



Presidential Commission  
*for the Study of Bioethical Issues*

TRANSCRIPT  
Implementing Federal Standards - International Efforts

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Meeting 5, Session 3  
May 18, 2011  
New York, New York

**DR. WAGNER:**

Well, good afternoon. Welcome everyone to the session 3 of our meeting, Implementing Federal Standards and International Standards. We have for our first panel Dr. Murray Lumpkin, Mack Lumpkin, and also Dr. Jerry Menikoff. Let me introduce Dr. Lumpkin to you first. He is a 21 year career Officer and the Deputy Commissioner for International Programs at the FDA, Food and Drug Administration. In this role, he is responsible for overseeing all of FDA's international activities and this includes overseeing the FDA's interactions with foreign counterparts, multi national health organizations, managing foreign capacity building and harmonizing programs, and administering foreign confidentiality agreements -- quite a large portfolio. In addition, Dr. Lumpkin oversees the activities of the FDA's Office of international programs and its 13 foreign FDA offices located across the globe, which were developed and implemented, these programs, excuse me, all developed and implements under his leadership. Mack Lumpkin, we're delighted to have you here.

**DR. LUMPKIN:**

Thank you. I've always said this is why they never let me in the Center for Devices, because I cannot make these things work. I do appreciate very, very much the invitation to be here. I'm delighted to be here and our Commissioner, Peggy Hamburg, who always loves coming to New York, seeing how this is from whence she came, asked me to specifically tell all of you on behalf of our agency, thank you for allowing us to be part of your discussions. I want to spend just a couple of minutes with you this morning kind of talking a little bit further about some of the things that Christine talked so beautifully this morning with you about, and that is kind of the FDA lens on the international component of the questions that you are talking about today. And it's a bit of an odd lens in a sense in that for those of you that know FDA and have followed it, our fundamental mission has not changed, we are a domestic consumer and patient health protection and health promotion agency. We have a domestic mission.

What has fundamentally changed in our life over the past 15 years is that the products that we're responsible for, and the clinical data that we're responsible for now have a global pedigree. And it's that global pedigree that is very, very different from the world before 1990 and I'll show you a little bit about it. So the question really is: FDA, where do we fit into this enterprise that you all are looking at? And as I said, I hope this is helpful to you, but I really have to say if I'm totally honest about it, I'm really very hopeful that you're going to be able to help us. Because I think at the very end I'll give you some examples of some of the very challenging and very perplexing ethical issues that coming up for us in the world that we're involved in that we could use some help and I'm hoping to a great degree that this commission will help us on that.

So where do we fit in? The basic piece that FDA does when it comes to looking at the medicinal products that are available in this country is that we are assigned by Congress to assess the benefit-risk profile of products that companies wish to market in our country by looking at the totality of the data that they submit to us, including the preclinical, the clinical and the manufacturing process data. After looking at these data in very, very many ways, if the demonstrated benefits of the product outweigh the known risks of the product for the intended population when used as directed, the product basically meets our legal and scientific standard for marketing in this country, provided that the manufacturer can indeed produce it in a consistent manner over time.

So when we're doing this, we obviously are looking at the scientific validity of the data, the clinical relevance of the data, the completeness of the data, and the ethics of the data. For the general principle is and always has been, under our implementing regulations is that we can't authorize a product if the data that are used to support this benefit-risk profile determination are unethically obtained. So the question for us within the world that you all are looking at, and we could spend days and days talking about many different aspects of not only the ethics of it, but the scientific robustness of it, is what does it mean for data to have been obtained in an ethical manner?

And I think for us that was probably much easier to answer 20 years ago because of the situation that existed as to the pedigree of the data and where it was coming from at that point in time. And if you look at some of the data that I'm putting up here and going back in 1990, about 96% of the clinical investigations that we would see data from came basically from either North America or Western Europe. By 2007 that was now down to 54%. Non U.S. and multi national studies are clearly an ever increasing proportion of the data that is submitted to us to substantiate marketing applications. In 2007 over 60% of the pivotal studies that were submitted to us as primary studies to support a marketing application of a drug had one or more non-U.S. study sites and this is not only as far as drugs are concerned, we're seeing it more and more in the world when we get to biologics and we get to medical devices.

The HHS Inspector General, about a year and a half ago began a look at this whole issue of foreign clinical trials and FDA's role in overseeing foreign clinical trials and some of the data they came up with in their report here, just to underscore what I'm talking about, is that in 2008 sponsors that submitted marketing applications to us had over 230,000 subjects that were enrolled in over 6,500 non U.S. sites in 28 different countries. And when you look at those countries, this is about 2008, Western Europe accounted for about 60% of the non U.S. sites and the other 40% was evenly divided as you can see there.

