to be a long-term effort. So, we built that in. We actually have the framework of a plan very much just like the teams I outlined. We go through safety issues, labeling issues, boundaries issues, enforcement issues, science-based issues, added an outreach component, recognize that we have to clearly have an ongoing dialogue with the community. We have just recently announced that we are establishing a special advisory committee or really a subcommittee of our umbrella food advisory committee.

The vote is solely to dietary supplement issues. So, there is a public forum with a science focus to help us with these areas.

I am not going to go through all the elements of the plan. It really incorporates a lot of things I said. We have to get our adverse event reporting system in shape. We need to come out with GMPs and we are very close to doing that.

We need to be sure a kind of sleeper provision of the law is that everything has not yet been invented and when there are new dietary ingredients, you need to come to the FDA prior to marketing. So, that is the one

area where we have a premarket function more like drugs or devices; whereas, everything else is postmarket.

I think one mistake that was made early on in retrospect and it is easy to say it, if I was there, I can't honestly say I would have figured it out then, so this is clearly 20/20 hindsight, but one mistake that was made was because there was so much emphasis when DSHEA was passed that is a law by large that companies can market without going through the FDA, that there didn't need to be any FDA staffing to deal with the issues.

It was viewed as what I call a low maintenance law and, yet, I can tell you as director of the food center, except for food additives, like a new sweetener or something, you know, we have a postmarket law. We have a whole center devoted to the oversight and regulation of those products, to ensure the same thing, the safety of them, the labeling of them, the composition and quality and purity of them.

So, it may not be a premarket law. It may be what I call a postmarket law. But it does mean it is a low maintenance law in terms of government oversight. That is, I think, a cardinal misperception that I think

surrounded it at the time.

So, we put this out. Interestingly, sometimes you get enough visibility. We got a request from Congress that said, okay, you have got your plan. What will it cost to implement it? So, if you can patient and not finish up your commission work in the next couple of week, we do have a congressional request for a submission on what it will take to implement this and we are in the stages of completing that.

But I can tell you it will be in the tens of millions of dollars. It won't be in the one or two, three thousands of dollars, which some people think of the FDA. It really depends on dollars, what you think is big or small. In the FDA that is viewed as sizeable and at other places maybe not. But it will be for us a substantial program to implement.

I think the one other area I want to emphasize and I have already done it a little is the area of the science base. It is in the plan, I think, quite admittedly, the area that is most general and least well-focused. It is also the most important. When I go out and give talks on this, I say the long-term success of

this area depends on the successful implementation of that section.

We are building bridges with NIH through Office of Dietary Supplements that are for complementary and alternative medicine. We have just got in some what I will call year end funding and have initiated a contract with the Academy of Sciences to start doing some retrospective reviews of some key ingredients out there, for what is out there in the literature.

We are trying to stimulate research and engagement on the scientific aspects of these products and think that that is critical, but we also admit it is still for us, I think, in the early stages. We want to be very sure that we are not duplicating what other people are doing, but taking advantage of what other people are doing and kind of bringing that to bear.

So, I think that is very important. I think the last thing which we I think probably don't feel real good about, but it is, if you will, the reality of what life is. Since this was a program, like so many laws that were authorized but not appropriated, somebody mentioned that earlier and since it was an area where FDA

virtually had no prior staffing and since now more and more much of our money is earmarked, we have, you know, really a very small group of people that we are able to dedicate to these tasks.

So, what we have said is we will put forward what I will call the real funding requests. In the interim, we will say each year for our center generally we have put out a priorities list of this is what are our goals for the year. We will be very clear on what we feel we can accomplish this year and put that front and center so that people know this is what we are doing and also you kind of know implicitly what we are not doing.

Do we feel great about that? No, but at least we have gotten feedback. At least we know. So, we are moving forward literally, you know, as best we can, but realize that progress will be incremental until we can get a dedicated program to focus on this.

I see my time is up. I am, at this point, happy to say I am finished.

DR. GORDON: Thank you very much.

Shall we go around? I am sure there are a number of questions and we really appreciate your giving

us a feeling for the work, both of you, the kind of work that you are doing and some of the issues that are coming out.

Did you want to begin, Wayne?

DR. JONAS: Again, we are focused on science here and research and we have heard a lot about evidence and levels of evidence really all morning and this afternoon. I am wondering is there any thought or any discussion of using what I heard you say, Dr. Feigal, on the sliding scale approach that is used for devices in terms of looking at safety and risk and then adjusting one's type and amount of evidence for approval for that, which is what I heard.

Correct me if that is incorrect, but has there been any discussion of that in some of these other areas, many of which are thought to be relatively safe, may or may not be. It may be that there are things that are not so safe when they are used within the context of other types of therapies and this type of thing.

But is there any thought of approaching that? My sense is that there really is a difference in approach between different sections of the FDA, as well as others

in terms of that. I think that is crucial when it comes down to deciding, well, what do we mean by science-based? What scale are we using? Is it a sliding scale? Is that appropriate for the particular topic that we are trying to address?

DR. FEIGAL: That is a very good question. One of the reasons the approaches are different is that we have multiple sets of laws and different approaches were taken at different points in time and different features were added.

The device paradigm is actually not a sliding scale. It is a sort of a step scale and when a product is classified as a Class I device, the evidence that is required is what is known as general controls. General controls simply consist of having a well-manufactured product that meets certain product that meets certain manufacturing standards and the reporting system for detecting adverse experiences and corrective actions and plans and being willing to submit to that.

Class II is the middle level, where there are special controls. Now, sometimes the special controls are engineering. Other times, they are clinical. They

are really done very much case by case. There are some Class II's where some clinical evidence is needed. It really depends on the device, whether the issue is going to be safety or the issue is also effectiveness.

You have to remember when you are dealing with a predicate, you are really trying to establish that you are substantially equivalent to another device, but it has to be for the same claim and that is where we get into some of the difficulties because in addition to having complementary and alternative devices, we also get some alternative claims, if you will. We get some claims that have never been made before or that are made in a way that is harder to verify.

For example, you will hear products, I don't know if a device has this claim, but I have heard this claim probably for dietary supplement in Joe's world, a claim of promoting something for prostate health. Well, what is the endpoint for prostate health?

So some of the discussions when you engage us are, well, what would be demonstrable as scientific evidence that would allow you, you know, to provide some evidence that the product did something like that? But

the interesting thing about the device world is that the evidence is done on a case-by-case basis and on whether or not you are trying to establish that you should be marketed because you are an alternative to something, which is already legally marketed or whether you are something that is novel.

The difficult thing for devices is that the way the law was written, novel things became automatically Class III, which required a PMA of the highest standard. The relief for that was that in the modernization act, they allowed a reclassification process for something that didn't have a predicate, so that it could be introduced through a process called the de novo process at a lower classification, much like Class II.

DR. JONAS: I guess maybe I misunderstood or perhaps I misdirected my question. My question was: Is something like this, okay, step programs, sliding scale, what ever you call it, been discussed as a potential approach to dietary supplements?

MR. LEVITT: Well, I think No. 1, in terms of dietary supplements, since most products do not come to the FDA, only the new ones after the law was passed and

we got, what, about 15 or 20 of those maybe a year. That testing is all done totally outside of our purview. So, it hasn't been felt to us that it is our necessarily first job to go out and try and establish what testing ought to be done in those cases.

We are looking at that area for new ingredients that do come to us, and I really feel we need a little more experience with what we have got. The legal standard is, it can't be a significant or unreasonable risk, but of course that is a very judgmental standard.

So I think we need to learn some by experience, but ultimately one of our items is to come out with guidance on what is the testing needed for that.

DR. JONAS: Do you think it is possible to come up with some kind of stepped approached based on safety and efficacy?

MR. LEVITT: Oh, sure.

DR. JONAS: Similar to what goes on in devices?

MR. LEVITT: I mean, logically, the answer is yes.

