

I am going to ask if the four people who also signed up -- we got our signals mixed a little bit here -- if the four people who also signed up for public testimony, can you all do that tomorrow? Would that be all right?

[Response.]

DR. GORDON: You can't do it tomorrow? None of you can? See, I don't want to run us too late. If you can possibly do it tomorrow. It would be wonderful if you could do it tomorrow because we should have really limited it.

So, Tony Martinez, you can't do it tomorrow? All right. The two people who can't do it tomorrow, if you would come up, and the others have my gratitude, our gratitude, and blessings.

So we have Carl Sandler and Tony Martinez.

Tony, would you like to begin.

MR. MARTINEZ: Thank you very much.

It is good to be here again, to attend another Commission meeting. I have had the opportunity in previous meetings to provide some observations and some insights that I hope will make this whole process fruitful.

This afternoon, I am really excited that there is going to be this discussion about looking into research and that you have invited a group of really very talented, brilliant, experienced people, but with that in mind, I want to go back to observe that there are two key policy themes that keep hitting home, and I hope you will bear this in mind.

That is, first, what all the professionals want is licensure and coverage, and I hope and submit that your questions to the witnesses should address that.

The second issue being, people want access and they want insurance coverage. Now, I find that it is great that the FDA has come to be here shortly, but I submit, and I am speaking as an attorney, that the FDA, as much as it is a scientific agency, is really more an enforcement agency. I don't know if you are going to get all the answers that you are looking for there.

I do want to bring up a couple of points to keep in mind when you engage them in testimony. First of all, their goal is to keep bright-line distinctions in the law between foods, drugs, medical devices, those things. They have a real tough time with the products of complementary and alternative medicine, which, really, many of them are dietary supplements, herbs and things.

The second issue that should be brought to your attention is that the division that has responsibility for most of these products, the Center for Food Safety and Applied Nutrition, gets the least amount of funds when it comes to the budget for the FDA. I think it is important to put on the record this lack of appropriate funding for this section of the FDA because they need the funds in order to do the job so they can enforce the laws

that are already on the books and be able to do a good job.

I wanted you to be aware of that. Lastly, I think it also brings in a good question to ask the FDA as a matter of policy, that when it comes to alternative medicine or anything with experimental drugs, the policy of the FDA is to make it possible to get access to experimental therapies, but the ultimate decision-maker is the FDA and the doctor, not the patient and the doctor.

As in the case of the little boy, Thomas DeVaro, who is suffering with cancer, he still can't get access. He wants to get access. The doctors want to give him access to antineoplastics, which is under FDA review, but the FDA will not grant that Compassionate Use exception.

Lastly, because I know the time, I notice here also for the record and I am glad that a representative from the Federation of State Medical Boards, a good question to ask them would be why is that the federation has really engaged in what I have seen from their publications and their conferences, really a very anti-

complementary alternative medicine policy. Why have they as an association consult with individuals, whose agendas are clearly anti-CAM.

Anyway, I wanted to bring this out and thank you for the great work that you are doing. I also sent to you, Mr. Chairman, the Minnesota legislation that you requested in the last one.

DR. GORDON: Thank you. I got the legislation and I am going to read it very soon.

So, thank you very much and thank you for consistently really being on point with us and making specific suggestions. Some of the issues, as far as licensure and coverage, we will definitely be taking up in subsequent sessions.

This session is really focused on research. If you have any particular examples or people you feel we should be in touch with or issues that are important, again, please let me know and we will move ahead with them.

MR. MARTINEZ: Will do. Thank you.

DR. GORDON: Are there questions for Tony?

[No response.]

DR. GORDON: Thank you.

Carl Sandler.

DR. SANDLER: Thank you. It is nice to see you again.

You, Mr. Chairman, recorded a birthday book to me when I was reading and given a birthday present a number of years ago at your house, one of your many books that I have read and enjoyed. Thank you.

DR. GORDON: You are welcome.

DR. SANDLER: I look upon you here and I must tell you I am not really a medical person. I am a Ph.D. nuclear scientist, a former chief scientist in the entire United States of America, going back 25 years ago. I represented all American consumers.

My life history of paralytic polio when I was five years old and a disability going back 25 years has got me into clinical medicine and, in fact, I do train medical people, physical and occupational therapists, doctors and others in continuing education and I am clinical.

I have a rather different point of view and that is why I came here today. For 25 years, I have been

doing research in medicine and related areas, as well as these other things, as being an environmental engineer scientist. Now, the reason for it is because I couldn't be here and I really wouldn't be alive if I didn't do it.

It turns out that the most important thing I know about medicine, which is physical medicine, that is about 80 percent of medicine, as you recall, is repetitive movement injury. That is about a $100 billion-a-year problem in direct costs in this country, and affects most of the people in occupations, and other things, which we have to deal with.

Physical medicine requires that we have movement beyond exercise. Exercise doesn't cut it. Lifestyle alone won't do it. You have got to integrate into what your lifestyle is, various things that are built in by design that are hundreds of thousands of millions of years old and that mostly medical and science people don't know about. Dancers know more about it. Certainly occupational therapists know more about it and so forth.

It starts with breathing. Breathing is one thing that almost all of us can't argue about. You have

to do it and almost 90 percent of the American population doesn't breathe properly. To understand this in terms of research, I had to go as far away as Australia and look at the 40,000 year history of the Australian aboriginals and of native peoples around the world.

There, the movement patterns, their breathing patterns and the problems on repetitive movement injury are different. They simply don't have them like we do, and they don't have the chronic diseases either.

Thank you.

DR. GORDON: Thank you very much.

Any questions from anyone?

[No response.]

DR. SANDLER: I will submit for the record later. Thank you.

DR. GORDON: Wonderful. Thank you very much.

Our next speaker is Dr. Stephen Straus, the director of the National Center for Complementary and Alternative medicine. Dr. Straus is going to give a somewhat longer presentation.

His agency is the chief federal agency concerned with research in complementary and alternative

medicine and, therefore, he has the mandate to lead the effort. So, we are going to give him an opportunity to talk about NCAM and also to help guide us and help us to help shape the even larger research agenda.

So it is great to have you here.

Session IV: Research Support and Collaborations

DR. STRAUS: Thank you, Dr. Gordon, Dr. Groft, members of the Commission. I appreciate the opportunity to speak and actually have some extended time to do so. This is opportune because I think this is really an important occasion for the American people to deliberate the broad range of issues around complementary and alternative medicine.

On a more personal level, tomorrow is the first anniversary of my appointment as center director. This is a good time for me to reflect with you what we have done over the past year and where we are going.

I needn't remind you, the breadth of complementary and alternative medicine, the degree to which the various modalities touch upon all facets of life, all ages, genders. All clinical specialties and subspecialties are touched upon.

This creates really a very broad range of opportunities for us to consider in a research institution. That at the NIH is our responsibility. You are charged with deliberating many other things. I have the simple task of simply thinking about research and not all the policy and education and licensure and access issues that have been brought up.

You are also aware that the mandate for the national center derives from the broad appeal that complementary and alternative medicine has for the American people, who are turning to these modalities increasingly, as ways of sustaining and enhancing their health, but, unfortunately, the public is not guided by evidence of the type that we would wish in making public health policies.

Our charge in the national center is to try to help create a scientific base so that individuals, practitioners and institutions are better informed in terms of making these decisions.

Now, there enormous controversy about these modalities and the controversy arrives in is sustained because of differences in belief and philosophy, but they

are sustained to a great extent because of the lack of evidence that exists to help resolve these controversies. But we know enough about at least certain modalities within the larger realm of complementary and alternative medicine to suggest that some of them very likely work and are safe and can enhance human health.

We have only to turn to the many reports over the past couple of years about St. John's wort, for example, and its use for treatment of mild to moderate depression. Within the past year alone, there have been two or three good control trials suggesting that it is superior to placebo and probably as effective and perhaps even better tolerated than one of the standard, old line tricyclic antidepressants, imipramine.

That data reassures us that there is something substantive worthy of larger investment. But when one begins to study these modalities, one learns not only are there potential positive effects, because after all if something were to exert a positive physiologic effect, it would have the potential to exert negative physiologic effects. Now, well-publicized evidence has shown that St. John's wort activates hepatic metabolism of other

drugs and can interfere with important drugs; birth control pills, drugs needed to suppress the immunity and sustain organ transplants and the like.

So, there are opportunities and there are challenges and there are challenges as well to try to craft a scientific agenda in a field that has largely existed in a parallel universe to that of scientific medicine and to bring these together is really an important responsibility. That is the essence of the mandate that Congress gave us in 1998 and underlies the establishment of NCAM, the center, in February of 1999.

Fortunately, this particular challenge to us has been met by enormous generosity on the part of the American people, who gave us nearly $70 million this first year to expend on research and Congress is projecting even greater generosity for 2001. We are waiting for the final figures.

But I thought I would tell you how we were approaching this mandate and how we are spending this money. We begin as one must in developing a cogent plan and our strategic plan was developed, reviewed by our advisory council. Many public organizations and

individuals commented upon it over the period of the summer.

It is now released and on our web site. We in our strategic plan delineate four major goals for the center and these are the kind of goals one would expect of one of the institutes and centers at the NIH. Our primary goal is investment in research. Because this is a new research field, we have also the responsibility to promote the training of investigators within areas of complementary and alternative medicine.

Because there is so much misinformation that bathes the American public and in some cases even handicaps rather than supports their ability to make the decisions, we have a large responsibility in outreach in communicating scientific findings in an objective way. A modality either works and is safe or it doesn't work and is unsafe. The data will speak for itself.