And this is not a phenomenon that is just happening here in the United States and I know you're going to hear from some of my colleagues from the European Union tomorrow. They have also, as you will hear tomorrow, been very much involved in looking at this issue because they are faced with the same situation we are and if you look at some of their data from 2005 to 2009 and looking at what they call market authorization applications, about 39% of the clinical data that they get comes from within the EU, meaning about 60% of their data comes from outside the EU. And Fergus Sweeney, who is one of the senior leaders within the European medicine agency, I think, made a wonderful comment at their session a couple of months ago on this question. And he said, you know, we're kind of at an interesting point right now, that it doesn't matter where you stand -- if you are in the United States, if you are in the European union, if you are in China, the majority of clinical trials are being conducted some place else. That no one anywhere in the world right now gets to say we do the majority of the clinical trials. So this idea of getting marketing applications coming into you where the majority of the clinical trials are being conducted someplace else is a phenomenon that as the pendulum is swinging, we're kind of at the point where everybody is at a place where the majority are being done someplace else from their vantage point. And when you look at some of Fabio Tear's work out of MIT, when he went back and looked through this last decade, a large part of it, looking at the change in global clinical trials, I think many people have rightly said that pendulum is swinging from where the majority of clinical trials were done in North America and Western Europe, to the point now where they are being done all over, to the point where they are going to be done in other parts of the world as you can see here. And many of these are areas of the world that have not been the traditional sites for the clinical trials that have used to support marketing applications.

Just a little more data from Philip Ward and the point here is, he was doing an article primarily on the growth of Phase 3 clinical trials in India and the data that he presented showing that it is growing in India Phase 3 trials 7 times faster than the global average. So this is data that for Phase 3 clinical trials started in 2008, which means that we will probably begin to see these data in marketing applications starting next year or the year after giving us about a four year lag time from when a Phase 3 trial starts until we see the data completed in a marketing application. Well, FDA has been looking at foreign data, getting data from overseas is not new to us. What is new to us is the amount of foreign data that we're getting from overseas. Our regulations go back basically several decades about the use of foreign data to support marketing applications. There is nothing in our regulations that says you have to do your clinical trials in the United States. There is nothing that says you have to do your clinical trials under a US IND if you are doing them outside the United States. If

you're doing them, obviously, within our country, you have to do, at least for the sites in the U.S., have to be under an IND.

But if you are going to bring in data from overseas and say, I want you to use these data to support the benefit-risk determination for this product, these are kind of the four main buckets of things we need to be able to do in order to use data from outside the United States and really when you think about it, they are what we use for data from the United States, too. And that is that you have to be able to validate the data, you have to have clinical investigators with recognized competence, you have to conduct them in accordance with GCPs using independent ethics board review, approval, and continuing oversight, and you have to make it applicable to the U.S.

And I know we talked a little bit this morning when Christine was here about GCP. I think really what we see in our regulations on good clinical practices is that it is an effort that we've had, that we've worked with people in many parts of the world to develop a standard that sets a framework that not only reflects our legal and regulatory authority here in the U.S., but also incorporates both the reality of the quality and the integrity of the scientific data and the protection of human subjects because we would argue that clearly the protection of human subjects is kind of the traditional area that ethics has looked at, but also to do a scientifically dubious trial or one that you cannot interpret at the end of the day, raises ethical questions about exposing subjects to investigational products when you don't get any valid information out of it for the community or for the individual to do there.

And one of the things in our 312 regulations is that we do not allow just certification to these things. There's certain things that as far as the descriptions and the data, and I know you all who have looked at our present regulations on this know when it comes to independent ethics community, Independent Ethics Boards (IECs), that indeed there are certain things listed here that we want people and we require people to do when they are giving us data from overseas.

We heard about this this morning from Christine, so I won't go into the ICHGCP, but obviously if people have questions about that, I'm happy to talk about that. And some of the other very worthwhile and helpful GCP documents that have spun off from the ICH, the ones from PAHO and [unclear], the ones from ISO and others.