DR. GORDON: Tom, and then Joe.

MR. CHAPPELL: I am delighted to hear all I

have heard. Thank you very, very much. It is really wonderful.

The strategic plan, page 13, looking for partnerships for two-way cooperation. I really appreciate that aspect. Again, very attitudinal and cooperative.

I wanted to ask you, though, if you could give us a little bit more about your vision for being science-based, as you progress in your goal to effectively implement this as law because I just want to say the reason DSHEA exists is because it is a place that occupies a reasonable zone, short of a drug.

Could you, within that area of sensitivity, just explain your vision for being more science-based?

MR. LEVITT: Well, I think the vision very generally is to be sure that there is, you know, a reasonable kind and amount, as you say, sliding scale for the kind of product, that is enough to convince consumers that the safety is there, that the claims are substantiated. That may be overly simplistic, but I think that is all that is being asked for.

MR. CHAPPELL: We know how much of a given herb

Adverse effects

Drug interactions

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to put in as a dose and we know that that is based on a great deal of research done by others. Is that what we are --

MR. LEVITT: I will take off my government hat. If I am a consumer going and buying this, I want to know or have the belief or have the confidence that somebody has done the testing, showing that the safety is reasonable, showing that the claims, whatever it says is at a high likelihood that that is going to help me for those purposes, but there is testing behind that.

To me, without getting into the drug standard of adequate and well-controlled trials and the device standard of balanced scientific evidence and all of that I think it really is what is scientifically persuasive and applicable in that place for that kind of product. You have products that have a history of use. Then you know you are going to have different and lesser needs than in other places.

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Drug interactions
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DR. GORDON: Okay. Thank you.

Joe and then Charlotte.

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DR. GORDON: Okay. Thank you.

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DR. FINS: Dr. Feigal, I want to follow up on the issues of safety and the tracking issue of an

approved device that goes to market and then is being used for an indication, with perhaps a sicker or more vulnerable population for an indication that was never intended for it to be used. How does that get onto your radar screen?

It is an especially, I think, complicated problem because of the federalism issue and what the states regulate, practitioners and you guys regulate devices and some of these practitioners may not be licensed. So, who is regulating that off-label, or that is probably the wrong word, for the use of these technologies?

DR. FEIGAL: No. Off-label isn't bad. I mean, that is a fairly good description of what some of these uses are.

We hear about things in a number of ways. There is a common reporting forum for adverse experiences for all products. So, we hear about some things for Med Watch. We will often hear from practitioners, who are upset about something going on in their community and will report something.

If someone has an approved device for which

they have collected evidence and someone is marketing something without clearance or approval, often they will refer that to us, particularly if there is advertising. Often, advertising will be brought to our attention by our own scanning advertising or increasingly difficult problems trying to watch the web.

So, there is a variety of different ways that these issues come in and then we do have to go through the process of deciding is this something that is being promoted by the manufacturer? Sometimes there is a distributor that has put together a new use for a product and is promoting the sales based on that.

Sometimes it is a practitioner. So, the overlapping jurisdiction does make it difficult, but more often than not it is sort of does fall to us and then we try and do follow-ups through our field staff, through warning letters. If we feel there is an eminent danger or safety problem, we have the authority to seize and, in other words, promptly remove products from the market.

DR. GORDON: Charlotte.

MS. KERR: I find your presentation to just be incredible and also the challenge you have. I respect

the work you have done, all of you.

At the same time, I am very perplexed and I want to go to your job, Dr. Levitt, specifically as your focus as director of food safety and talk more about food and not so much about the dietary supplements at the moment. I think I want to talk at almost, I don't know what level, but a third grade level and I want to say, number one, what is the definition of "food"? I want to say something about what our homework is here tomorrow, in particular, which is to talk about a world view that informs what we are about and historically what has happened as we moved through in healing and science.

I look at your example of Olestra that was submitted and how it was put forth as an example of the center's commitment to maintain food safety. I know this is an enormous conversation, just as I think food is probably the basis for all of our conversations here in healing, all the basic elements. Water is the basic nutrient, which is a food.

I wonder how does world view inform what you are doing? For example, issues that are coming up in food, like Olestra, you know, how is that a food? What

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if we had an ecological paradigm? I don't know that we would be able to put Olestra into the paradigm as a food.

I wonder about the issues of the Franken [ph] food issues in Europe, you know, and seeing how you are so committed and all of us here honorable in our endeavor to restore and maintain the vitality of Americans, how are we thinking about food?

How do you do that?

MR. LEVITT: I have another whole presentati on that.

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DR. GORDON: We may ask you back again to do it.

MR. LEVITT: That would be fine.

DR. GORDON: Because it is, obviously, a really important subject.

MR. LEVITT: I think, number one, is that I think increasingly, although I suspect over time there are blips up and down, depending on what is visible ont he horizon, but at least in the decade of the mid to late 1990s, the whole issue of food safety has become just a paramount concern.

MS. KERR: Absolutely.

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MS. KERR: Absolutely.

MR. LEVITT: The incident that happened in the Pacific Northwest about 1993 in the Jack-in-the-Box with the hamburger, where several kids went in for a hamburger and came out not alive, that was a watershed event. I call it the thalidomide of food safety.

That has brought about really very revolutionary changes throughout the food safety systems and has brought the whole issue of pathogens and food safety from microbiological hazards very much to the fore; whereas if you went back a decade before, there was much more focus on chemical hazards. You remember alar in apples and pesticides and cancer, quote, causing agents in the food supply.

But I think the world view is that consumers have a very high expectation that food is safe. That doesn't mean absolute safety, but it is a pretty high degree. You see this a lot with the foods derived from biotechnology. We ourselves question why is this so accepted in medicines, some of the real breakthroughs, but not in foods. One of the responses we get is where is our benefit. You know, if you don't need to use pesticides, that is a farming benefit. That is not a

consumer benefit.

We have a very high expectation for we want foods to be safe. That doesn't mean we know they will be but that is our expectation. So, we had a whole series of programs designed to, you know, come as close to there as we can. Well, at the same time, the CDC puts out estimates that for food-borne illness we are seeing 76 million cases of food-borne illness a year, 300,000 hospitalizations, 5,000 deaths. I mean, those are compelling and sobering statistics, which has launched really an entire farm-to-table war on pathogens by the Federal Government, state government, private sector, consumer groups. Everybody has been thoroughly involved. But it starts with a very high expectation of safety.

I know we are over. I want to bridge into the previous discussion because I think one of the areas that with experience we need to hone in on more is what is the expectation of safety for dietary supplement products. For Olestra, for a food additive, which Olestra is by law, the standard in the law is a reasonable certainty of no harm. That is viewed as a very tough standard to meet to give that high assurance.

The standard in DSHEA is a different standard. I suspect it was not a coincidence of what is called the significant or unreasonable risk. What exactly does that mean? The law doesn't tell us. What is reasonable in the context of a dietary supplement that people go and choose to have, as opposed to, if you will, ubiquitous within the food supply.

These are questions we are going to have to come to grips with as we move forward in order for dietary supplements to help answer your question, which is how much is enough? What is the degree of confidence and safety that is needed? To what extent do benefits play? Our statute really is silent on benefits for dietary supplements. It speaks only in terms of safety. It does not speak in terms of benefits or effectiveness or any of those terms.

Yet, they are promoted for a utility of some kind and consumers want to know what that is and does that affect our safety assessment or not? There are different views on this, I can assure you. But I think in terms of world view of food safety, very high expectations and the need to define and understand where

within that are dietary supplements.

That is the best I guess I can give you in a short version.

DR. GORDON: Charlotte, I really appreciate your having brought this up. My feeling and I sense the same thing around the table is that we would really like to continue this conversation as time goes on in future sessions. Because I know we can't cover it all now and we really so much appreciate your being so present and forthcoming in bringing us the information and engaging in this dialogue.

