FOOD AND DRUG ADMINISTRATION

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CENTER FOR BIOLOGICS EVALUATION AND RESEARCH

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VACCINES AND RELATED BIOLOGICAL PRODUCTS ADVISORY COMMITTEE

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OPEN SESSION

THURSDAY
NOVEMBER 29, 2001

The Advisory Committee in Versailles Room I and II in the Holiday Inn Bethesda, 8120 Wisconsin Avenue, Rockville, Maryland, at 8:30 a.m., Dr. Robert S. Daum, Chair, presiding.

PRESENT:

ROBERT S. DAUM, M.D.	Chair
MICHAEL D. DECKER, M.D., M.P.H.	Member
WALTER L. FAGGETT, M.D.	Member
BARBARA LOE FISHER	Member
JUDITH D. GOLDBERG, Sc.D.	Member
DIANE E. GRIFFIN, M.D.	Member
SAMUEL L. KATZ, M.D.	Member
KWANG SIK KIM, M.D.	Member
STEVE KOHL, M.D.	Member
PETER PALESE, Ph.D.	Member
DIXIE E. SNIDER, JR., M.D., M.P.J.	Member
JUAN FELIX, M.D.	Invited Participant
THOMAS FLEMING, Ph.D.	Invited Participant
MICHAEL GREENE, M.D.	Invited Participant
PAMELA McINNES, DDS.	Invited Participant
MARTIN MYERS, M.D.	Invited Participant
DENNIS O'CONNOR, M.D.	Invited Participant
SONIA PAGLIUSI, Ph.D.	Invited Participant
WILLIAM REEVES, M.D.	Invited Participant
ELLEN SHEETS, M.D.	Invited Participant
ELIZABETH UNGER, M.D., Ph.D.	Invited Participant
EDWARD WILKINSON, M.D.	Invited Participant

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A-G-E-N-D-A

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

8:33 a.m.

DR. DAUM: Good morning. A couple of announcements before we get down to business, so to speak. First, for panel and committee members there are bins up in front for paper that you've carried her laboriously and don't wish to carry home. Please use them.

Secondly, for panel members Denise and Rosana are, as always, kind enough to help us arrange transportation to airports or other destinations. For panel members at the table, please feel free to ask them to help you should you need.

Thirdly, I would like to call on Bill Freas -- where is he? There he is -- to make the briefest of announcements.

DR. FREAS: Thank you, Dr. Daum. I would just like to announcement that at the end of the meeting, whenever that is, that will be at the end of the closed session, we will have a short retirement ceremony for Nancy Cherry.

Let me just take two words to comment quickly on Nancy's distinguished 10-year career at FDA. Committee members know that she's always working late at night which seems to be the norm. But she's

also here at this meetings long before I even roll out of bed in the morning to make sure everything is set.

We really are appreciative of all the hard work that she has been doing. On behalf of CBER and her colleagues, we're going to have a little cake. We invite the public. We invite everybody on the committee to share this little party with us.

This is the unofficial requirement party just because she won't officially retire until January 3rd but we wanted to have something and to celebrate her distinguished career here while the committee members were here. Thank you.

MS. CHERRY: Thank you. I was trying to keep it quiet until the end of the day but I appreciate it. Thank you, Bill, Bob, everyone.

DR. DAUM: And for committee members and temporary voting members, guests at the table, you've got about three hours to talk her out of it. We're hoping to be able to apply pressure.

I can tell you in a short time as chairman of this committee that no Nancy, no meeting. It's just as simple as that. I'm incredibly grateful for the support and constant vigilance that she provides. Jabs in the elbow notwithstanding, it's been a great collaboration.

The strategy for this morning that I would like to propose to the panel is to have some free discussion first to look at issues that people felt were hanging from yesterday to raise issues that either we need more clarification or that you would just like to hear some committee discussion with regard to the questions only one of which currently fits on the screen but is up there for your viewing pleasure.