And I think what I want to show you here before I just give you some of the things that have been particularly perplexing to us is that to give you just some idea of the inspections that we've had to do outside the United States because of clinical trials and being done in other parts, it's kind of a roll call of the United Nations. Looking at places where we had to send

GCP inspections because people were using data from studies done in these countries. Part of this is we don't have the ability to inspect each and every study. We don't have that even here within the United States. And one of the things that we have spent a fair amount of time on is trying to work more and more with our counterparts overseas on how we can collaboratively work together so that indeed we don't have to inspect every one of these, that people are getting at more of a comparable level overseas.

That is just to show you some of the training and GCP that we did with did with Chinese counterparts.

And just to put on the table for you all here on some of the ethical issues that we get faced with to go back to that first question of what does it mean for the studies to have been conducted in an ethical manner. There is indeed as we talked about this morning, the idea you can go down the check list, did you comply? But I think part of what we're seeing here is compliance with certain rules and regulations might be a first step, but it's not the end all and be all. That there is a thought process, that there are actual real-time situations that arise that take people have to sit down and think about what it means, how we're going to use those kind of situations and interpret them within our own context.

One of the ones we have is ethics committees especially the ongoing oversight, the conflicts of interest we heard about today, and documentation, and what does that mean with these overseas? This very perplexing issue of individual ethics versus population ethics and the one that people have brought up to us of saying even if everybody has done things perfectly when it comes to the ethics of the individual and the protection of the individual, if indeed a company is not going to market the product in the area where the study was done, has there been violation of population ethics? Has there been a violation of the social contract with the community, as opposed to the community benefiting from the data from those within their community who participated? And the question then, because when people submit applications to FDA, the companies are not required to tell us where they are going to market it, where they're not going to market it. That is not any of our business, it's never been our business in the past, it's not a question we can ask. But it does raise the question in the sense of, well, is this ethical data in terms of our being able to use it.

We have issues on clinical trial designs, some of those were brought up this morning. One of them is basically the issue of standard of care in other parts of the world and what does it mean if standard of care in another part of the world is different from standard of care here? Can we use data to make a marketing decision here in the U.S. from a trial

design that is considered ethical in another setting, but would not be considered ethical within the U.S. setting?

For those kinds of questions, and last slide here, last, but not least, some of the questions you guys brought up this morning are the same ones we deal with: what does it mean to define legitimate consent? We all agree that consent is an integral principle, it's an unalienable principle of what we are talking about here, but what does it mean practically when it's coming from a society where men and women have different legal rights? What does it mean when it comes from a society that's hierarchical with elder decision-making models? What does it mean in societies with high levels of illiteracy?

What constitutes coercion in situations where access to standard medical care is limited or nonexistent and where trials are presented and give people a chance to indeed have care that perhaps otherwise they would not have access to and at what point does that cross the threshold of coercion versus actual informed consent to be in there?

So it's kind of this thing at the end which to us is the ongoing issue here, is that: what is the perspective by which these are judged? Do you do it by your perspective as the reviewing authority for your own jurisdiction or by the perspective of where it was done? Thank you very much.

**DR. WAGNER:**

Mack, thank you very much for that presentation. (Applause)

Dr. Menikoff, we turn to you. Jerry Menikoff is the Director of the Office of Human Research Protections, OHRP, at the U.S. Department of Health and Human Services. His office is responsible for protecting the rights, welfare, and wellbeing of subjects involved in research conducted or supported by HHS. And Mack, we need you to turn your mic off. That's okay. And his office helps ensure such research, human subject research, is carried out in accordance with regulations described in the Common Rule. In addition, OHRP provides leadership in the protection of human subjects participating in this kind of research by providing clarification and guidance on the regulations, developing educational programming and materials, and maintaining regulatory oversight. And prior to joining the Federal government, Dr. Menikoff was an Associate Professor of Law, Ethics and Medicine at University of Kansas. It's a delight to have you here, Jerry. Take it away.

**DR. MENIKOFF:**

Thank you. Well, thank you for the privilege of addressing you and thank you more importantly for the work you are doing on this important subject. I could echo Dr. Lumpkin's points that we look forward to your inquiry in this field. It's certainly again highly relevant to what my office does.

Dr. Gutmann noted earlier in terms of Guatemala, you characterized it as egregious and I'll certainly echo that on behalf of HHS. Horrible things happened and we are as committed as any other part of HHS to making sure in the future that no such thing happens and in fact that things that are far, far less horrible aren't happening either. So we view this as a work in progress and a partnership, and I'll tell you more about that. I'm in a fortunate position. Christine Grady gave such an excellent presentation earlier on, so you already know a lot about what my office does and so hopefully I can be brief and allow more time for questions. So let me make a few points just sort of clarifying and amplifying on some of the points that were noted earlier.