Finally, because the practice of complementary and alternative medicine also largely exists outside of the established conventions of academic and institutionalized medicine, it is our belief that we have the responsibility to help use the information that is

accrued through the scientific process and allow that information to allow individuals, practitioners and institutions to incorporate those modalities that are safe and effective, what we call the process of facilitating integration.

I am going to spend my time talking in greater detail about our approaches to each of these four strategic domains with, of course, the greatest emphasis on research.

Research, as I have been accustomed at the NIH as a bench and clinical practitioner for 23 years, often moves from understandings of molecules and mice before it goes into people. There is a hierarchy of evidence even in the clinical arena from initial trials, small studies, to larger, more formidable studies, to definitive clinical studies.

In the field of complementary and alternative medicine, these modalities are already in the field, but as a rule have very little preclinical support. There is often not even cogent hypotheses about mechanism. So, there is a challenge to us as to how we approach the hierarchy of evidence and how we construct a research

portfolio in an area where the hierarchy of evidence is very different from that conventional scientific medicine.

We are approaching it, therefore, not by emphasizing preclinical research, not by emphasizing mechanism at this time, although we study those and they are important, but by studying things that are in the clinical arena now. So, our largest investments involve human subjects as opposed to molecules, cells and mice. Our research investments are not only primarily based on clinical research issues, but we are creating infrastructure to provide opportunities for those studies to be conducted well.

To facilitate that, we have created a center's program I will describe and the research conducted in those centers and through the large portfolio and rapidly growing portfolio of investigator initiated applications is really tied as one would expect to the NIH areas of research emphasis. All of us would agree on what the most important public health priorities are. Those are no different across the NIH.

Where there are those same targets for

complementary and alternative medicine, that helps prioritize our work.

Finally, although we had about $70 million this year, that is a small fraction of the NIH budget and our expertise, which of necessity must cut across all disciplines of medicine, cannot be adequate to be entirely subsumed within our staff in NCAM. So, if we are to be successful, we need to leverage both our financial and intellectual resources against those of the other institutions.

One of the gratifying findings in my past year is the degree to which my fellow institute and center directors have been very eager to collaborate with us. In fact, if anything, the opportunities are far more numerous than we can all address at this present time. They are working with us to prioritize them.

I mentioned that one of our first efforts to develop a research portfolio was to help support infrastructure and we are doing so in part through the development of the center's program. We are currently funding four institutions in the United States to conduct research into botanicals. Together with the Office of

Dietary Supplements and other NIH institutes, we are funding centers whose investigators are identifying and characterizing important botanicals currently widely used by the American public.

We are assessing the bioavailability and activity of those botanicals. We are exploring their mechanisms of action. We are conducting some preclinical studies, and they are conducting early phase, Phase I and II, clinical evaluations as well. Those centers provide a focus for training of new generations of investigators in this field. Importantly, the results of their deliberations help us identify botanicals that are ready for larger, more definitive investment.

So this is an important part of our center's program. We are also funding 11 other centers covering arthritis, pediatrics, drug addiction, chiropractic, craniofacial health, women's health, aging, cardiovascular disease. I am pleased to say that with the press release today, which you should find, NCAM has announced the funding of its first two specialized centers for cancer research in complementary and alternative medicine.

Our first two centers in this area, I am pleased to say, also reflect our capacity to draw in the best and brightest from the research community to join with us. Dr. Adrian Dobbs and his colleagues of Johns Hopkins University will be undertaking four studies. Dr. Steven Tom and his colleagues at the University of Pennsylvania are running four studies in our second center.

We have actually had no difficulty recruiting outstanding investigators. Many individuals told me before I took the job that we wouldn't have that kind of partnership and I am gratified to see that that pessimistic viewpoint was incorrect.

Not only do we have excellent scientists joining us in these 15 centers, we are already conducting five large randomized multi-center placebo controlled clinical trials, the kinds of trials with the kinds of objective endpoints that would, I think, change the opinion of many in academic medicine about opportunities in conducting rigorous research in CAM.

Our first study of St. John's wort for depression, the largest, longest term such study, is

conducted by investigators with their center at Duke University. All patients have been enrolled and data are nearly all accrued. They will be by this winter. That study is being conducted in collaboration with our colleagues in the National Institute of Mental Health.

We are conducting a study a study of shark cartilage as adjunctive therapy for treatment of non-small cell lung cancer through the aegis of the community-based cooperative oncology program sponsored by the National Cancer Institute. With the National Institute of Aging and other sister institutes at the NIH, we are conducting the largest prospective study ever done of the development of dementia in aging Americans, Three thousand healthy Americans, age 75 and older are randomized to ginkgo biloba or placebo. With the Arthritis Institute, we are conducting two large definitive studies, a multi-center study of acupuncture for relief of pain associated with osteoarthritis and a five arm placebo controlled trial of glucosamine chondroitin sulfate, alone or in combination versus a cyclo-oxygenase 2 inhibitor versus placebo in 1,500 Americans with chronic osteoarthritis of the knees.

What is important in each of these trials is our capacity to leverage our resources and those of other institutes in co-funding these studies with us, allows us to fund multimillion-dollar studies with strong, rigorous, objective endpoints. It is not sufficient for 12 people to get up and say I feel better. It is not the standard of evidence that we need to entertain.

Now, there are key principles that I am articulating, obviously, in this kind of research portfolio. First of all, we need to use the same kinds of designs and outcome instruments as allowed definitive studies of conventional practices. Where one can, placebo controlled trials are best. They are the strongest and represent the gold standard, but there are some modalities that can't be blinded. You can't randomize patients to a massage study and have them and the therapist not know who is getting a massage.

But one can do large studies with parallel observation groups with good endpoints. Because some of our studies involve more than tests of a single modality, but entire systems, we have to exercise real flexibility and creativity in studying those. Those are challenges

that we are tempting to meet as well.

In addition, to the same extent that one would not study a neurosurgical intervention without having neurosurgeons on the team and performing those interventions, there are many CAM interventions that will, of necessity, require partnership and the practice of skilled CAM practitioners. I could not deliver acupuncture effectively, but I could help identify scholars and truly experienced individuals to participate with us.

So, these are ways to develop a portfolio of aggressive and rigorous research that to the degree possible emulates the best practices of conventional scientific medical investigation. But there are also domains of CAM, as I alluded to ten minutes ago, for which there are hypotheses in some cases at best and often very little preclinical data.

We need to be open to explore those other modalities that don't have a place right now in the medical textbooks, that don't have an explanation, but for which there is huge interest and there is a large anecdotal experience to say that it is helpful. For

those areas, we need to pursue those anecdotes with developmental studies to see what looks more promising and worthy of larger study. We have a series of mechanisms we put in place to accrue not only these better understood, more conventional types of research through investigator initiated applications, through center's portfolio, through our calls for applications in targeted areas, but we are also calling for applications in more difficult areas.

This is where the imagination of the American medical and scientific community is being challenged. We are calling for applications at this time for what we call our frontier medicine portfolio. Here our goal is to do exploratory studies with substantive funding for the first time of things for which there is huge interest, as I say, but not a lot of scientific support; bioelectromagnetic therapies, issues of therapeutic prayer and spiritual healings, certain uses for homeopathy and other forms of energy healing.

These need to be conducted in a cohesive way and we have presented a mechanism to do that. We can discuss that in greater detail if you wish.

In addition, we actively go out into the community to seek ideas that are worthy of exploration and developmental study. We have a particular model we are approaching first in the area of cancer and as Dr. Gordon and Dr. Fair know well, we have the Cancer Advisory Panel for Complementary and Alternative Medicine. That is an 18 member, chartered advisory panel to me and this panel includes expertise in oncology, clinical trials, statistics, pathology, radiology, bioethics and, of course, complementary and alternative medicine in a variety of its modalities.

The goal here is to identify novel opportunities that are worthy of study. One mechanism that CAPCAM is beginning to explore is what we call the Best Case Series. My colleague, Dr. Jeffrey White, the director of the Office of Cancer and Complementary and Alternative Medicine in the NCI, might have mentioned this this morning or may do so in his second round with you later this afternoon. He has done a very energetic job of advertising our interest to the alternative medical community, to have practitioners send us in a synopsis of their experience with alternative practices

that have seemed to give unexpectedly good results.

We have actually a rather simple series of data that we request of those practitioners and it is that type of process that has allowed our current funding of the regimen described I believe earlier this morning by Dr. Nick Gonzalez for treatment of advanced pancreatic cancer.

Dr. Karen Antman and John Chabot, and their colleagues at Columbia University in New York and the New York Presbyterian Hospital, are working together to explore the Gonzalez regimen. We are exploring Best Case Series opportunities as well with Dr. Alexander Sun, who has a very novel regimen of an intensive vegetable supplementation to the diet. He has preliminary and certainly provocative data on its efficacy in non-small cell lung cancer. We are exploring how to carry that further.

Our cancer portfolio, therefore, runs from these very exploratory things, which we have the important assistance and guidance of the CAPCAM to initiatives that we call for in our research opportunities. This year and in the coming year, just in

the cancer area include our call soon for applications to study special CAM approaches, to pain management.

We are calling for applications to look at botanical drug interactions because they can not only enhance, but as I said, also potentially interfere with other drugs that cancer patients and other patients will need.

With the NCI, we have called for applications through a novel mechanism we call Quick Trials of Novel Cancer Therapies. This is an expedited review process to explore new studies. We have issued a call for applications to provide supplements to NCI's many other cancer centers, to try to be an incentive for those great institutions to begin to explore cancer therapies.