Once we get a sense of the fact that we are sort of starting to be repetitive and not raising crisp new issues, then I would like to take stock to address the question directly. At that point we may have heard from half or two-thirds of the panel on the issue but we will ask every member, regular and temporary, to comment directly on the question.

So with that sort of introduction, I've rigged things a little bit with an issue that was on my mind and would like to ask Marty Myers to initiate the first issue. It doesn't mean that we have to stay fixated on this issued. We can wander around on anything the committee's pleasure. Then we will eventually reach a point where we start focusing directly on the question.

Marty, you were kind enough to accept this

gauntlet from me and would you start us off.

DR. MYERS: I thought we would talk around the very important issue that I remain a bit confused about. I would like to ask a question to the people who are experts in this.

When we were talking about the contextual issues yesterday, the specific issue really didn't get laid flatly on the table so I would like to put it flatly on the table.

Specifically in Dr. Schiffman's presentation, at least as I understood it, he implied that persistent infection of a year's duration would, in fact, imply that there was a standard of care that would be implied. Somebody with persistent infection might, in fact, require therapy.

As I look at the data, it seemed to me that places a woman at very high risk of high-grade disease and might require long-term close supervision. If, in fact, it implies a standard of care of treatment, then, in fact, the experts in the field have already defined this as a surrogate. It makes it very difficult to consider using CIN 2, CIN 3, for example, a high-grade disease, as an endpoint because everybody will have had intervention before.

My question is really to those people who

understanding the management of these individuals. If a person has a persistent infection, does that imply a specific therapeutic intervention or is that a supervision? I think that's a critical issue.

DR. DAUM: I think so, too, and I'm glad people want to respond. Let's start with Dixie and then Drs. Wilkinson and Felix.

DR. SNIDER: Actually, I want to elaborate because I had an opportunity to talk with Dr. Schiffman more about that particular issue which was troubling me greatly as well.

If I understood him correctly, during his presentation he was telling us that the optimal time wasn't really known but that, in his opinion, it was somewhere between one and two years.

The reason he -- if he's in the audience, perhaps he should speak. The reason he came up with one year was not because of the data that he has in hand, but because he has been receiving lots of pressure from organizations who feel compelled given the current body of knowledge to come up with some definition of what recurrent infection is. Persistent. I'm sorry. What persistent infection is.

For lack of the more extensive data from his study not being available, not yet being analyzed, the

one year is somewhat arbitrary in terms of his personal recommendation. There is some concern on his part that a number of organizations, standard settings, professional organizations may take that number and do exactly what Marty is implying.

It's just a little elaboration, I think accurate, from Mark about how this transpired. Then I, too, would like to hear what some experts think about that particular situation.

DR. DAUM: Thank you very much. Let's continue with Dr. Wilkinson, then Dr. Felix, and Dr. Sheets.

DR. WILKINSON: I would just like to address the issue of persistent viral shedding. The ASCCP guidelines that were developed, these are guidelines not standard of care that were developed in September of this year, had access to National Cancer Institute data that is yet unpublished relevant to persistent viral shedding which Dr. Schiffman alluded to yesterday.

First, let me say that viral shedding in and of itself would not be an indication for treatment but it may be an indication for reevaluation of the patient by colposcopy.

In that setting under the guidelines, and

these are submitted at this point, but basically an acceptable -- not recommended but an acceptable statement from the guidelines is that an option in follow-up of women with LSIL, where an option has been chosen to follow the patient rather than treat the patient, the recommendation is colposcopy first, biopsy any visible lesions, with mild dysplasia the option would be that you could follow the patient.

There's only a couple of exceptions. Adolescents and elderly women are some exceptions. The point being that at the end of a year or at some point, possibly two years, your option would be that as an acceptable option to do HPV testing for high-risk HPV type.

If the HPV is positive at that point, you then go to colposcopy, an examination of the patient. If we have persistent viral shedding, there is very good evidence that NCI presented that your patient probably has a persistent lesion.

I would emphasize this is an acceptable option and it's not the standard of care that these guidelines -- ASCCP does not establish standard of care. American College of OB/GYN does so that is something that can looked at at that point.