We would like to both ask for any thoughts y have in the interim and then we would like you to come back and work with us again. I am not sure whether it going to be public information or at one of the sessic if that is okay.

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MR. LEVITT: Whatever is your pleasure, we will do our best to help you in your mission. Your mission is hard enough. We will do whatever we can to help you.

DR. GORDON: Thank you very much.

I suggest we stretch for about three minutes while the next panel comes and sits.

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[Recess.]

E V E N I N G S E S S I O N

DR. GORDON: We thank everybody for bearing with the time. The information is very interesting. There is a lot of it and through a little crossed signals, we wound up going a little bit behind time. Because of that, Dr. Winn, who has an appointment in a little while, is going to go first and we will ask him a few questions and then we will listen to the other three speakers and ask questions after their finished.

So, Dr. James Winn.

Session VI: Research in the Regulatory Framework

DR. WINN: Thank you very much, Dr. Gordon.

My name is Jim Winn. I am the executive vice president for the Federation of State Medical Boards of the United States. I welcome the opportunity to meet with you today. My position in this whole controversy perhaps is a little different than any of the other presenters that you have heard before or will hear after in the fact that I represent the regulators and perhaps not directly involved in any kind of research agenda.

Having said that, though, I think that what I would share with you today might have some importance to

you and the opportunity for you to ask questions to me as a representative of all the medical licensing authorities in the country, would be important also.

I had originally prepared a power point presentation for you today and so at the last minute sort of changed format. So, you have some handouts that really reflect the previous presentation. I hope that won't be too distracting.

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What I would like to do is sort of skip throug the first part of that presentation, which basically lay out the background for the Federation of State Medical Boards. But I would like to highlight a couple of areas and that is to reinforce the medical boards' responsibility to the public.

That responsibility is to protect the public's health, safety and welfare and to do that by assuring that they are protected from unqualified and unfit physicians.

This is accomplished primarily by assuring that only qualified individuals are allowed to render medical services to the public and that rules and regulations are developed and standards are enforced for medical

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This is accomplished primarily by assuring that only qualified individuals are allowed to render medical services to the public and that rules and regulations are developed and standards are enforced for medical

practice. Then when it becomes necessary, to take an appropriate action against a licensee in the interest of the public's protection for grounds of unprofessional or incompetent or unlawful practice.

The physicians have a number of responsibilities if they choose to practice medicine. I would just mention that perhaps the most importantly of that is to maintain professional standards, to practice within the ethical and practice standards of the profession and to maintain professional behavioral in conduct.

To do that, you have to know the Medical Practice Act in the state in which you have chosen to practice. Now, that sort of leads us into CAM and the concerns of the regulatory bodies, at least those that regulate physicians. There is certainly no argument about the proliferation of complementary and alternative medical practices. When we have a rapid proliferation like that, there are certainly some concerns that get raised about whether or not the public is being exposed to unsafe practices.

Many of the practices and proposals, therapies

and so forth tend to lack scientific research or clinical validation. There is not an easy way to determine whether they are safe and effective for the public. Unfortunately, there are some of these practices that are outright fraudulent and deceptive in their nature.

There may be multiple reasons for the proliferation of these therapies. On the one hand, I think many people say, well, there has been a demand by the public for these therapies. But there also perhaps underlying some of this has been the willingness of traditional practitioners to embrace some therapies, particularly some of the marginal therapies because of the effect of managed care on their financial status and practices.

Also, I think, the technology situation, where there has been a marked increase in technological advances in medicine, has created a greater divorce between patients and their practitioners, is something that they really expect. They expect to have a relationship that is lacking. In many cases they feel that they have been disempowered in their own medical care.

I think the medical boards basically are concerned about adverse impacts on patients and, unfortunately that is our job, to look at the adverse side of it and try to make sure that doesn't happen.

There are three basic areas of harm that we might identify. One is economic harm and that is basically just where it results in a monetary loss but there is no real health hazard, where the therapy is just totally ineffective or has no reasonable expectation it is going to help. But it doesn't harm anybody.

Indirect harm would be that which while not providing harmful therapy, results in a delay of appropriate treatment for a serious illness. Of course, then direct harm, which would be directly linked to the treatment provided the patient.

The federation in 1997 convened a special committee that was called "The Special Committee on Questionable and Deceptive Health Care Practices and the objective of that committee was to provide guidance to medical boards in evaluating, investigating and prosecuting cases regarding questionable and deceptive health care practices for which they had received

complaints about.

The report basically provided a guide for how to assess both conventional and unconventional practices. There was not a distinction between whether this was alternative or complementary, but, in fact, any such practice that was complained about would be evaluated in sort of the same light.

The bottom line, as far as medical boards are concerned, that what whatever the practice that is being given or the therapy that is being given. The physician must, in fact, abide by the rules of good medical practice. There is not a release of that simply because the doctor is providing a different type of treatment than what has traditionally been provided.

In your notes, there are some lists of some of the elements utilized in the evaluation of health care practices. I am not going to spend time this evening on going through those, although you might have some specific questions later about that area. The federation has moved forward after that research report that was issued a few years ago.

This committee has continued to look at and

review on behalf of medical boards different practices and to provide information about those practices so that the medical board remained updated on current information regarding practices that they were receiving complaints about.

Now the federation will move forward to develop guidelines to assist state medical boards in educating and regulating physicians who use CAM in their practices. In other words, we want to have the medical boards be able to tell their licensees what the expectations are if they are practicing in an integrated environment or co-managing patients with licensed non-physician alternative providers.

So, the objective of this would be to have CAM utilized in a manner that is consistent with safe and responsible medicine. We believe that those guidelines will be substantially complete within the next six to eight months and will be promoted to the medical boards for their usage.

Now, part of the questions that were posed for me from this group was does the medical boards or the regulatory community view things, such as office-based or

practice-based research. I think that medical boards will expect physicians who engage in research, either in an institutional setting or a practice setting, to fulfill their ethical responsibilities and they will apply guidelines, such as those that are promoted by the American Medical Association, that a physician may participate in clinical investigations, only to the extent that those activities are a part of a systematic program, competently designed and under accepted standards of scientific research, expected to produce data, which are scientifically valid and significant.

There is this issue and I think it will become a bigger issue for medical boards of the disciplinary sanctions to be imposed against individuals who engage in investigative fraud. Our counterparts in Western Europe have already had to address these situations.

Four medical boards have already adopted rather specific policies; Illinois, Kentucky, Nevada and Texas. These are basically based on what I said before that the physicians are obligated for good medical practice.

My time is running short. I won't dwell on these other areas, except I would like to ask this group

to focus on our concerns and that is that we need, as medical regulators, good solid information about alternative and complementary therapies. Things like chelation therapy, that has been around for a number of years and as you know, has created a great deal of controversy with medical boards.

Despite it being around for a long period of time, there is almost no credible evidence that it effective for what it is claimed to be. In fact, over the past several years, the claims of effectiveness have actually increased. What we need is good research that would tell us whether or not this is effective because quite honestly if it does what it is said to do, then medical boards should be holding physicians responsible for not submitting patients to that before more invasive procedures are used.

If, in fact, it doesn't do that, then doctors should be held accountable for using a therapy that has no benefit but has the potential for patient harm. So, I think that we would want you to focus first on a research agenda that helped identify the effectiveness of those therapies, which carry some risk to the patient, but if

they, in fact, are beneficial and the benefits outweigh the risks, then they should be embraced.

If on the other hand they have no significant likelihood of effectiveness and they have a likelihood for patient harm, medical boards should hold physicians accountable for exposing patients to that risk.

I have run out of time and I thank you for your attention and certainly I will answer any questions.

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

Are there questions for Dr. Winn?

DR. LOW DOG: Do you have any idea of how many complaints have actually been registered by patients towards physicians, who are practicing integrative or CAM therapies?