We are also calling for applications specifically to study CAM approaches for end of life care for patients with cancer and HIV/AIDS. All of these are mechanisms that will enrich our research portfolio. We have such mechanisms as well in the area of arthritis, in the area of aging, in the area of nursing research, in the area of cardiovascular research and asthma and the like. Time wouldn't allow me to discuss all of these.

So, the major emphasis of NCAM's efforts thus far is to develop a research portfolio that will garner the respect of mainstream medicine and convince CAM practitioners and the general public that, in fact, we are serious about exploring their interest in doing so in an unbiased fashion.

I mentioned as well that we need to be joined in this endeavor by competent investigators. Many of our investigators have been leaders within their subspecialties, but we need to draw new cadres of individuals, including young individuals, who can enter this arena with a fresh vigor and enthusiasm without attached biases that often exist in older, more established fields.

We are doing this by supporting the entire portfolio of NIH mechanisms for training and career development. We are funding pre and post-doctoral fellowship training. We are funding training through all of the allied health professions schools. We are supporting junior, mid-career and senior level faculty to provide them protected time to move into this field or expand their research endeavors within these fields.

I will speak about one other particular training opportunity I am quite proud of. It is very clear that medical students in the United States today are eager for some formal training about complementary and alternative medicine, not just because they are curious about it as the public is in general, but because they know that their patients will be bringing questions to them that they need to have some concept of to answer.

We are not interested in teaching the average physician to be a chiropractor or a homeopath, a naturopath or an acupuncturist, but they need to understand what those words mean and what those practices could or couldn't deliver to the care of their patients. In this regard, last spring we called for the first time for applications through the NIH R25 mechanism, as I have learned it is called, for development of model curricula.

We put this on a fast track and this month we have funded the first five institutions for the first time have NIH funding to develop model curricula, four in medical schools and one in a nursing school. This is a substantive investment of $1.5 million for the first year. We are talking a serious response here.

I mentioned at the beginning that there is research and there is research training. We have the responsibility of helping the findings of research be integrated where appropriate into the general practice of medicine. We do it through training. We do it through research. We are also calling for special grant applications and health outcomes research and health services research to begin to look at the community at large in medicine and academic institutions, to begin to find out what the real obstacles to integration of safe and effective practices, what institutional strategies can be used to get around those obstacles, to remove those barriers and create opportunities.

We have identified funding to explore these as well. We want to see the best institutions and the best social scientists join us and explore this important philosophical issue within our own community.

Finally, in terms of our strategic plan, because I have really wanted to leave a lot of opportunity to take your questions, rather than merely summarize some of the things that have excited me over the past year is opportunities to help articulate this

information to the American public.

We have a web site. We have a clearinghouse and a toll free number. We have a citation index that specifically identifies CAM literature. We have a news letter. I meet with many organizations, many advocacy groups, practitioners, patient groups around the country. I spent my first year trying to set up some structure and a general approach and philosophy in the center. For better or worse, I now have 14 trips scheduled between now and June to go on the road outside of the Washington area and begin to articulate this message.

Part of this is also our approach to town meetings as you are appropriately reaching out across the United States. We held our first town meeting last March in Boston in collaboration with David Eisenberg and his colleagues at Harvard University. Our second town meeting is going to be this March at the University of Arizona in Tucson in parallel with our meeting of all of our centers' directors and we expect to continue to move to important areas of the country and hear, as you are, from the American public and practitioners what their interests are and, frankly, hear from them whether they

think we are doing a good job.

We can sit in Bethesda and pontificate. We can design an agenda for the nation, but instead I believe we are asking the best scientists to send us their ideas in the format of research applications that go through peer review. We solicit information from practitioners in the general community through many mechanisms and we are attempting to identify a paradigm that will be particularly successful in meeting these important challenges.

Thank you for the opportunity to make these extended remarks and I am eager, if you wish, Dr. Gordon, to take questions.

DR. GORDON: Thank you very much on my behalf, and on behalf of all of us for giving us a sense, both of the scope of your efforts, which is considerable, and also of the spirit of openness and inquiry that you are bringing to it. It is great to hear.

We will take plenty of time to talk with you.

Dean, you are first.

DR. ORNISH: It is not a question so much as a perspective. I remember being at the very first meeting

of the complementary and alternative medicine, it wasn't even called that at the time, many years ago and I just think what you are doing is remarkable and I just want to say "thank you" for doing it.

DR. STRAUS: Thank you, Dean.

DR. GORDON: Yes. Tom and then Effie and then Joe.

MR. CHAPPELL: With the mention of the portfolio of the research portfolio, could you give some dimension in terms of time and money? How long a period are we looking at before we provide impact? Is it 10 years. Is it 20 years? This is a large undertaking and the extraordinary with which you talk about it makes it sound quite simple, but it is not simple. There is so much complexity here.

How much time are we talking about before we see workable solutions?

DR. STRAUS: I have been a scientist at the NIH for 23 years and a few years at Washington University before that. There are certain research areas that have occupied me for most of that time. I have spent 21 years trying to understand why it is that this simple, lowly,

herpes simplex virus actually can continue to recur in us.

We have made enormous progress in that regard. We still don't have definitive answers, but along the way I did the first studies for suppression of genital herpes with antiviral drugs. We learned a lot.

So, I am a lifer in the science field. I can only speak from that perspective. I have the long view. I think that is, in fact, the only view that one can have because the best discoveries of science result not only from painstaking, long-term deliberation, but from thoughtful fortuitous observation.

So, some of the best observations that may be relevant to CAM may come from the Dental Institute or from something published in, you know, Physics Letters or Tetrahedron or something like that, basic science journals of importance.

But to be more specific, let me give you examples. This ginkgo biloba study, which all of the individuals who advised us and met with the groups to assemble those particular protocols felt that that is a study that can't be done in less than five years and it

is costing us about $16 million.

If you want to get an answer, it takes time. The American public, age 75 is at risk of dementia, but if you figure what percentage of them develop dementia in a given year, we could not do that study faster unless we accrued 40 or 50 thousand people. So, a practical compromise was a mere 3,000.

The St. John's wort study will only have taken a couple of years. The osteoarthritis studies will each take about three or four years. We can get information more quickly in smaller pilot studies. Our developmental research portfolio, what in NIH parlance we call R-21 applications, which fund things in the neighborhood of $100- or $125,000 a year, are two years applications.

At the end of two years, we expect those investigators to have substantive publishable data that could then be considered worthy of larger, more definitive investment or not.

Our mainstay of research at the NIH, investigator initiator applications, is what is known as the RO1 mechanism. These are grants that go from 200, 500 thousand dollars and up. Their average duration is

about four years for a study.

Studies that I have conducted myself in the clinical area have often taken a year to design, three or four years to conduct, a year to analyze and a year to publish. That is actually pretty average.

I would say that the American public is understandably impatient. Fortunately, at least, in terms of many of these modalities, they are already in the public domain; also, perhaps, unfortunately, because we are not providing the evidence we would wish. But all I am saying in many words, perhaps too many words, is that this is a long process and the duration depends upon the mechanism and the question.

There have already been publications that emanated from work from the former Office of Alternative Medicine. We have seriously ramped up the level and seriousness of intensity. I think it likely that our largest trials won't be in the literature for at least another year.

MR. CHAPPELL: Is your portfolio prioritized around the areas of need, symptoms-based need in our society?

DR. STRAUS: Right. What I didn't go into in great detail in talking about priorities and we just alluded to some of the ways we have done our prioritization is we have tied our areas of emphasis to the major public health areas. So, it is no accident that we are investing in cancer and pain and issues of aging and dementia and the like.

Our largest investments reflect opportunities that are appropriate for large investment and not just public interest and need. Public interest and need will get us into the game, but we engaged in studies of glucosamine and chondroitin sulfate because there were smaller placebo controlled trials suggesting that they worked. We were ready for large investments. If you look at our portfolio, at this time it is heavily skewed in a dollar sense towards things like acupuncture and botanicals and other chemicals and biologicals.

Those are things for which there was already more data. IN terms of the number of applications, they cover the waterfront and we are building a structure within our center to periodically sit and examine our portfolio by CAM modality, by health care area to see

where the lacunae are, where the holes are in that portfolio.

Starting this past winter, we have created what all institutes at the NIH do is a series of planning retreats for our scientific staff twice a year to really look exactly at our portfolio and it is those holes in the portfolio that have always guided where we will call for new investment, as opposed to passively awaiting for applications to come to us.

MR. CHAPPELL: Thank you.

DR. GORDON: Effie and then Joe.

DR. CHOW: Dr. Straus, having been also on the first panel many years ago, thank you very much for the enlightening synopsis. Really exciting.

There is a certain problem that we face with CAM is that many practitioners don't know the system and they are getting tremendous results, perhaps unbelievable results and they are not good at writing. They have no idea about research.

Do you have any thought about how you would reach or, you know, like carrying out research on people who really have some results but not quite the best. Do

you have ideas how we could reach those or is there anything built in your program?

DR. STRAUS: That is an excellent question and we have given it a great deal of thought and I don't believe we have yet arrived at adequate or proven mechanisms to do so. Let me say that to the same sense that I wouldn't presume to do acupuncture or neurosurgery, I wouldn't presume that the average practitioner can do science, not because it is in some way too sophisticated or too intellectual for them to grasp, but their interests in background and training are not commensurate with what it takes to do good objective prospective science.