What is within OHRP's jurisdiction? Because in fact it is very different in fact, than FDA's jurisdiction, I think that is relevant to the questions you're addressing. In particular, the core part of jurisdiction relates to HHS funded research, regardless of where it is conducted. On the other hand, the biggest part of that generally is NIH, and by and large, NIH at least on the extramural side is not doing a mind-boggling amount percentage-wise of research outside of the U.S. My understanding it is within a couple of a percent. So it is not huge. Fortunately you are collecting information about this and you will have a lot more information put together in one place than has existed up to now. Let me just give you the other part of our jurisdiction. There is a phenomenon noted earlier called checking the box. Domestic institutions, but not foreign institutions, are allowed to voluntarily submit themselves to OHRP's jurisdiction on all of their research, regardless of funding source, and two-thirds of the institutions out there, again just domestic institutions, do voluntarily do that. That gives us a huge amount of authority over a great deal of research that is not HHS funded. Again, almost all of that is not international, it's largely domestic. You would only have authority over stuff happening in this country or at least over research that is done by personnel of these institutions, and most of that is within the U.S.

Let me say a little bit about the rules that are enforced by OHRP. Again, you have heard a lot about this. OHRP enforces the HHS version of the Common Rule. This is a rule that has been adopted by, sort of in a cookie cutter fashion, by 17 different divisions of the Federal government. They each have their own authority to enforce it. So again, our authority is limited to the HHS funded aspects of that. The Common Rule does not in any way, at least in terms of its core provisions, distinguish between studies that take place within the U.S. and studies that take place outside of the U.S. Again, the core issue is, is it HHS funded?

That said, the rules do have provisions, that again have been noted

already, relating to what is commonly called Equivalent Protections. And this is a very important and commonsense concept that basically HHS, similar to any other branch of the Federal government, doesn't have the absolute best answer to what protections are adequate in terms of protecting participants in research studies. And so the regulations contemplated that there can be circumstances in which it would be determined that the procedures or rules of some other organization or laws are adequate.

Up to now, OHRP, or more broadly HHS since the Secretary makes determinations, has not made any determinations that a particular set of protections are equivalent. But we are well aware that research, as Dr. Lumpkin has noted, is becoming more and more international and we certainly again acknowledge that there aren't just one set of protections that are adequate and we have actually been actively working for quite some time to develop criteria for determining equivalent protections. By doing this, we don't want to actually exacerbate problems and so to pick up on a theme that was noted earlier, we're very engaged in being harmonious these days. We could envision OHRP or the Secretary setting up standards for OHRP-regulated studies that are somehow different than FDA standards because FDA has already been engaged in something essentially similar and therefore we are working very closely with FDA to hopefully come up with rules that are highly harmonious so we do not end up having two sets of standards to apply here.

And I think this gets back to another theme that was echoed earlier, that the rules, it isn't just about compliance. The heart of this is about ethics. And I think from the viewpoint of somebody in another country, whether or not you are exploiting them or not, it doesn't matter necessarily whether or not it is an issue that it was a Federal government funded study or on the flip side of that, that it happens to be a product that the only reason the product is being studied according to a certain protocol is because the U.S. is the gorilla in terms of being the biggest market out there and we know these companies are not about to engage in the study unless the rules will comply with FDA. So bottom line, we think there are basically similar ethical rules there and we are very eager to come up with similar standards in terms of FDA's, and recognize again that the U.S. doesn't have the clear answers to this and we certainly welcome your input in terms of this. So it's wonderful that you're discussing all of this.

Let me say a bit, since you were interested in OHRP's involvement with international research, in spite of the fact that it's a small part percentage-wise of our regulatory scope, we actually are very active in that field. The division, we have four divisions, the Division of the Director has a subunit that is specifically dedicated to international

activities. The Deputy Director of OHRP is actually in charge of that subunit, a recognition of the importance we give it.

We publish, this gets back to a question raised earlier, we publish something called "The International Compendium of Human Subject Protections," it's right on our website so if you just Google OHRP, you can find it. It has the rules relating to human subject protection for over 100 countries. We are regularly adding countries to that. So everybody should feel free to take a look at that, if you want to find out more about that.

We regularly, members of our division regularly meet with people around the country and interact with researchers, with regulators, with bodies representing governments across the world. The Division of Education and Development responds very openly to any inquiry about the rules, about guidance, about how to interpret something. We're very free about answering questions and about 5% of its response is actually related to international inquiries.