DR. WINN: No, I don't have that information with me. The federation keeps track of actions taken, but not complaints received by the different medical boards. So, I don't have access to that information.

DR. LOW DOG: Do you have any idea how many actions there have been?

DR. WINN: I don't have it with me, but we certainly could go through that. I mean, I could do a

quick search of the database and let you know. But I don't know off the top of my head how many actions have been taken.

DR. GORDON: That would be great.

Wayne and then Conchita.

DR. JONAS: I really appreciate your comments. I think there are a number of issues that you bring up in terms of access. We hear access, access, access and along with that has to go accountability. It is kind of like safety and efficacy. They kind of go together. I am surprised that some of the individuals involved in complementary medicine haven't said wait a minute. I don't know if we want to be integrated or not because then evidence, accountability, scientific rigor, as well as health care management will then become ours, which may or may not be very useful.

I think it would be extremely interesting and useful to try to at least get some input as to whether there is a way in which some of the areas that you all are concerned about, the specific practices could get on the research agenda in terms of what public money ought to be investing in, such as chelation therapy. I mean,

this thing has been floating about for years and we still don't have information about it. So, you know, we talked about how does the public get input, but I think it would be extremely useful to figure out how can some of the state regulators or some of the people that are out there looking at these practices from a regulatory point of view also be brought into helping in terms of the research agenda.

That would be, I think, extremely useful, at least for me and perhaps for the board. The other issue that probably someone else will bring up is also how to deal with a practitioner that is doing something that perhaps us from a research point of view want to investigate and, yet, it is considered a non-standard or a fraudulent type of practice. You know, how do those intersect.

DR. GORDON: Do you want to pose that as a question?

DR. JONAS: I could pose that as a question, although you could do it better. I mean, the issue is is, you know, there is a practitioner that is using, perhaps, some kind of unusual treatment that has claims

and wants to be involved in that and, yet, it would be perceived from the state point of view as being fraudulent practice and that person should be disciplined. So, a lot of practitioners, of course, would withdraw from participating in research because of the perceived risk that that might then expose them to.

DR. WINN: Well, let me see if I can answer that. I think that is sort of one of the objectives that we want to accomplish with our committee in developing guidelines is, for instance, if a research project is going to be undertaken in this area and the individual is not part of an institution. So, the institutional review board is not involved.

How does that occur? Well, probably the medical board should meet with that individual, understand what the research protocol is and how this will be accomplished so that the patient's safety is involved. One of the things that all sort of gets mixed up because some practitioners will tell you, well, I am doing research, but then you look at it and the patients haven't signed a consent form. They didn't know they were part of a research project and they were paying for

therapy. So, that sort of begs the issue of really what are you doing here.

I think it ought to be on the table, clear and easy to understand for everybody involved and I don't think a practitioner, who is legitimately doing research is going to have any kind of problem.

DR. GORDON: I want to just follow up for a minute and then come back to you, Conchita.

I am sorry you can't stay because I would have loved for you to be able to hear some of the people who are grappling with this issue. So, we will send you some transcripts of what happens.

We have people who are trying to do research. They are perfectly happy to have IRBs to constitute them or get them, but they are in private practices and they are lacking, sometimes they need help with expertise from others. Sometimes they need economic health to pull together the data or do the analysis.

I am wondering if you can think now or, you know, in these next weeks and months of some ways to facilitate this process so we don't get into a situation that I know has happened, where people who are doing

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research that, you know, they fully intend to study, sometimes they have IRBs, sometimes they don't have IRBs. They are genuinely committed to the research. They are not doing harm. There are no patient complaints and, yet, they run afoul of state medical boards.

So, I feel we need to grapple with this really in a very intimate way because it is a major problem. It is a major problem for a small number of people, but our thought has been that we might get even more interesting research if we can figure out strategies for working with us.

DR. WINN: Well, we would be happy to work on that because I don't think that medical boards are interested at all in being a barrier or obstruction to legitimate research. What we are interested in is making certain that the public and patients are protected. So that consequently that is the number one priority and then the second priority would be okay if you are protecting patients, let's go ahead and figure out how you can do the research, but you are not putting patients at risk just because we need to know something. That would be, I think, inexcusable for practitioners to do.

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DR. GORDON: I appreciate your answer.

Conchita.

DR. PAZ: My question comes just to develop that a little bit further, is how to get more states to develop CAM policies. You just mentioned four here, but that is such a pitiful amount that how can we provide that more.

DR. WINN: We are an organization that has no authority to make every state endorse that, but what our history has been, for instance, with pain management and so forth, that once we put out a very reasoned process of policies and so forth, the states will, in fact, develop that. So, what I would tell you that probably in the next 24 months, you will see a significant number of states have policies about CAM therapies.

DR. GORDON: Thank you.

Joe.

DR. FINS: It is the exact follow-up. I was going to compliment the federation on its recent work on pain management. One of the upshots of that, there has been a lot of state medical boards that have actually looked to pain experts to be on the boards to assess not

only do they have the therapeutics, but also concerned with the research aspects.

Is that something that you would consider as being a beneficial recommendation, to recommend CAM participation on medical boards, you know, people like Dr. Jonas, for example, to sit on a medical board in his state to help you guys sort out whether or not --

DR. WINN: Certainly, and there would be no objection to somebody of Dr. Jonas's statute, but the process as you probably know is really politically gubnatorial appointments that go to the medical board. So, there are people who engage in CAM therapies, who currently sit on medical boards. Many boards do have practitioners who have practices primarily of a CAM nature.

But I think the suggestion is appropriate that medical boards should, in fact, have if not people on the board, consultants available to them to assist in their evaluation of cases and any kind of complaint that comes forward.

DR. GORDON: Thank you very much. We really appreciate your coming and we hope we will be able to

continue -- do you have your hand up?

DR. JONAS: I just want to follow-up on this just a little bit. I mean, this is not necessarily a solvable problem but the variety of opinions and types of regulations that are in our states really make it extremely difficult to come up with any kind of uniform policy because there are states that have attempted to or even perhaps will see successfully eliminated, the whole regulatory aspect in terms of this. The Minnesota law, for example, is a real issue in terms of what actually is going to happen with that. So, there is wide variety of attempts to address this.

DR. WINN: Right. I agree and that is the reason we need the national effort that we are trying to --

DR. JONAS: Right, and since this is a federal commission, it would be extremely useful for us to think how can we appropriately address that in a way that does not interfere, obviously, with state rights in terms of authority --

DR. GORDON: Thank you for coming and being with us and we hope we will continue the dialogue.

DR. WINN: Absolutely, Dr. Gordon.

Again, my apologies to you and the Commission for my requirement to leave early for another meeting.

Thank you.

DR. GORDON: Thank you.

Next is Dr. Floyd Leaders.

DR. LEADERS: Thank you very much for inviting me to come.

We are going to have a little shift of paradigm here and go just about as far to the other end of the spectrum as we can get. I work for a profit-making, hopefully, organization that is interested and committed to bringing mechanical products through the FDA as drugs. We are speaking to exactly what you said, why would anybody want to do that.

The reason is very straight forward, that we believe that botanical products, the natural products, have much more potential than just for over-the-counter products or products that can be sold in the DSHEA marketplace. It would be very hard to sell a product for the treatment of cancer in a food store. So, that is the reason.

I was asked to speak on three different aspects. The first one was how do the current regulations impact on doing research on botanicals. Keep in mind that what I call research, you probably would call development. We are doing research within a regulatory framework. They even have a name for it. It is called regulatory science. That may be an oxymoron, but it is, indeed, the environment in which we work.

Within that framework, there are several things that have inhibited what we are doing from the private sector purpose. The first of these, I will say is money and I think you heard that from both Dr. Woodcock and Dr. Levitt, particularly Dr. Levitt in the dietary supplement area.