So, our first capacity to test these ideas that are in the domain is to look at the literature and invite experienced scientists to join us and they are doing so.

The second thing has to do with the ability to create mechanisms for individuals, who do have training in complementary and alternative medicine, to learn to do science and it is for that reason that we are eager to fund individuals who have degrees in chiropractic, for example, to go on to get doctorates, to get Ph.D.s. The

discipline of chiropractic is just beginning to teach research approaches. I as a physician needed to take several years of additional training to become a medical scientist. It wasn't sufficient that I spent seven years becoming a physician.

So, we have that mechanism as well. In addition, I mentioned the CAPCAM process of trying to solicit ideas from these practitioners, with the understanding that we are not asking them to test the practice, but to help guide others to help them test it. One of the first examples, it is controversial, but we are willing to be controversial where the situation demands, is to invest in an institution like Columbia University to explore Dr. Nicholas Gonzalez's observations.

Those are the approaches that we are doing.

DR. GORDON: Thank you.

Joe.

DR. FINS: Thank you very much. It was really a spectacular overview and all the good work that you are doing.

I really want to just make a point and then ask

you a question that is related to these issues of outreach. The Best Case Series, I think, is not only good for CAM, it is also good for medicine. It is a methodology where practicing clinicians of whatever stripe they are can share an observation and anecdote and have a serendipitous observation that can then lead to very good science.

I think that is emblematic of a methodology that should be disseminated widely in all the institutes. So, that is a wonderful thing.

I just want to ask you a little bit about CAPCAM and how it works in reality and anything that we might be able to do to help make it work even better. If people submit research protocols to a study section, what is the mechanism that allows your group to actually input on the decision-making process about whether or not it gets funded and so that there is a collaborative view of it and not just a study section, which may or may not be as philic to these novelties as CAPCAM itself might be.

DR. STRAUS: So, let me first separate these issues because CAPCAM and study sections are different. So, a study section is a group of individuals who are

called together to provide peer review, the same way that we review articles submitted to journals. The NIH gets approximately 30,000 research proposals of substance a year that go through peer review.

Applications that investigators write and submit to the NIH unsolicited, in all cases go to the Center for Scientific Review, which has a large series of standing study sections. If it is a therapy in cancer, for example, it would go to a study section that deals exclusively with clinical trials for cancer patients.

Dr. Fair, I think, would have more experience with that particular example even than I. That panel is expert in the design and conduct of clinical research, but may not have any expertise in complementary and alternative medicine. Those review panels historically call for ad hoc individuals to add expertise where necessary. NIH intramural scientists are usually not called as ad hoc'ers, but as an intramural scientist at the NIH on a number of occasions, I was called to provide ad hoc advice in certain areas.

So, those things occur. I would like to believe and I think the data is very much in favor of it,

that they are doing an excellent job because not only did our number of applications to NCAM increase this past year over the prior year fourfold, but we have actually funded twice as many applications. So, that process is working.

Let me say when we call for special targeted areas of emphasis, when we call for our centers' applications or for applications for frontier medicine or if we have special initiatives in pain or end-of-life care, we construct our own what is known as special emphasis panel, which will include many of the same kinds of individuals that the Center for Scientific Review would put on their peer review panels. These are experts in those areas from around the country and our staff has the opportunity and the responsibility to see to it that those review panels contain adequate representation from all the domains.

DR. GORDON: Charlotte first and Bill and Tieraona. That is going to be it. We really need to move along.

MS. KERR: Thank you for your presentation.

Two quick questions. The first is you have an

18 member advisory panel for cancer. Do you happen to have any nurse researchers on that advisory council?

DR. STRAUS: Yes.

MS. KERR: Thank you.

The other is this morning as you know, Dr. Joseph -- is it Pizzorno -- spoke from Bastyr. One of the recommendations he suggested was holding a consensus conference on CAM research protocols. I wonder if you would respond to that.

DR. STRAUS: Well, NIH consensus conferences are operated out of the Office of Medical Applications of Research. There is a new director, who I have met with. The consensus conference process is a complex one that requires prioritization and the question has to be one for which there is already substantive evidence. You don't want to have a consensus conference, where there already is consensus that something works or a consensus conference where you will embarrassed that the experts you bring in have very mixed opinions and are unable to derive the consensus.

So, those kinds of proposals can be made to OMAR, as it is called, and they will make those

determinations. Those consensus conferences is not the consensus of the NIH. The NIH sponsors a conference of individuals in the medical community, who are charged to arrive at a consensus.

DR. LOW DOG: Again, mine is quick, too.

DR. GORDON: Let me just something. I know everybody wants to ask Dr. Straus questions. We all need to be very brief because we are already going over time.

DR. LOW DOG: With all your work on botanicals, I just had a couple of questions. One, I think the need for genotoxicity and mutagenicity and interaction with P450 and all of these things are very important. Are you collaborating with other organizations that are doing a lot of work with botanicals and studies with standards, United States Pharmacopoeia, consumer labs, Herb Research Foundation, American Botanical Council, are you doing a lot of collaboration? Because I do tend to see that we end up doing a lot of repetition so that we have got numerous sort of groups sort of doing the same thing and when we have limited funds, how much of this could we do together?

DR. STRAUS: Right, Dr. Low Dog, it is a good

question. I will say that we are obviously funding major botanical expert institutions, who do collaborate with all those groups. I meet with representatives from -- I have not met with all of them as yet, but this is obviously an important issue. I have charged one of my special assistants to help assemble a special colloquium this coming spring, in fact, to meet with various aspects of industry because I think that they have a responsibility to develop meaningful and cogent data as do we. It is important that we collaborate and not work at cross purposes.

DR. GORDON: Dean.

DR. ORNISH: A quick question. Unlike studies of a new drug, where you can control access to it for a control group, when you study things like ginkgo biloba or St. John's wort and you are doing these large scale randomized trials, which I applaud, given the Internet, all the information that is out there, how do you keep the control group from being contaminated?

DR. STRAUS: That could be a difficulty in some studies, but the majority of Americans are not yet using ginkgo biloba and healthy Americans over age 75 are not

using it at the same rate as some younger Americans. To a certain extent, as you well know, Dr. Ornish, clinical research is an issue of trust. You set out your expectations and informed consent and you ask people not to do it. There are times in certain kinds of studies in which one then does blood levels to monitor for achieving and there is an illustrious tradition through biomedical research of people attempting to second guess and to cheat.

You have to build that into the assumptions of the study design to some extent. But, by and large, my experience is that patients really want to get it right and don't want to stand in the way of getting a good answer.

DR. ORNISH: So, you ask the control group specifically not to take --

DR. STRAUS: Of course.

DR. GORDON: Wayne.

DR. JONAS: Steve, I want to say that you are doing a great job. I mean, you have been a year on and moved forward and developed a lot of things, an infrastructure. I can foresee this continuing on in a

very successful pattern. So, congratulations.

DR. STRAUS: Thanks for your encouragement, Dr. Jonas.

DR. JONAS: You are really taking the bull by the horns and moving forward and using the resources appropriately.

I have one very short, small question and then one more general question, which you may not be able to get to, but I think it is at the heart of what we can do here in terms of saying how can we facilitate research that will be integrated in terms of complementary medicine.

One simple question is who is paying for the five arm glucosamine trials? It is, obviously, a huge trial. What percent of the trial is coming from NCAM?

DR. STRAUS: Well, there are various parts of that study. It has got a number of years of out-year costs. The vast majority of the funding at this time is from NCAM, but we are getting very substantive co-funding from the Arthritis Institute.

DR. JONAS: Do you have a sense of how much percent-wise for NCAM and Arthritis Institute?

DR. STRAUS: I actually can't give you a percentage.

DR. JONAS: I think that would be helpful to know, if we can get at least a general idea of whether it is 50 percent, 10 percent, 20 percent, 80 percent, whatever.

DR. STRAUS: Some of these studies you might recall were negotiated before I came on board at the NIH. My posture is to ask my colleagues to ante up. It is not our responsibility to relieve them of their obligation to study this field, but to inspire them to do more with us.

DR. JONAS: I think that is very important and leveraging is essential in all cases no matter how much you have.

This relates to the second question, which is could you address or help us understand better some of the risks of focusing on clinical research. One of the reasons the hypericum [ph] trial is a three-armed trial is because we wanted to make sure the trial worked. We wanted to make sure that the active, known, proven antidepressant actually worked. The reason for that is, obviously, because the sensitivity of clinical research

can be fairly fickle at times and if the trial didn't work then, you know, we would use that information differently than it did.

Now, that kind of thing is not built into a lot of trials and doing clinical trials that do that are quite expensive and even then, they may not give us clear answers as to whether things work or don't work. There are a number of examples of that.

Garlic, we thought, worked for lowering blood pressure. Now there are some real questions about it. Vitamin C, we thought didn't work for cancer and now there are some questions about the route of delivery.

Acupuncture doesn't work better than its own placebo for smoking cessation, but it works better than no treatment and at least as good as other proven treatments.

DR. STRAUS: I think in the interest of time, you are answering the question very well.

[Laughter.]

DR. JONAS: The issue is what are some of the risks in flipping what is the normal research strategy approach that we take in NIH and in science, in general,

which is building from the bottom up, so that when we do the clinical trials, we are more likely to get a foundation of good results and flipping that and doing it the other way around.

DR. STRAUS: So, as somebody who has spent a lot of time thinking about this, you are aware that these are complex issues. I will try to be telegraphic in the response.