The Division of Policy Assurances, for one thing drafts changes in terms of policy and guidance. It is very engaged right now in terms of what I indicated earlier, what will be either equivalent protections or waiver rules that might accomplish the same thing. Again, we're very interested in that.

We also register both IRBs and create Federal-Wide Assurances, and there is a large international character to both of those. Of the 6,000 IRBs registered with us, about 2,000 of them are outside of the U.S., so about 37%. And of the nearly 11,000 approved Federal-Wide Assurances approximately 2,500 or 22% of those are from outside of the U.S.

Finally, our Division of Compliance Oversight investigates complaints of noncompliance, and again assuming the right things are alleged and we see merit in the complaint, we will investigate something regardless of where it is taking place. And I'll note in particular in terms of not-for-cause investigations, when we go out of our way to look into a particular institution and see how good a job they are doing. Over the past five years, approximately 40% of those have been directed to international institutions, which is way higher than the actual percentage of international research that's within our scope.

So let me just close with what I think is a key point, and I think it's similar to a point that was made earlier. No single office or branch of the government is in a position to really make sure that everything is working. And what this really is, is a partnership -- a partnership amongst governmental units both within the U.S. and outside of the U.S., within funding agencies, within researchers, within subjects. I

mean everybody works together, and in terms of this partnership I could tell you certainly in terms of NIH and HHS funded research more broadly, we work very, very closely with the funding agencies, and in fact they are often the feet on the ground in terms of paying a great deal of attention to what is happening in terms of research.

Again this is certainly a work in progress, but it is strong system, not a perfect system, but we welcome input and we're certainly -- a major theme is we're very engaged in improving the system. Because I haven't touched on a number of issues that might be tangential to the issues raised by Guatemala, but the system certainly does need improvement and we are interested in improving it. I'll leave it at that.

**DR. ARRAS:**

Thanks very much for those two presentations. Jerry, could you say what roughly what percentage of domestic and international studies your unit is able to actually monitor?

**DR. MENIKOFF:**

Okay. We do compliance, you know, not-for-cause compliance visits, they're a small percentage. I gave you numbers that there are 10,000 FWAs out there and 6,000 IRBs. These are very small numbers. Percentage-wise they would be small. I mean, the way the system works, the way the system functions, I was very serious about the point about being a partnership. In terms of making the system work, you need all the players together and that includes the funding agencies, us, working with FDA. Okay.

**DR. ARRAS:**

Just a quick follow up. So very small percentage, like 1 or 2%?

**DR. MENIKOFF:**

I'm on now. Okay. It's probably under 1%.

**DR. ARRAS:**

My question is, do you see this as a problem for your agency? In other words, do you think the ability to be able to monitor a larger percentage would be a really positive step for your organization?

**DR. MENIKOFF:**

I actually don't view that as one of the greater problems. Again this, gets back to there are many, many players. And I think I would, similar to themes that came up earlier today in terms of one of your earlier panels, I thought it was interesting, one of the persons who was at one point criticizing some degree of international research also made the point, I thought later on in the talk, with regard to for example NIH funded research because of all the protections that are built in there in terms of

all the things that have to be done to get NIH funding and that how scrupulous NIH is about that sort of thing, my suspicion is that there isn't the huge problem there in terms of that, or at least, the problem isn't unique in terms of international research. So whether our, certainly it would be nice to audit certainly a higher percentage probably because that would send a stronger message, but do I think that is a huge problem? Probably not.

I mean, I would love if we were getting more complaints and you're never clear what percentage of the bad things that might be happening there are being brought to our attention. But at the moment I wouldn't have put that way, way up there and that gets back to part of what FDA does. Because FDA actually has far more resources in terms of doing that and my understanding is even in terms of percentages, it's a small percentage of the studies that they review, but they do have sites around the world and they do actually look at again that percentage and they help us out actually in terms of sharing that information.

**DR. SULMASY:**

Great. This will be a question for Dr. Lumpkin. I wanted to ask a little bit about the decision a few years ago by the FDA to drop the Declaration of Helsinki, and adopt the GCP in its place, and particularly the role of the questions about the ethics of using placebo in studies where there is a standard of care might have, the role that might have played in that decision?

**DR. LUMPKIN:**

I got it figured out. All right. No, it's a very good question. And I think when we published the new rule, those were questions that were brought up and when you go to the Federal Register and look we tried to answer those questions in there. I think they go to several. Number one, I think we believe in the concept of GCP. There is incorporated the ethical principles, not only in the documents such as Helsinki, but many of the other documents that have been mentioned here today. But that it gives you a much stronger framework for actually requiring certain things to happen that a principles document itself does not. So I think we've tried to argue them and we believe strongly we haven't sacrificed principle, by looking at a much more harmonious way to look at this and so to give you a strong framework, but to give one the flexibility that one needs to say this is what we've agreed to in many, many different parts of the world.