There are not enough resources to go around to do the things they have to do. The other major thing, however, is mind set. Now, this is particular for our industry but I have a feeling it may bleed off slightly into other areas also, that we have a very good example here, the botanical guidance document, that Dr. Woodcock talked about.

First, let me say that is a giant step forward.

I am extremely pleased to see that come out. We have been working on it since 1994 and I am very pleased to see it because now we have something we can look at. It scares me a little bit that she says it is a cookbook. We will come back to that later.

But mind set is extremely important in that document. I don't know how many here have read it. I have just spent the last week involved in more telephone calls than I have any desire to be because we have responses to get in by next Tuesday. But this particular document is a very good start, but let me put it in context of our group of people, that it basically takes the new chemical entity paradigm and overlays it with the botanical requirements, which some of them will be very difficult to do and other ones will not be so difficult.

We can get into that more. I just want to hit the high points and if you have specific things you want to talk about, I am available, obviously.

The second one is how can research methods and approach be expanded to address the safety and efficacy. One thing that has not been mentioned here at all and you will not hear it mentioned probably is to lever off a

previous human use. I can't say that strongly enough. That is the one difference between the botanicals that we are working with and other people are working with and a new chemical compound as just been synthesized that has never been in man before, women, too. Never been in humans before.

But we need to learn how to evaluate human data and with all due respect, the FDA does not have enough personnel of the right kind to really know how to evaluate that. We are still in the position of looking at animals to predict human safety when we can't have human safety in humans, the species of choice.

In the guidance document, I will use this as the specific example, to get into the clinical trials, you can get in fairly easily without a lot of the things that are necessary. But by the time you come out at the end of Phase 3 clinical trials to get NDA approval, you have effectively done everything that a single chemical entity has to do. We have thrown away all of the knowledge we may have about how this works in humans.

So, my plea would be, and I will come back to this, my plea would be to consider how the resources can

be brought to bear to allow previous human experience to count. Maybe that can apply to other things as well.

Last is should changes of any be made to the regulations? If so, what should they be?

The main one is, perhaps, proprietary, intellectual property rights. I am going to offend some people from other places around the table, but I don't think even NIH has enough money to totally fund the development of this whole group of products. It is going to take private sector doing it. What motivates the private sector to take risks is the chance to make a profit off of it at some point. Whether they make too much or not, I won't go there.

But there has to be some kind of return on investment. I told you this was going to be a paradigm shift.

We need to establish, if we can't get patent protection, because you are here -- I am probably the only person here not asking for money because I think our industry has to fund this. If you have a way to give it to a private company, I think we would take it, but I don't really see how that can be done.

So, I am not asking for money. But I am asking potentially for the impact you could make into some of the regulations and some of the looking at these, that if we cannot get patent protection on these products that have been around for a long time, is there any way to grant regulatory exclusivity that would allow a company to justify making an investment of $150-, $200 million to bring a product through all of the quality control, all of the manufacturing, all of the research hoops that we need to go through to really show safety and efficacy, so they can't be beaten over the head.

The third thing, the change in mind set we have already talked about. I want to talk about DSHEA. Now that I have been involved with CDER, I will talk about CIFSAN [ph]. There is a major impediment in the Dietary Supplement Health and Education Act to inhibit research.

When the act was passed, they were looking at these products as foods, an orange is an orange is an orange. It may be green if it is from Florida. It may be orange if it is from somewhere else. Botanicals are a very weird breed. They are the group of products that

basically test the law. It is unfortunate because they are manufactured like a biological in that they are manufactured under heavy process control. They are sold and advertised as foods, dietary supplements, by congressional fiat. They are used by the public to treat disease.

We all know that everyone here drinks coffee in the morning because they like the flavor. You can't say it stimulates because that would make it a drug. So, that is just an example. The problem with botanicals, and this is a four line sentence, the process defines the product.

Under DSHEA, you can take data from a product made by one entirely different process and use it to support your product and that can be made by a different way. It is like using data on grapes to justify wine; quite different ways of looking at it. This has been overlooked in the law.

I don't think the industry wants to go back and revisit that because just like having a constitutional convention, you are never sure what would come out. But if you want to ensure research, give people some chance

of getting paid back for doing the research. It is that simple.

Thank you.

DR. GORDON: Thank you very much.

Next will be Mr. Robert McCaleb.

MR. McCALEB: Thank you. I would like to thank the Commission for inviting me to address you today.

I am going to start with just a brief response to my friend, Floyd. He and I disagree a little on this. When something has been used for many, many centuries for particular medicinal or health beneficial use, it is difficult to give the rights of exclusivity to any one company for that. We don't believe that anyone should ever have the right exclusively to make a claim for ginseng or garlic or any one of the other 2,500 or so herbs that are sold in this country, unless they can actually invent something about it.

I also think that in terms of the application of a claim to research, the research must support the claim being made for that product; that is, if the research is on a particular type of extract, I agree that only that type of extract should be allowed to make a

claim that is based on that research.

Let me talk a bit about the state of nature products research in the United States. In the last 40 years, we have essentially shut down natural products research in this country. We have failed in the last half of the last century to approve a single new drug from plants unless it was produced as a single mono-substance, such as Taxol, and even that had some protection under the law to give it some exclusivity it might not otherwise have had.

Because of that, these things fell into disuse and because of that, they fell out of the pharmacy and medical schools and out of the organizations that grant money to do research. There is a cascade that has really shut down the research and approval of botanicals in this country for use in health care.

One of the tragedies there is that so many botanicals are used for preventive medicine or for health maintenance. In the absence of the ability of our Food and Drug Administration to approve preventive medicines, we really literally only have a few, things like sunscreen and motion sickness pills. Those are really

two of maybe only four preventive medicines ever approved for over-the-counter use by the FDA.

So, in the absence of approved preventive medicines, we use dietary supplements for health maintenance, for preventive medicines. DSHEA works and I think that is one of the first things I would like to point out as a part of my message is that there is more research right now ongoing and more completed in the United States or funded by American companies since the passage of DSHEA than has been done in decades before.

Why is that? It works in exactly the same way that it has worked in incentivizing European research. The ability to make a claim on a realistic threshold of evidence is what drives companies to do research and it is also what drives the public sector to invest in research as well.

So, we have seen in this country what we have seen in Europe. Just the ability of a company to make a claim or to achieve a claim without a $200 million expenditure has driven research so that companies can make the claim to doctors and pharmacists that their product is clinically researched.

In addition to research incentives, we now have more informative labels on these products that give much better information to the consumer about what the product is intended to do, better third party information. Although there is a confusing level of information out there, there is certainly some very high quality information that has been produced since DSHEA and because of it.

We need to improve the path, I think, to stronger claims. It has been suggested that one of the ways to do that might be to allow the elimination of that disclaimer on a DSHEA regulated label if a certain threshold of evidence is achieved for it or the ability to use certain types of research in advertising or labeling a product.

If a company did research on its own product, clinical research on its product, maybe it would be allowed to make a stronger claim than a company that was sort of piggybacking on that research or using what they called borrowed science.

One of the ways to a stronger claim is over-the-counter drug status. Now, this is something that was

a very strong recommendation of the Commission that I sat on, the Commission on Dietary Supplement Labels. The FDA did not take us up on that recommendation, but many people within and outside the agency have praised the model of the German Commission E, which was actually very similar to our own over-the-counter drug review process.

That is, we had panels of experts, who sat and discussed what they knew and what they seen in the evidence on particular drugs and how they might be approved. They approved those based on their opinions of that evidence. There was no gold standard and in some cases things were approved with not a single clinical trial. We have a real mystification of that process in the United States. Few Americans probably recognize how little evidence was required to achieve over-the-counter drug status.

But all dietary supplement products are sold over the counter. They are not prescription products. So, we think it is a legitimate model. I am not suggesting that they be removed from dietary supplement status, but only that there be a natural products OTC panel empowered to look at natural products, pull in

experts in specific medical disciplines and make some decisions about the safety and efficacy of the substances sold now as dietary supplements that could then make stronger claims as over-the-counter drugs.