There are risks, not because clinical research is insensitive. It depends upon the effect size as to whether something is very potent. A lot of these modalities are not very potent. I have done placebo-controlled trials that had very powerful statistical results with 32 individuals in the entire study because 100 percent of the people on placebo had one outcome, and 100 percent of the people on the drug had another outcome. We don't see that in this area.

I held the initiation of the glucosamine trial to add a fifth arm because I felt it was necessary to do that. I feel that that is important in designing studies and I would rather not do a study because of the issue that the sample size is going to be larger, it is going

to be a little more expensive than we wished, if it can't be done well. I would rather do it well than a lot of mediocre things that we would be criticized about.

But there are risks because although there are many things within conventional medicine that have not been subjected to large placebo-controlled randomized trials. They arise, their use arises within a body of information, preclinical and clinical. You know the molecule. You know the mechanism. You know what it does in cells. You know what it does in mice.

Therefore, it is logical that it may possess an activity. As an infectious disease person, many antibiotic regimens I use have not been subjected to placebo-controlled trials, but we know that they kill bugs and we know that they are effective in pneumonia, if not sepsis, if not otitis, if not meningitis.

The lack of that broad underpinning of science creates the greatest challenge to CAM research, which is why I insist that we do preclinical studies and we look at mechanism at the same time and not merely pursue whim and anecdote.

Thank you.

DR. GORDON: In the interest of giving everybody a little change, Bill and then --

DR. FAIR: I just wanted to second Joe's comment about your presentation and also about the Best Case Series. I know you have a lot of detractors about initiating the Best Case Series, but I think clearly you are on the right track. I mean, if you look in allopathic medicine, the practice of surgery is without doubt the best example of the Best Case Series. Later on, surgical procedures may be subjected to double-blind or randomized control, but in the beginning they are all Best Case Series.

My question to you is, having done as well as you have done thus far, is what kind of recommendations would you like to see from this committee to help your job in the next few years?

How do we help you? You have given us an awful lot of information here. How can we help along this way?

DR. STRAUS: I think that is an excellent question, Dr. Fair.

I would say that this is too young an enterprise and I am still too new to it to have proven

its worth and my worth. So, I think the first thing to ask is patients. The second is that however the creation of NCAM was arrived at, I believe, and I am encouraged to hear that you believe as well, that we are on track. I think that track should be encouraged and supported. Everybody has an opinion about everything. It is important that science has input from the public and advocacy groups, constituency organizations, its elective representatives.

But the real decisions of science and how to do it need to be left to people, who are professionals at that. I would encourage whatever ultimate deliberations you have to reinforce the fact that science is a process not a philosophy. There, obviously, are biased scientists, but it is a process that has greatly advanced the human condition over the past centuries.

Anything you can do to support basic science, clinical science, to encourage advocacy organizations, to encourage industry, to encourage the broad sweep of the American public to get behind asking questions critically and credibly will serve us well.

DR. GORDON: Thank you.

Reminds me of R. Nixon
"I am not a crook"!

He may not be here next year. He may be Secretary of State.

[Laughter.]

George.

DR. STRAUS: I will stay in science. I am not a politician.

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DR. STRAUS: No. I think there are harder trials and there are easier trials. The scientific method of generating hypothesis of testing rigorously and letting the data speak for itself could work. We are funding several studies in massage therapy. We have a considerable investment in Dr. Taylor's groups at the

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[Laughter.]

George.

DR. STRAUS: I will stay in science. I am not a politician.

DR. BERNIER: I again, want to congratulate you, Dr. Straus.

DR. STRAUS: Thank you.

DR. BERNIER: Many feel that the clinical research trials are going to provide the answers to a great many of the questions that you are dealing with. As you look down the road, do you see there are a lot of areas like massage therapy that won't be lending themselves very well to clinical trials per se or is that just an anomalous one?

DR. STRAUS: No. I think there are harder trials and there are easier trials. The scientific method of generating hypothesis of testing rigorously and letting the data speak for itself could work. We are funding several studies in massage therapy. We have a considerable investment in Dr. Taylor's groups at the

University of Virginia in Charlottesville, as you may know, and others who are interested in massage.

There are methodologic questions that make it hard, but as Dr. fear correctly pointed out, one can accrue a compelling body of knowledge and information through many different strategies and we have to commit ourselves to do that. I do think that we are going to find answers. Science actually never lies.

Our interpretation of the data may be incorrect and the results may not always be in accord with our hypotheses. They generate new hypotheses and we may not even like the answers. Also, in terms of certain approaches that are not very robust and don't have what we call very large effect sizes, various studies can conflict in results, which is why we are not doing just one study of acupuncture. We do several and we do several studies of massage therapy. That way in the aggregate, we try to build some body of evidence to suggest that there is merit or not.

One of the things that the American public is going to have to accept and, frankly, they largely do accept it when they are properly informed is that some of

the stuff will not work and will not be safe and there will be some people whose own vested interests are hurt by that. But that is too bad.

I have done a lot of wonderful trials that have gotten published in good journals that have been negative, but that negative data is useful just the way positive data is useful.

DR. GORDON: I want to thank you very much, Dr. Straus. It has been great working with you here, as well as outside of this arena.

One thing that I wanted to leave you with and maybe ask you to ponder, rather than respond to now since these are big questions, are some of the issues that have come up in our planning session earlier this morning and that are part of our world view. Maybe we can talk about them in the future.

One is the issue that people have back to about outreach to people who are doing good or what appears to be good clinical work and are not quite sure how to do the research, beyond how do we facilitate the Best Case Series mechanism? Just something to think about.

The other is the whole issue of --

DR. STRAUS: Sir, as a member of CAPCAM, you will see us developing some new models to present in the coming months.

DR. GORDON: Terrific. That will be great.

The second is the whole issue of health promotion and in this research area, how do we begin to do research on strategies for health promotion?

The third is, and this came in our first discussion of world view and I am sure will come again tomorrow, is the whole issue of devoting more attention to studying integrative programs rather than single modalities.

The fourth is the whole question at both a basic science level and the clinical level of individual differences. So, I am just putting those small topics out, but I think that those are some of the issues that we would love to sort of say to you that these are issues that we are interested in and we want to continue talking with you, as well as among ourselves about those issues.

DR. STRAUS: Thanks. Fortunately, there are a lot of other wise people to advise you on those thorny issues as well.

Thank you.

DR. GORDON: Thank you very much.

We are going to take a break now for 15 minutes.

[Recess.]

DR. GORDON: This is Session V, facilitating CAM research and regulatory challenges. I want to thank our panel for coming and for bearing with our lateness.

The first speaker will be Dr. Janet Woodcock.

Session V: Facilitating CAM Research and Regulatory Challenges

DR. WOODCOCK: I am the director of the Center for Drug Evaluation and Research at the FDA. I am pleased to be here. I regret that I will have to leave at 4:30 because of some other prior commitments.

I wanted to talk about regulatory challenges for the study of drug-like products. I passed out a handout. I just sort of want to walk you through what the regulatory framework is for alternative and complementary products, basically that are substances of some kind, not devices, not foods, not procedures. They would be drugs if they are used for disease claim. In

other words, if the intended use has to do with the disease and they don't meet the category of dietary supplement.

So they would be considered drugs, whether they are ingested or topically applied or inhaled or parenteral or whatever. Now, these products typically, I think, are botanicals that fall into this category, but there may be other types of alternative and complementary products that are not botanicals that would also fall into the drug definition, based on the fact they were intended to be used to treat or mitigate or prevent disease.

Now, when human research on a drug is contemplated, it is required that an investigational new drug application be submitted to the agency. It is called an IND. That technically is an exemption from the actual requirements that if you ship a drug around in interstate commerce in the United States, you have to have marketing approval.

So you can get this IND, this exemption from that approval requirement in order to study a product, say, during drug development.

These regs, which, I have appended a copy to your little handout of just the outline of those regulations, apply, in addition to regulations on human subject protection and IRBs that would ordinarily apply to any kind of research on human subjects.

Now, I was asked to identify what are the barriers then to research in this area, given that an IND is required. Frankly, the drug development system has traditionally been set up for synthetic, highly purified drugs, even though most traditional and original drugs came often from plants and that is kind of the roots of drugs, but nowadays in the current system the ideas that have been developed and the framework has really been tailored somewhat to the synthetic drugs that are made in the sort of ordinary drug development process.

Now, we have identified this as an issue and our solution, at least for botanicals is we have published in August, and actually it is just very timely, this document. I can give this to Steve and make it available to you.

This is called Botanical Drug Products. It is a guidance document. A guidance is non-binding advice

from the FDA on how to do something. In this case, this guidance is for botanical drug products, how to study them and then if you wish to, how you would go through the approval process.

The basic issues that we wanted to address, we wanted to open the door for the study of traditional botanical products without the barriers that currently exist, particularly in the chemical characterization, the pharmaceutical testing, and the toxicology, especially for products that have been extensively used in people in various settings for a long time.

This is just a proposal and we are seeking comment. There is a 60-day comment period, but people can comment on this at any time. We will issue a final guidance based on the comments that we get. That could be subject to ongoing revisions if necessary.

This basically constitutes a kind of cookbook. If you want to study, in people, a traditional botanical product, how you could go about that and actually get into a trial where you test the effectiveness and safety of that botanical without jumping through a tremendous number of hoops of animal testing and so forth.

That is predicated on the fact that that botanical has been used in people before and as some of identification or characterization attached to it in other words so you kind of know what you are testing. If the product, for example, had been marketing as a dietary supplement and there was human experience from that marketing or the product had been marketed in other countries and someone was able to sort of collect that experience and provide it. That kind of information could form the basis for going ahead and doing a human trial.