I think it's important to remember on the Declaration itself, it's not something that is incorporated into how we do stuff in our own country, you know. It's going back to what we talked about this morning, it's never been incorporated as a sine qua non for what happens in our own country. Because we have other ways of assuring that the principles of

Helsinki are met within our own country, and I think GCP does the same thing on the international part. The European Union has not incorporated it into its rules. It, like we, recognize the principles that are there, but as far as a way of trying to say: this is the framework and this is what we mean by how one would interpret it, I think we believe that the GCP actually gives you stronger way of doing that.

Now, the placebo part is an interesting part and I know that many people have brought that up. I think it is an issue for international context, but it's an issue for our own country. So the issue of the ethics of placebo controlled trials are ones that come up quite often with the various clinical trials that we have here and I think we continue to believe there are times where it is quite ethical to do a placebo controlled trial. There are times where it is grossly unethical to do a placebo controlled trial and that is where, as you talked earlier today, judgment comes in. You can't write that into a reg. It's not black and white, one has to use judgment. One has to look at what one is trying to do, the context, the situation, what is actually happening, and I think the GCPs gives us the flexibility to use that judgment to decide with the larger communities when it's ethical to do it and when it's highly unethical to do it.

**DR. SULMASY:**

Does the GCP say anything specifically about placebo?

**DR. LUMPKIN:**

You know, I don't know that it specifically says anything about they are ethical, they are unethical, in fact I know it doesn't make these kind of definitive statements there. I think though that people when they recognize the, from the scientific robustness perspective, that in order to have data that is interpretable for individuals and the community, it has to come from a well controlled trial. And what does it mean to have a well controlled trial? There are many ways our regulations and those in many other parts of the world recognize different ways to control the trial and placebo is one way, active is one way, no treatment is one way. There are, historical is one way. There are a lot of different ways that you can do an adequate and well controlled trial, but you have to explain why it is well controlled and why it meets the needs. There are times we wouldn't take a historical control. There are times we wouldn't take an active control, if the active in and of itself is not interpretable outcome, because there are no data to support the activity of that particular compound itself.

So I think the scientific and therefore the ethical issue is do you have a well controlled trial that will give you interpretable data at the end, and in certain situations, placebo is a way to do that. In certain situations there are many other ways that we recognize, and others, you can get to the outcome that you want.

**DR. WAGNER:**

If we can move quickly, we can get the final three questions in. Anita.

**DR. ALLEN:**

Dr. Lumpkin, I was fascinated by your statement that the FDA does not give concern for where a drug will be marketed. And I thought about that, in light of the great interest and progress you are making in the areas of personalized medicine and population specific medicine. Can we be blind to where? Because sometimes where is approximately for to whom. So can you clarify the relationship between our concerns about cost and benefit, risk and benefits and our blindness to regional marketing?

**DR. LUMPKIN:**

I think the issue for us is where we have jurisdiction. We obviously have authority within the United States, but our jurisdiction ends at the U.S. border and what my statement was meant to convey was that when somebody comes in and submits a marketing application to us, they're asking us based on these data and based on how we want to present this product, may we do this in the United States? They do not have to ask us, may we do this in Canada? May we do this in other parts of the world? That is not our jurisdiction. Those countries are sovereign nations. They have their own -- they get to make their own decisions on what happens there. So what I meant by that, is when a company comes in, in their marketing application, if they have marketed it previously in other places, they have to tell us that. But they don't have to tell us the future as to well, you know, here it is for the United States and by the way, we're going to go here, here, here and here. That is what I meant, it is not a matter of we don't care. It is something that falls outside our jurisdiction.

On the issue of the personalized medicine, that's a definitive question even within our own country and you are absolutely right. We are seeing more and more times where people are looking at products and clinical trials that are not designed for a population as they were for most of the 20th century. But they are designed for people who meet a certain genetic profile or people who have certain ways that we have better technology now to help us decide who can benefit greatest from this product and who would have the least tendency to have risk from it. And that situation, absolutely care, because that is the claim for whom you are going to be using it, but that would be within the U.S. context for us.

**DR. WAGNER:**

Drs. Lumpkin and Menikoff, thank you so much for joining us for this section. (Applause).