I think we need to increase the focus on traditional medicine, recognizing that DSHEA leaves that out. Many of the forms of traditional or folk medicine used in this country are based on historical, cultural information or on energetic principles that don't really fall within the scientific model that DSHEA embraces.

These are often less static than the European phyto medicines that have become most of our dietary supplements in this country, but they are used by more people worldwide than any other form of botanical medicine and they are used by most of our minority populations; African Americans, Hispanic populations, Asian populations.

As Dr. Federman said, anecdotal information can be good. When you have anecdotal information, that is, experiential information that comes from trained observers over generation after generation of humans, you have something more than just someone saying I think this

stuff helped me. You have a higher level of evidence. I think that is what Dr. Leaders was alluding to also, that we need a way of looking at historical information and using it in our evaluation of efficacy and safety.

We need more international outreach in terms of accessing the information from European and Asian clinical practice. Remember now, some of the things that are being sold in our pharmacies and grocery stores have been used under physician supervision for decades now in Europe. We need to get access to the clinical experience that those physicians have and incorporate that into our decision-making process, too.

There is also safety data from decades of pharmaco-vigilance programs in Europe that so far we have been unable to access. I don't know of anyone else who has been successful there either. But I would really love to see this group make an effort to get at that pharmaco-vigilance data that every European country requires of its phyto medicine manufacturers. I think this would be very useful information for the American public.

Information systems, we need a greater focus on

information systems. There is confusing information, contradictory information and there is misleading information on both sides. There is hype on the marketing side and there are scare stories on the media side and on the government side. We really need to cut through that maze of information and try to get information, especially for consumers and practitioners that is quality evaluated, so people can trust the information and utilize in their decision-making process.

I would certainly include in that, as a specialty library, that we need more library funding and collaboration to utilize the resources that are currently untapped. There are a lot of people in this country who have specialized collections that could provide a greater level of information than we currently have.

I would advise extreme caution in public statements by our regulators and scientists. We have heard some already, sort of overstatements about ephedrine adverse reactions. The birth control issue with St. John's wort has been a subject of speculation, but the truth is there is no direct evidence that St. John's wort affects the effectiveness of birth control at

all.

There are two anecdotal cases of breakthrough bleeding, but that is common with birth control anyway. So, really, that is something that someone found in dinavir [ph]. Cyclosporin activity was affected, speculated that it was a cytochrome P450 effect and then went from there.

Finally, I believe true cooperation and collaboration between government, academia and industry can help us all through research and education toward a more appropriate, safe and effective use of complementary and alternative health care modalities.

Thank you.

DR. GORDON: Thank you.

Dr. Anthony Rosner.

DR. ROSNER: Thank you very much. I want to thank all the panel members for inviting me to share a little bit about our background and sharing some real concerns and possible solutions to alternative medicine research.

I particularly want to thank the panel members for establishing such a congenial and inquisitive

atmosphere. This has very much the feeling of the Chantilly meeting some eight years ago. So, as an alumnus of the esteemed class of 1992, I am happy to outline a little bit of what the foundation has done and talk about barriers.

Now, I did list the barriers and I guess the sort of Audubon field guide, which is at your disposal. There are ten critters here that I think you need to be aware of and I also listed 13 possible solutions. So, please bear with me. Strap yourselves in and I will try to do justice. But forgive me if there is a little bit of the hit and run aspect to what I will be talking about.

Our foundation has been around for 50 years and it has essentially bootstrapped about 175 projects in the area of chiropractic. We are very pleased that the first federal funding that was talked about earlier by Bill Meeker really came at centers that had been funded by us initially. We have also supported some 125 research fellows, maybe 25 residents.

As you probably are aware, 25 years ago, chiropractic research was vastly underdeveloped and

appeared very much as an oxymoron. It was in 1975 that a conference at the NINDS concluded that, this is a quote, "There was little scientific data or significance to evaluate this chiropractic clinical approach to health and the treatment of disease."

Since that time, we now have seen 40 randomized clinical trials supporting spinal manipulation, comparing with other treatments, meta-analyses and systematic reviews and multidisciplinary panels representing the governments of the United States, Canada, Great Britain, Sweden, Denmark, Australia and New Zealand. These have all expressed similar recognition of the robust evidence in support of spinal manipulation for managing low back conditions.

Well, this brings us to the problem of barriers. Dr. Federman had talked earlier, I guess, of savage prejudices and, unfortunately, these exist. Most of these do remain in place. Some of these have just been lifted, but I did want to go through this list with you.

No. 1, we have to talk about collaborative arrangements. This goes back to 1993. The Office of

Alternative Medicine required that researchers in alternative medicine collaborate with people from an orthodox medical background. These would be individuals familiar with conventional research methodologies.

Obviously, this was meant for educational purposes, to improve the quality of research, but my only cautionary note here is that if funds are not sent to alternative medicine research centers in great amounts, there is the risk of strangling some of the origins of where these ideas came from.

So, we have to be aware of an equitable distribution of funds and resources. Obviously, NCAM's establishment of specific research centers, chiropractic, that would be Palmer University and recent RO1 research programs, which individual researchers in CAM can step forward, these are obviously major steps in the right direction.

The second issue, domestic institutions, there have been a number of major milestones in research that have significantly lowered barriers to both the practice and research of chiropractic and these have been accomplished abroad. We talk about the low back studies

of Meade in Great Britain, tension headache studies of Dilsen [ph] in Denmark, the first randomized trial addressing colic. This is possibly a non-musculoskeletal condition, and this is in infants. This is in Denmark. Numerous asthma case reports and a pilot for randomized clinical trials from Australia to lay the foundation for future clinical trials, these are just a few of the outstanding examples. So, the requirement of many past federal programs restricting grants to domestic institutions only would represent an impediment to the accomplishments of potential research in alternative medicine, which recognizes no national boundaries and which has clearly benefited from additional resources available beyond American borders.

No. 3, composition and proceedings of institutional review boards, undoubtedly these are an indispensable component for ensuring patient safety and knowledgeability in the clinical trial. Unfortunately, from my own experience at a major medical institution, there have been instances in what a proposed randomized clinical trial that seemed to pass some preliminary scientific review, was rejected out of hand for what was

probably the harboring of anti-chiropractic sentiments by the head of the IRB.

Obviously, while implementing panels to monitor the behavior of IRBs may seem a bit excessive, the issue does bear further scrutiny in the event that viable and safe alternatives in the patient's interest fall victim to prejudice within an IRB. This leads directly to the fourth problem, study sections, for many of the same reasons I just talked about.

We need an equitable number of individuals within each study section of a grant proposal, who are familiar with and sensitive to the conduct of therapeutic regimes to be tested. Common sense dictates that as eloquent and sympathetic a presentation of the therapies to be studied be made to the study section as a whole.

Fifth, we have to talk about publication bias and quotas. There are examples of editorial bias and quotas, which have prevented the most robust of chiropractic research from reaching the necessary audiences. A headache study by Beline [ph], for instance, which was rated the highest by two independent systematic reviews, was denied publication in The New

England Journal of Medicine, Headache and Cephalgia, before it finally appeared in the Journal of Manipulative and Physiological Therapeutics.

Two years later, there are examples in which editorial comments to the principal authors of studies have clearly indicated that obtaining negative results, results for spinal manipulation was the criterion for acceptability. Thus, it is with dismay that I find two inferior and widely publicized studies of chiropractic, which did get published in The New England Journal of Medicine. These have been rebutted extensively elsewhere and to add frosting to the cake, there have been statements from two previous editors of this journal, offering little encouragement.

They have been quite biased with little qualification in their negative assessments of CAM.