There are other requirements in the IND. Of course, you have to follow a protocol and so forth. The FDA is prepared to provide assistance to people on how to set up such trials and so forth. We do this routinely with pharmaceutical sponsors, but, of course, they know the know the system. It is easy for them to come and talk to us. They may not think so, but it is relatively easy.

Our guidance really urges that people consider doing controlled clinical trials early in this process and so it is not aiming people at getting into the IND

and then doing observational or anecdotal type of studies or small studies. We think it is very important to start learning substantive information about the botanical product early in the development.

So, a dose response trial could be done or a placebo-controlled trial or something like that could be done. It could be a trial big enough to really tell you something about whether there is activity for this indication you are looking at or not.

We work people through the steps. It is written in plain English initiatives. So, hopefully, it should really be responsive to some of the barriers that people have identified to getting into the ordinary system of how drug development and clinical testing is done.

Now, you asked about regulatory changes that might be necessary. One change we have identified is in our combination products regulations. Again, these were written and targeted for drugs, purified drugs and they are really considering like a cold and cough medicine, where you combine two known ingredients together and we have different requirements for doing that and so forth.

What we are doing is actually working on a draft proposed regulation change that would address these issues for botanicals, again, to open the door.

Not having such a change in regulations would not impede testing of products, but it could impede approval of botanical products if they got to that stage. So, we will have to keep pressing on that.

As far as FDA resources, you asked about that, that probably would be a factor. Our resources are somewhat strained in the area of drug review and what we find is that people who are not experienced in drug development require considerable assistance, including small companies require often considerable FDA assistance in almost every aspect of developing their drug. So, we would expect that that would put some additional resource needs on us.

What we have chosen to do in anticipation of all that is happening, we have written some internal standard operating procedures. We hope to group most of the review of the early trials of botanicals together in our OTC group, over-the-counter group, so that a single group of people will be dealing with the sponsors.

if a product, say, would become very promising for some disease, then at some point there would be a handoff to our subspecialists after those original trials have been completed. But we are trying to form a group that would deal with most of these and we think that, of course, some of these products would be intended for the over-the-counter market, many of them, and would not be intended for the prescription market. Some of them might, you know, so, basically our over-the-counter group would be handling that and we have created a position within our over-the-counter group that will be dealing with botanicals, a physician who knows about Chinese medicine as well.

But, anyway, our resources are strained and that could perhaps limit our ability to assist sponsors if, in fact, people really are able to respond to this guidance and come in with studies.

Now, what about approval of products, alternative or complementary products, that had gone through this process. We would approve products that had been demonstrated through our standards of evidence to be safe and effective. So, the requirements for clinical

safety and effectiveness for approval of any of these products as a drug would be no different than for any other drugs.

We would expect at the time a product became that close to further drug development, where it was actually considered to be for approval, that it would have to be characterized well enough that you know what you have. Of course, this is an issue for many plant substances and other complex substances, the testing of them, the reproducibility and stability and constant dose and everything is difficult.

So, we think that additional chemistry and manufacturing standards would be required at that point, but those could be tailored to the individual product. There may be other types of substances that are not plants that would also be considered drugs and we are certainly open and probably would apply the same type of reasoning to these substances that we are attempting to apply here to the botanical substances.

So, I think we have or will be accomplishing what we hope to carry out, which is to open the door to human testing and development of these products so that

we can truly find out whether they have usefulness in the armamentarium.

Thank you.

DR. GORDON: Thank you very much, Dr. Woodcock.

I am going to say a couple of words about how we are structuring this panel. Because you have to go, I think we will take a few minutes, if we could, now for people to ask questions of you. Then Dr. Feigal will be speaking and then Dr. Levitt and Dr. Lewis and the fifth person here is David Dorsey, who is the counsel for the FDA.

You are here to just answer questions. But you are not going to be making a statement then.

Okay. So, if there are questions for Dr. Woodcock, please.

Yes, Joe.

DR. FINS: I have a couple of questions. I know that for drug approval, there is often a private governmental partnership in the cost of the approval process. Is it the same for this process, given the constraints of resources that you have?

The second question is that given the fact that

you are mentioning that you have strained resources and one of the points in the Executive Order was to increase access to these issues, what kind of funding would be necessary and how does the FDA make decisions about putting resources into botanical issues versus drugs?

The third question, in case you don't have enough, is this notion of degree of modification; that is, when does a botanical become a drug? Is it the delivery route? Is it the dosage, et cetera?

Those are three simple questions for you to tackle.

DR. WOODCOCK: The first question, I think you are referring to the Prescription Drug User Fee Act and the program whereby sponsors have to file a fee at the time they submit their application. Generally, small manufacturers and others who do not have a robust business have an opportunity for fee waiver. That is how that program and orphan products and so forth, so that is how that probably would be addressed unless if a major pharmaceutical firm would submit a marketing application for one of these products, we would charge them a user fee or another company that was, you know, already a

going concern.

Your second question, can you repeat that?

DR. FINS: The priority setting of botanicals, how do you use your resources?

DR. WOODCOCK: We try to get everything done that we need to get done. We have had some inquiries about botanicals and that is what precipitated us to assign a position and to create this guidance and work on this regulation and so forth. We will, obviously, respond to people who submit INDs. We also have what is called a pre-IND program. People can call us up and come in and meet before they file their IND to get different advice and so forth. This is labor intensive and I can tell you we do not have a formal process to assign resources. Congress sometimes tells us how to spend our resources, but otherwise we try to just get done what comes in.

Now, your third question was how do you determine whether something is a drug, a substance. As I said, and that is why we brought our counsel with us, a substance that would be used to treat, mitigate, prevent and so forth, disease, unless it were a device or

whatever, a food, would be a drug. Substances that are intended to alter the structure and function of the body could be dietary supplements or drugs. All right?

We included all those definitions everything in the package. So, those substances that are dietary supplements are ingested. So, substances that are intended to do structure function or treat diseases or whatever that are inhaled or injected or rubbed on would all be drugs.

DR. GORDON: I just want to clarify for one second. Ginkgo, if it is used in a clinical trial to treat dementia or to prevent dementia, is a drug, but it is also a food. Is that right? So, it is sort of like an electron. It is both a particle and a weight.

DR. WOODCOCK: There you go. We issued a regulation, right, on the dividing line, which we can submit to you for your perusal, if you would like, and it describes what types of claims would make the same substance would be a structure function claim and make something a dietary supplement or food or whatever and what types of claims would make it a drug.

DR. GORDON: So, it is the claim in that

instance that makes it what it is. Is that right?

DR. WOODCOCK: That is correct. The intended use --

DR. GORDON: Tom and then Conchita.

MR. CHAPPELL: Thank you.

I am curious to know a little bit more about, this is sort of a new opening then from DSHEA versus NDA. This new is an in-between way to learn about the prospects, the probabilities. This is really very important and very helpful.

Would you advise companies to, quote, think of partnering in this process or to just work through attorneys? This is always a big question for us in our company. Yet, the simplicity of it all is to sit down and talk about it beforehand. I hear you saying this pretrial provides that opportunity.

DR. WOODCOCK: That is correct.

MR. CHAPPELL: You would welcome and encourage that with or without counsel?

DR. WOODCOCK: Yes. The Center for Drugs also has a small business assistance group in their Office of Training and Communication. You can find them on our web

page and they are specifically constituted to try and help small businesses, which are new to our processes. They may not be that small, but our process can seem formidable to people, to help them through those steps.

The guidance I have described, certainly, it is congruent with all our current regulations. In other words, it is a legal way for us to do things. It just shows how we can incorporate the existing knowledge on botanical product from human use and experience into our assessment of the safety to go into clinical trials and do clinical trials.

MR. CHAPPELL: Last, the formulations that are both in part meeting monographs of an OTC, like a decongestant, but has echinecea [ph] and time and so forth that are DSHEA items, these half DSHEA, half OTC remain dilemmas for us all or --

DR. WOODCOCK: Well, that is why I mentioned the combination product regulations. Okay? Certainly, you could do studies of those combinations and those studies would be, say, you had pseudoephedrine or something like that or whatever as one of the ingredients or say you had an antihistamine as one of the ingredients

and you wanted to add something to it, you would have to show eventually in your trials that the addition of the botanical product provided an additional benefit.

MR. CHAPPELL: But not based on secondary language or DSHEA claims?

DR. WOODCOCK: Well, that is a different issue about whether you want to combine products and have one be a supplement and one continue to be a drug. I am saying if you want to do human testing on those products for drug claims.

MR. CHAPPELL: Okay. Thank you.

DR. GORDON: Conchita.

DR. PAZ: I am a private practitioner, who sees people in their office on multiple, over-the-counter substances, along with their medication. How might one go about either finding out either adverse effects, combinations with medication or how might one report those particular events when they do occur? Because they do.

DR. WOODCOCK: I will defer to my colleagues from the Center for Foods about pure dietary supplements and their issues. For drug interactions we have issued

some public health advisories. Those would be on our web site and Med Watch sends them around to groups.

As far as reporting, you can report drug interactions to Med Watch, directly to Med Watch, and we will not only get those, but we will send them over to the Center for Foods for the dietary supplement piece of that.

DR. GORDON: Wayne.

DR. JONAS: Thank you.

I am really glad to see your effort moving forward to kind of develop these areas. I think it is very clear this is essential.