The sixth point, this goes on to the press and the journals, this type of bias and editorial policy, obviously, has ramifications in what is actually stated in papers and subsequently published in the lay press. One study published in The New England Journal of Medicine, for instance, stated a conclusion that was far

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beyond anything supported by the data. Specifically, the study discouraged the routine referral of patients to chiropractic.

It said, "Given the limited benefits and high costs, it seems unwise to refer patients with low back pain for chiropractic or intensive therapy." This is to me an egregiously out of bounds statement for a scientific journal and, of course, when the lay press gets its on it, which they did, it only got worse and we saw such scare headlines as, "Study Targets Worth of Chiropractic," "Chiropractic Care Blasted in Two Studies."

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You can imagine this only poisons the atmosphere, inhibiting further research efforts, inducing third party payers to deny reimbursements for chiropractic services, in which the outcomes have yet to be definitively disproved. So, news releases such as these need to be actively discouraged and the public needs to be further enlightened as to research and potential of multiple modes of alternative therapy, not just chiropractic.

Mainstream versus alternative status of

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chiropractic, this is an unusual bird because when we talk about low back pain and headache studies, chiropractic has more or less moved into the mainstream category. Bill Meeker had called this the elephant in the room. But we have other types of interventions. We have other types of conditions for this intervention seems promising.

Here we talk about scoliosis, otitis media and infantile colic, to name a few. This I would suggest is the lion pacing in the wings, besides being the elephant in the room for mainstream practices.

Origins of mainstream medicine, No. 8, this is not infallible. The preamble to the five year strategic plan of NCAM says as CAM practices once considered unorthodox, are proven safe and effective by rigorous scientific investigation, they become part of mainstream health care.

This is certainly the way we would hope to transform good research into practice. Clearly, this would be the mission of NCAM, this commission and our foundation, but since only a minority of medical procedures have been supported by documentation, we have

to be wary that all procedures are, in fact, going to be supportive.

No. 9, paradigms. In The New England Journal of Medicine, chiropractic has often been confused with high velocity thrusting of the spine and this would reduce it to a one dimensional specialty of cracking joints. It represents much more of that. We are talking about the use of hot and cold packs, electrical stimulation, soft tissue procedures and nutritional counseling as other types of therapies that have been licensed.

The last problem that I will state, I will not talk about the solutions, these are in the handout, is the RCT, Tieraona Low Dog had asked about, other types of approaches. Here we have to appreciate that in randomized clinical trials, the placebo has inappropriately been represented. This is dealing with a sham procedure, which is some times confused as not having an effect at all. Meta-analyses outside of chiropractic have been misinterpreted such that depending on whose scale one uses, totally diametrically results can be obtained. So, it is a question of what values are

put into scales such as this.

The third and final example with pharmaceutical companies has to deal with antifungal agents in which one agent was inappropriately administered orally instead of intravenously and in this case there wasn't ever a chance for a fair comparison. Yet, you know, this was laid out as gospel.

So, in closing, I guess I want to just caution the Commission to understand that there are other types of clinical evidence, as David Sackett has pointed out, and I would wish that the Commission place far greater emphasis on cohort studies and case series in reaching its research goals rather than to assume categorically that they provide inferior guidance to the clinical decision-making than RCTs.

It should be quite clear that a well-crafted cohort of case series is really more informative than a flawed or corrupted randomized clinical trial.

DR. GORDON: Thank you very much for this extremely well-written, thoroughly-documented, written testimony. I think it will be extremely helpful.

For others who will be testifying, I think we

need to encourage people to prepare exactly this kind of testimony wherever possible because not only can we listen to you and talk to you, we can go and check it out for ourselves.

DR. ROSNER: I hope so.

DR. GORDON: Which is really very helpful. For any of you, we would appreciate any documented evidence, anything you would like to send us you think would further our knowledge, we would welcome.

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We have some opportunity for questions. Bill and Tom first.

DR. FAIR: I would like to clarify one thing with Dr. McCaleb. You said that in the last 40 years, there has not been a single natural product in the United States. Is that correct?

MR. McCALEB: Right, approved as a new drug.

DR. FAIR: Then you mentioned Taxol. What was the different situation with regard to Taxol that got Taxol approved?

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binblastine [ph], Taxol, captophecan [ph]. There are a few examples there.

Taxol was approved for one substance as a sort of orphan drug as I understand it, for one type of cancer, but is actually being used for breast cancer, which is much more common and would not have qualified it for that orphan drug protection. In any case, the point I was trying to make is that for complex botanical extract for anything other than a pure chemical entity, we have failed to approve any as new drugs since 1962 when the efficacy provisions were added to the statutes.

MR. CHAPPELL: Dr. McCaleb, thank you for your recommendations and I would like to explore a little bit more about the natural products OTC idea panel and so forth. You are suggesting that botanicals can have a sort of monograph equivalent that could be set up as a standard so that everybody could make the claim, so long as it was meeting that monograph.

Is that what you are envisioning?

MR. McCALEB: Yes. This was the unanimous recommendation of the Commission on Dietary Supplement Labels, that because botanicals and natural products are

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different and more complex than the single chemical entities that are commonly studied in health care, that a special panel should be empowered with pharmacognicists and anthrobotanists and the kind of people who specialize in this area.

Then unlike the model of OTC review, where you had a cough/cold panel and the different specialties, that this panel could then pull in those specialties as needed, bringing in doctors who specialize in a particular condition, to assist them in making decisions about a botanical or other natural product that was to be used for that purpose.

The point was to have a panel of experts, who were really specifically focused in this area of natural product health care, to sit on an ongoing panel and look at the evidence and make decisions.

MR. CHAPPELL: So, your view is we would have an upgrade of DSHEA that is short of an NDA or drug?

MR. McCALEB: Right. Certainly still the --

MR. CHAPPELL: In terms of claims.

MR. McCALEB: -- prescription drug process is still open to botanicals, but, yes, this would be a panel

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approach of expert opinion, making decisions rather than the full NDA process.

DR. GORDON: Wayne.

DR. JONAS: There is a lot of talk about incentivizing the private sector and this is of great concern to us about how to go about doing this. Obviously, it is very clear that the NIH will never be able to fund probably even a fraction of the potential therapies that have even been identified in multi-center, large, randomized, five-armed placebo-controlled trials.

So, how to incentivize the private sector to invest in this area is part of what we are going to discuss actually tomorrow and also, I think, a little later on today.

But what I heard you say, Floyd, is that there is a problem in the patenting process or at least there are issues that are obstacles in terms of the patenting process. As far as I can tell, we haven't really addressed that and don't have it as a major item on the agenda. I am wondering is that something that would be an important area to specifically look at in terms of its influence on this incentivization process and should that

be something the Commission should be looking at and if so, how.

DR. LEADERS: Let me come back to that because I understand where Rob is coming from on the taking these products and giving the exclusivity to one particular person or one particular company. I fully appreciate that. I am not talking about the general kind of products, like the ginkgo biloba, the hypericum [ph] and so forth. I am talking about a botanical that is used not like Taxol, where you take out a single active ingredient, but maybe an extract of Taxol that has several of the other ingredients in it also.

There is a place for some of these products. The patent protection probably can be gotten on some of those that have not been as widely used. But there needs to be a guarantee or some kind of -- there is really no reason, nothing to motivate a company to invest the kind of money we are talking about.

I think that it should be looked at. There are several proposals to Congress on this kind of thing. I don't think that they --

DR. JONAS: Specifically addressing the patent?

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DR. LEADERS: Dr. de Felice's [ph] act on and I can't remember the name of it, but it basically would set up a whole new process. I am not sure one is needed. But if there were a legislative way of saying if you have a particular extract and you have documented this and you have gone through all the hurdles, you should be able to have some kind of legislative time to get your money back.

DR. JONAS: Should we ask for the patent office and some of those folks to be in here and talk to us about it?

DR. LEADERS: Yes, it would be interesting because we have patent lawyers here in the Washington area. We believe we can get proprietary protection on some of them. But I think it would stimulate research, yes. I think that is another way of doing it.

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DR. JONAS: I had one question for Dr. Rosner.

That is, what is the status of the chiropractic research network? Is there such a network? I know there used to be and the reason I ask that, of course, is because this is a potential mechanism for collecting data in actual practices and the question of what is needed to

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encourage that, if we are going to be doing outcomes or observational or cohort research as you describe it is crucial.

DR. ROSNER: I know. You are talking about a database per se or --

DR. JONAS: Well, I mean, it is more than a database. No. I am talking about research practitioners that is organized in such a way that you can actually collect practice-based data. I mean, this exists in a number of conventional areas. I don't know of any good network like that among complementary medicine practitioners.

I know the Naturopath Liana [ph] has put together, and you all had some and I am just wondering what the situation is with that and is there some way in which that can be developed?

DR. ROSNER: Yes. We have had a number of ongoing discussions about this problem and there have been localized attempts at this. I guess the most courageous effort has been mounted at Palmer, as far as organizing a database for both practitioners and researchers to get into to understand what information

sources are available, how to conduct a case study.

One of the things we are very sensitive about is starting at the very beginning, which is record keeping. This is something we are constantly visiting practitioners and lecturing about because it is really the very first step.

DR. JONAS: I think it would be useful to hear what could occur to help develop this and perhaps you and also Bill could discuss that and give us some suggestions as to how to do that because, clearly, if there is no infrastructure, if there is no organized way of collecting data among practitioners and, yet, the practices are delivered out there in diffuse groups, then there will be no way of actually collecting this observational data.

DR. ROSNER: Again, these are localized efforts, but this is something that David Eisenberg, we basically started Eisenberg with a grant from our own and other sources before he went on to federal funding. This is now covering eastern Massachusetts, as you know, practitioners in acupuncture, massage, chiropractic.

It is a database as far as methods used or

concerned outcomes within cost will follow. So, these will probably be models to what we will be proposing.

DR. GORDON: Are there any other questions before we go on to the final panel?

Yes, Tom and then Bill.

MR. CHAPPELL: As I understand it, single herbs are going to be researched, have been researched and the cost is what it is. Someone will have to pay that price and right now, NCAM is farming that out to centers and we are getting documentation on the mechanisms and the effectiveness of single herbs.

Is that correct?

MR. McCALEB: It is correct, but there is also prior to the funding, where companies are taking their own formulas and doing the research, yes.

MR. CHAPPELL: We are doing that as well. Are formulas or single herbs --

MR. McCALEB: Both.

MR. CHAPPELL: I wanted to address just the singles. Single herbs, it seems to me, obviously, everyone has an interest. It should be public domain, public cost, public domain. The private protection I

hear you asking for, Dr. Leaders, is the blend, the proprietary, the imagination, the unique perspective on a blend of certain herbs that need to be protected is going to have its cost of research. Is that where you are looking for the exclusivity?

MR. McCALEB: Yes, that is one. There was a conference here in Washington last year on the use of natural products in the treatment of cancer.

There was a conference here at NIH on the use of natural products or botanicals in the treatment of cancer. There were a couple of those that fascinated the heck out of me. Some of them were single chemical. Some of them were Chinese of the variety where you have more than one. That is the kind of a product, something that would be -- I will give you an example that was at that conference, a product that in theory lowered the viral titer in hepatitis B and C.

Also, after treatment or during treatment, the fibrosis in the liver went away. Those kind of things would be extremely interesting for a very serious medical practice. That is the kind of thing I am talking about, to give the incentive to really bring a tool like that.

DR. GORDON: Bill.

DR. FAIR: Just a quick question.

Are there any difficulties with going into a foreign country and taking a plant and bringing it back to the United States, legal difficulties?

DR. LEADERS: Yes.

DR. FAIR: Is that one of the factors also that has stopped the development of this field?

DR. LEADERS: Yes, it has. My advice would be to work with somebody in that country. Don't necessarily bring it back to the United States. Why not work as a partnership within that country?

DR. GORDON: Thank you. Thank you very much. Thanks for your testimony and for being with us.

Again, we will stretch for about two minutes and then we will sit for the final panel.

[Brief recess.]

DR. GORDON: I want to thank the four of you very much for your patience and your hanging in there with us and also for traveling to be with us and to share your experience. This is a very important panel to us because we have kind of indirectly been referring to you

during a good deal of the day in talking about some of the possibilities and some of the challenges of doing research when you are in private practice.

So, I am glad to welcome you and also glad to welcome Dr. Jeffrey White from the National Cancer Institute, who was here with us at the beginning of the morning and who has been a major force in helping people to do research in the field.

So, let's begin with Dr. Nicholas Gonzalez.

Session VII: Outcomes Research Part I

Interface Between CAM

DR. GONZALEZ: When I think about my work, I think about it in terms of a good idea that we are trying to keep alive. It certainly isn't my idea. So, I am not giving myself credit. At lunch I gave the five minute version. I will give you the 11 minute version now. I promise I will keep it short.

But without discussing some of the history in terms of viewing the regulatory problems in the past, it is not going to put it in a full context. The roots of what I do actually go back to the turn of last century 100 years ago and the Scottish embryologist, John Beard,

who was a full professor at the University of Edinburgh. He was a Ph.D. who first suggested pancreatic proteolytic enzymes represent the body's main defense against cancer. He didn't pull this out of the air. He had spent 30 years studying the embryological development of the pancreas.

He was well-versed in scientific method and published a series of articles in 1902 to 1905 showing both in animal models and some preliminary human evidence that pancreatic enzymes not only might prevent cancer, but might be useful as a cancer therapy. He was universally derided and ridiculed, I should say near universally, because there were several physicians, eminent physicians at major institutions that took Dr. Beard very seriously and working with him, used injectable pancreatic enzymes, proteolytic enzymes, to treat advanced cancer.

Their successes are documented carefully and clearly in the orthodox medical literature in journals such as JAMA, the Journal of the American Medical Association, the Medical Record, the British Medical Journal. I have those articles. They are very

interesting. In my estimation, they represent the first cases of cancer regression. They use the word "cure" with nonsurgical therapy.

However, at the same time, Madame Curie, very well-known, very well-loved, an international celebrity, announced to the world that radiation therapy was a simple, easy, non-toxic way of curing all cancers. Of course, she would die from radiation-induced cancer damage. A whole generation of radio-oncologists were follow her to the grave.

We learned subsequently during the 1920s and the thirties after Beard was gone, that radiation wasn't simple, wasn't non-toxic, didn't work for most cancers.

DR. GORDON: Excuse me, Nick. Could you slow down a little in the interest of the efficiency of the transcriber.

DR. GONZALEZ: If I go too slow, you will fall asleep.

Madame Curie announced to the world and subsequently died from radiation damage, I said that, and a whole generation of radiation oncologists would follow her to the grave. During the 1960s, the eccentric and

controversial dentist, William Kelly, resurrected Beard's enzyme therapy and developed a very complex, nutritional and enzyme therapy to treat cancer. His attempts to revive Beard's work were met with great hostility from regulatory agencies.

He was repeatedly thrown in jail. First he was a dentist. Dentists aren't supposed to treat cancer. Secondly, this was the 1960s, where if you mentioned cancer and nutrition in the same sentence, it virtually was a federal offense. This is one example, as I said earlier at the press conference, where both local, state and federal agencies worked together very well to harass Dr. Kelly. It was a miracle that he was able to survive.

I first heard of Dr. Kelly at the end of my second year of medical school in 1981, when I was at Cornell. I had gone to Cornell because I was interested in cancer research and Cornell was associated with Sloan Kettering. The then president of Sloan Kettering, Robert Goode, had sort of adopted me as kind of, as I said earlier, maybe he thought I could be useful cleaning test tubes or something in his lab.

After I met Kelly, I went to Dr. Goode and said