I am wondering if there are some things that would be useful for us because we are going to be thinking about, all right, how can we help you move better and further in these areas. One of the things that I have heard a lot and experienced, actually, is that you need more resources. You need not just authorization. You need appropriation to be able to deal with this.

So, if there were some suggestions you had for us of specific policy or regulatory items that could

provide that in the FDA, that would be helpful, I think.

That brings up another question is that, obviously, the guidance is there, but dealing with these things is really a unique phenomena. It is very much like biologics in some sense. They are really not drugs. They are really not devices. What are they?

I am wondering if it would be useful to have a place in the FDA with sufficient staffing that specifically dealt with this and then could work with various groups of various levels to encourage the examination of botanicals as treatments in these areas.

I think to know if and how that might occur for us, I think, would be extremely important. I am just wondering if that is something you could comment or something you could provide or if you think those are good ideas?

DR. WOODCOCK: We might be able to provide something on the resources. I think my experience is that in general it is best to have it, for something that is unusual, it is better to have a core team that deals with it on a routine basis and it becomes very good in the art and has connections to the outside world in that

particular area.

So, I think that would be a very desirable thing for us to have and we certainly have a number, as I said, of practitioners within the Center for Drugs, who are very interested in herbals and who are well-versed in certain herbal conditions and so forth and very knowledgeable, but generally they are spending their time reviewing synthetic drugs.

So, I think that is a very good idea. Those people have to matrix with all the subspecialists as you get into endpoints in specific disease areas and everything. So, with the resources available, I would probably create a team such as that.

DR. JONAS: Is the FDA looking at other countries? Because I know a number of other countries have begun to develop kind of their own offices, even sections of their equivalent of the FDA to deal with these types of things.

DR. WOODCOCK: Well, I personally have talked at great length to Canadians about their structure that they put in place. The Australians, we have also looked at what they have done and their levels of evidence and

the different things they have done.

So, obviously, we have to do things that are congruent with our statute and our own statutory frameworks that we have to work under. But I think they have taken some very good common sense approaches to this and we have something to learn from them.

DR. GORDON: Thank you.

Effie.

DR. CHOW: I am happy to hear your progressive work in this area. I want to dispel a myth. In educational circles they are saying that it takes $250 million and 15 years, approximation, to put a drug on the market. Can you verify that, or dispel that myth?

Also, what about studying the herbs, is there an average that you can see that for monies for researching this?

DR. WOODCOCK: The first question has to do with how much does it cost to develop a drug and the estimates vary widely. The $250 million, as I understand, or other high figures represent the cost to large firms that include all the R&D to discover the different candidate drugs, all the development work to

select from the candidates, the ones that will be taken forward, all the trials, the costs of all the failed candidates that go into clinical trials, of which there are many, and then do not win, you know, maybe have safety problems or not as effective or they just choose not to carry them forward.

All those costs are put into that estimate. So, another way of stating that estimate would be to get one drug on the market, starting from the laboratory phase, it would cost $250 million in some companies.

Now, I think if you are starting with a compound, you are further along that process, but I don't think you can give an estimate for how much it would cost. It would really depend on what kind of trials you had to do and what you were trying to prove.

DR. GORDON: Thank you.

Tieraona. Then that will be the last question.

DR. LOW DOG: Really, thanks for all the work that you are doing. We were all very happy to see this when it came out in August.

I have a question, though, that I hope you can answer.

Say we do a trial on St. John's wort, have a standardized product and this trial comes out where it was equivalent in efficacy to Zoloft. So, whoever was the manufacturer of this St. John's wort company, then applies for that to be a prescription drug.

What, then, happens to all of the St. John's wort that lots of companies make as far as -- I mean, what happens if you find an herb, which is sort of abundant and somebody takes that to a drug status, what happens to that in my garden and what happens -- do you understand my question? It is something I don't know what we do when we come to that place.

MR. DORSEY: I will try to answer that. Part of the definition of "dietary supplement" in our statute says that if an article has been marketed as a dietary supplement and then is subsequently approved as a drug, it can still be marketed as a dietary supplement.

I guess the proviso would be that the articles being marketed as dietary supplements wouldn't be able to say, you know, for the treatment of depression or as good as Zoloft or whatever. Because that would mean their intended use would make them drugs. So, you would

actually have two categories of products out in the market.

You would have the approved prescription drug, which could say of itself for the treatment of depression and then you would have the dietary supplement products, which could say of themselves for a better mood or whatever they say.

DR. LOW DOG: Right. Healthy neurotransmitter system, right. That is kind of interesting, though, because we could have an identical product. Let's not get into bioequivalence and all that between products, but you could have an identical product then, one that was being sold through your hospital formulary at a lot higher price and then you could just go down to the local grocery store, but nobody would really -- the consumer, just speaking on behalf of the consumer, the consumer could just get the same thing at the drugstore or the health food store as what you would be getting from the pharmacy with a prescription.

Is that correct?

MR. DORSEY: I think that is right. I guess what it suggests is that why would anyone go through the

process.

DR. LOW DOG: That is my point. To make the claim, I mean, because that would be part of this is so that you don't have to trick consumers on the label by saying health, restore a healthy neurotransmitter balance. If it actually is clinically shown to be an effective antidepressant, then it would be advantageous to the consumer to be able just to know that, to not have to play a lot of label games.

I just had a question. I thank you for answering.

DR. GORDON: Thank you, Dr. Woodcock.

What we would appreciate is both receiving the information that you suggested you would send and also if you have thoughts or proposals or ways to facilitate this transition toward having a really thoughtful focus on how to work with herbal therapies and others that would fit into this category, we would really appreciate anything you could send us.

Thank you very much.

Dr. David Feigal.

DR. FEIGAL: Thank you very much.

I am the director of the Center for Devices and Radiological Health. I would like to make some general comments, but actually leave plenty of time for questions because I think that is probably the best use of your time. I have brought some general information about the center, the organization, what parts to call, and I will leave that behind.

One of the things to realize about the device industry in the United States is how large it is and how vibrant it is. Every business day, the device manufacturers introduce into the marketplace approximately 50 new devices that have not been previously marketed. About half of those are exempt from any type of premarket review because they have been classified as Class I exempt devices.

The majority of the remainder are approved through a process, which is known in a term that probably only a government person could love, a 510(k) process. I believe that is the statute, not the regulations. That is a standard that clears drugs. It doesn't approve them. Not drugs, devices. It clears devices based on a standard of showing that the product is substantially

equivalent to a predicate device and if you were to think broadly about the concept of this, it is probably most similar to thinking about a generic drug, except that you can't have bioequivalence for a scalpel and you can't have drug levels to compare peak levels and so forth for a CT scanner or for an acupuncture needle.

The device amendments, the laws that really clarify the regulatory paths for devices, did not exist until 1976. So products, which were legally marketed before 1976 were the original predicates and they were largely presumed to be safe and effective. There was a process in the late seventies, early eighties of classifying devices, putting them into about 5,000 different classifications, which are written up in the code of federal regulations and identifying a risk-based level of evidence.

One of the interesting things about devices is that that level of evidence is allowed to change over time, so that, for example, there was a time when you had to clinically study contact lenses. Now you don't have to do clinical studies at all to manufacture some types of contact lenses out of well-known materials to well-

known standards. It really comes down to engineering specifications.

In fact, 90 percent of all marketed devices have no human testing whatsoever in order to be brought to market. Our standard is different. The drug standard is adequate in well-controlled trials. The device standard is clinical trials and other valid scientific evidence. So, it is a much more flexible standard.

There are many parallels in drugs, in investigational new drug exemption. An IND has its parallel in devices with the investigational device exemption, IDEs.

But in contrast to the four or five thousand devices, which are approved each year, there are probably only three or four hundred IDEs each year and the IDEs to actually study clinical trials are reserved for devices in high risk settings and in settings for novel devices and other settings where informed consent is required.

This isn't to say that a device manufacturer may not collect clinical data, but it does not necessarily play a role in our decision-making process. There are, for example, some well-characterized hip

joints, hip implants, and for marketing purposes, the manufacturer probably needs to have some clinical experience, but they may not need that experience to get approval from us if it is made of well-known materials.

It is a knock off, if you will, of a previously marketed device. Let me stop with the broad materials. The only thing to say is aside from the 510(k), our version of the new drug application is the PMA, the premarket approval. It is actually very similar to a new drug application. It typically does have, in fact, it almost always has human trials.

There are only about 60 of them a year, 60 to 100 a year. So, it is a relatively small subset of devices that require a PMA. One question that often comes up is what class am I in and is it possible to change our class. Our web site, which has about 5 million hits a month, one of our more popular sites is a site run by our Health Industries Program Group, called "Device Advice" and it has got an algorithm that you can interact with. If you have got something you think you have invented and would like to market, it will help you walk through and see if you can classify it or how to

determine what level of evidence that you would have.

Let me make some comments about CAM. We don't have any kind of separate classifications for complementary and alternative devices. A device is a device and the kinds of intended uses and claims for them, we treat them the same, whether it appears to be something rather novel or something is very well-established.

One of the things that probably occurs to anybody, who rides an airline and looks at the catalog in the back seat is look at all of these things being advertised, all these bracelets and inserts that you could put in your shoes and all of these kinds of things, do these things have FDA or what is their standing with devices? Typically, what you are looking at are Class I exempt devices, devices that needed no premarket clearance.

Now, they are making a claim, which actually is not, often not, part of an approved claim. So, in fact, there should be a process for them submitting evidence for that. One of our challenges in terms of our resources is to look at which types of products and which

types of claims should be a priority for us to pursue and insist on evidence.

I think we set our priorities where you would expect us to when claims are made that involve major diseases that make claims that might lead someone to not use a known, conventional therapy, those types of claims. But I think it is one of those situations that it is difficult because it appears that those products are being legally marketed.

I think it is somewhat equivalent to the speeders on the highway, that they are not all stopped, but it is not that the speed that they are going is legal.

One of the other comments to make is that the usual FDA framework is that you are working with a manufacturer, who is distributing and promoting a use to practitioners. What often happens with complementary and alternative devices is that actually a practitioner has taken an approved device and is promoting new uses for it.

Sometimes you will actually see an unapproved diagnostic device that is claimed to be able to monitor,

for example, an unapproved therapy. The claim may be that the combination of the two will allow you to obtain some sort of relief from some sort of condition.

This is made more complicated by the fact that advertising in many settings is regulated by the Federal Trade Commission and the practice of medicine is regulated by the states in the way that it licenses various types of practitioners. Nonetheless, someone who is advertising and promoting an unapproved use for an approved device is, in fact, doing something which is not legal from the FDA's standpoint and which would require that they submit evidence and have that claim either cleared through a 510(k) process or approved through a PMA process.

Part of our problem is that since many of these devices are devices, which are not required to file premarket approval because they are exempt devices, they are not even on our radar screen. We really don't see these unless we have complaints or see other types of reasons to take action. It is a constant issue for us in terms of what level of priority to take for those devices.

The final comment to make about what makes devices somewhat complicated is that many of the predicate devices have a use, which we nickname sometimes a tool indication. No one ever took a scalpel and showed that it was efficacious for taking out the appendix. So, your question is is this a good cutting tool and you don't get down to making very specific claims.

On the other hand, if you take a cutting tool and you shape it in such a way that it clearly is designed to remove the endometrium, you start to say, well, what disease did they have in mind and what exactly is going to be the marketing for this.

Why would someone want such a tool as opposed to a general purpose tool. That is one of the areas that we often get into protracted discussions about what exactly are the limits of the claims, what exactly can you do with this. It often, again, comes back to things which are on the market but not exactly with that claim.

But if we take the marketing authorization for acupuncture needles, that is an example really of a tool plan. There was no requirement to show that acupuncture was safe and effective. It was taken as a given that

acupuncture as a licensed practice was something that was approved.

On the other hand, some of the alternative ways of practicing acupuncture by applying heat to the same points you might have used in acupuncture needle or pressure, some of those do not have the long established use, those, in the judgment of the center, were back to asking how would you demonstrate that those, in fact, did get substantially equivalent results to a predicate device or demonstrate that they were safe and effective in a PMA.

Let me just stop there and see what types of questions there are. My overall comment about the devices is that one of the things that you see historically with the consumer protection laws that the Food and Drug Administration is responsible for is that as time went on, Congress got more and more detailed in the laws. We suffered from being last or I guess next to the last if we picked the dietary supplements.

So, we have some of the more complex laws. As Dr. Woodcock mentioned, we have an active program to interact with people who have questions about what have I

got, how do I get to where I want to go. If I want to market something what do I have to establish to market? If I need clinical evidence, what is the evidence?

Congress, to make sure that we got the spirit right, asked us and actually put in the law that we are only allowed to require the least burdensome pathway to market for PMAs and 510(k)s. So, it is the concept that the amount of evidence should be that minimum data set that allows you to establish either substantial equivalence or safety and efficacy.

DR. GORDON: Thank you very much, Dr. Feigal.

In the interest of time, what I would like to do is to continue with Mr. Levitt and Dr. Lewis's presentation, and then we can ask all three of you the questions.

MR. LEVITT: Very good. Thank you.

I am Joe Levitt. I am the director of the Food Center at FDA, which has lead responsibility over regulation of dietary supplements under DSHEA, unless, of course, as you have heard, it is a drug and not a food. We have already had some of that discussion and I welcome a little more probing into that area because it is

something we live with all the time.

Let me just correct one thing, which is, I invited Dr. Christine Lewis to come here with me, both to help answer questions and to just introduce you to the person within our center, who really has dedicated responsibility over this area. It is not her only area. She heads up the Office of Nutrition, Labeling and Dietary Supplements.

But virtually everything that happens with dietary supplements is under her purview, but she has a lot of things that do not involve dietary supplements that are also under her purview. We do not really have enough of a staffing at this point to really warrant a separate dedicated view. I will come back to that in a minute because it is clearly of interest.

My background, as I mentioned briefly, I think, I am a lawyer. I have worked at FDA all my career, about 22 years now, all around, in the Chief Counsel's Office, where David Dorsey works. I worked in the Commissioner's Office for nearly a decade. I worked in Medical Devices for five or six years.

I took this job two and a half years ago. The

only really important part of that history is that I was working in Medical Devices when DSHEA was passed, thinking in other things and not really involved at all with the whole passing of DSHEA, which was a very controversial time, on a very controversial issue.

One thing which I have tried to instill, if you will, is a new attitude about that law, what our responsibilities are under the law and basically it is a law like any other law. It gets passed, grow up, let's work with it and let's figure how to do it.

About a year and a half or so ago, we decided that although it is interesting, you know, you think you have done a lot. People actually, when DSHEA was passed, there was a lot of activity within FDA. In the first four or five years, we actually counted up 25 Federal Register notices that had been published relating solely to dietary supplements.

But, yet, the general image was that FDA hadn't done much at all in implementing the DSHEA and somebody even suggested that to the extent we headed efforts, it was to undermine DSHEA, not to implement DSHEA. So, what we said we would do is we would, if you will, call a time

out and say let's pretend that DSHEA passed yesterday. What would it take to implement this law fully on its face properly?

We spent about a year. We had public meetings both on this coast and on the West Coast. I chaired them both personally and we developed what you have in your notebooks of our strategic plan for dietary supplements. For me, it was very interesting in kind of getting into a newer area. We began in what I will call the East Coast meeting, the first meeting, which was attended by mostly people that are in Washington, it was in Washington, and mostly by people that are involved in the dietary supplement area. They market it. They use it. They are very interested.

We got largely, I thought, a very useful what I would call "To Do" list. Most everybody said, well, if you have limited resources, you have to look at safety first. That certainly seems logical, which means you have to look at your Adverse Event Reporting System. You need to look at good manufacturing practices, which are authorized by the law to assure consistency of the product and even to be sure you are enforcing.

Interesting, I didn't expect to hear that, but even within the industry, they say wait a minute, if there were rules, if you expect me to follow them, you have got to make that guy follow them, too.

So, a high interest in a level playing field. What was interesting and very important that we didn't really expect, from a lot of different quarters there just started to be calls for we need more science here. We need to get away from just being kind of marketing and into where is the science base.

Even though everybody came at it from a different direction, you should look to NIH, you should look at the Academy of Sciences, you should do it privately, whatever it was, nevertheless, it was a theme that pervaded, which we were actually very enthusiastic to hear. There were other emphases about need, the focus on substantiations, botanicals that we have talked about a little before, clearly resources, what we call leveraging, how you leverage outside as well as inside.

It was really, I thought a very useful meeting. I joked afterwards that you wouldn't have known it was a meeting about dietary supplement by its tone. It seemed

like a perfectly what I will call civilized meeting, not what I was prepared for, you have to understand.

However, we went out to the West Coast and apparently what had happened was word had gone around and through some of the communities that were not well-represented at the first meeting, which was largely the medical community and the consumer community and the tenor of the second meeting was just utterly different.

It was high skepticism, high distrust for the product line and basically they told us we don't trust the safety. We don't trust the claims. We don't know what is in it. FDA, your job is to go out and tell everybody how lousy these products are and that it is caveat emptor, buyer beware.

We had one mother, whose son had died, she believed, from a dietary supplement. We think it actually was one of the GHBGBL, really drug variations that tried to sneak in under DSHEA. We had people questioning the need to be an adverse event reporting system to report, not knowing there was one, so, clearly some education to do and a lot of concern about taking advantage of marketing to vulnerable populations,

especially marketing to children, marketing to elderly and kind of taking advantage.

You also got a lot of the earlier themes, once you got past that. Again, everybody agrees you have to do safety first. You have to look at adverse event reporting. They need to be enforced. You need to have science and so on and so forth.

But they were clearly contrasted. So, I kind of felt we have to kind of take those two as the bookends and put them together. So, what we did is we went back and basically formed five teams, safety team, labeling team, what I call boundaries team, which gets into what is a supplement and what is a drug and so forth, an enforcement team and a research team.

We got all that together and we kind of first came up with what I will call some interim insights. One is that this is not something we are going to fix overnight. This is something that we have to have a long-term commitment to.

No. 2 is that science has got to become more central to this process. If we are going to have credibility behind these products, we are going to have

to get both in reality and in perception a stronger scientific basis underlying these products.

Clearly, it is going to require a lot of work. It will require resources, but we also felt that this is doable. This is something where a blueprint is clearly achievable. One of my mentors used to say if the job seems to big, break it down in small pieces. They all seem so big. You add them up and you can kind of figure out you can see your way to the end.

So, we took that and we put this together. We decided that it had four primary objectives. No. 1, we are going to fully implement this law. As I said, it is the law of the land. That is what our job is at the Food and Drug Administration.

No. 2, the ultimate goal needs to be a high level of confidence in the safety, labeling and composition of these products. That is what we need to get to through whatever we do.

Three, we need to make a science-based regulatory approach, what I say look at what makes our other successful programs successful and apply that here.

Fourth, as I said, recognize that it is going