DR. DAUM: Thank you, Dr. Wilkinson.

Dr. Felix, then Dr. Sheets, and Dr. O'Connor.

DR. FELIX: I'll be brief because Dr. Wilkinson basically stated all the facts. I'll just add that I know of no organization, nor of any expert panel that will recommend therapy based on viral information. They will recommend examination of the patient but never therapy just based on viral shedding.

Clearly not only not the standard of care of, in fact, it's never been recommended officially to actually perform therapy due to viral shedding in itself. Just evaluation and diagnosis.

DR. DAUM: Thank you very much.

Dr. Sheets.

DR. SHEETS: I think there are actually two issues on the table when Dr. Schiffman was talking. I think they have been somewhat blurred in terms of their overlap here. One is the issue of what represents viral persistence in and of itself separate from a side logic abnormality.

I think there is fairly good data to show that persistence of viral shedding six months apart for a year, or maybe two years, is certainly a person who cytologically normal at that time has great risk

for the development of a lesion in the future.

That's a separate issue from people who have -- women who have a cytologic abnormality and are concurrently a high-risk viral type. Then we go and subsequently a year later look for presence of that viral type as a surrogate of the lesion being still present on the cervix that gave rise to that cytologic abnormality.

That is a different scenario. That is not what is being discussed as a surrogate marker for failure of the vaccine in this mortality or this current discussion.

Those women who had cytologic abnormalities who had high-risk viral shedding at the incipient visit for vaccine therapy would not accrue in a trial. Correct? So that is a different scenario than someone who is shedding the virus at some point in the future with or without a cytologic abnormality.

I think that when Dr. Schiffman was talking about using viral shedding, as Dr. Felix pointed out, as a point for therapy or further evaluation by colposcopy, that was in the context of cytologic abnormality as the American Society of Colposcopy and Cervical Pathology guidelines indicate for LSIL at this point so there are two different categories.

DR. DAUM: Can we press you a little bit, or can I press you a little bit because that's very helpful. The only circumstances is it true -- is what I'm saying true that the only circumstances that someone would seek viral shedding in a totally asymptomatic woman with no lesions is for research purposes or documentation purposes? There's no medical care issue there at all.

DR. SHEETS: Currently in 2001 there is no medical indication for a cytologically normal woman to be tested for HPV from a medical point of view. There are no guidelines that indicate to do that. This would be a research setting at this point in time.

DR. DAUM: Do I hear in the first thing you said, though, is there talk or plans of incorporating routine screening?

DR. SHEETS: I think there certainly are a body of people in this country who think that HPV could be a surrogate for cytologic evaluation of woman, but that data is not mature for the United States.

DR. DAUM: Not about to happen.

DR. SHEETS: Not about to happen.

DR. DAUM: Thank you very much. That's very helpful.

Dr. O'Connor.

DR. O'CONNOR: I thought about this yesterday and had some discussion with a number of people and what I will give you are what I gleaned from discussions and basically my opinions.

Most papilloma virus infections regress over time. Those that don't are the infections that can result in high-grade dysplasia or worse. The interval before persistence become clinically significant is unknown but it is probably one to two years.

We do not know what factors are necessary for persistence but why only certain HPV DNA types are associated with significant disease. Although persistence carries an increased risk of significant disease, there's no evidence that these woman should be prophylactically treated because what are you treating?

I don't think there is enough evidence to suggest to me that woman with persistent unexplained oncogenic HPV have an inordinately high risk of finding underlying high-grade CIN being defined as CIN 2 and 3.

I feel that based on what I've heard there is, however, enough evidence to suggest that persistent oncogenic HPV has enough of a risk for

eventually finding an underlying CIN of any grade that you can it a vaccine failure. That's as far as I would take it

DR. DAUM: Go ahead, Dr. Sheets.

DR. SHEETS: I think to elaborate on what Dr. O'Connor is saying is that when one thinks of surrogate endpoints for this vaccine therapy using approximate surrogate such as HPV, high-risk oncogenic type positivity, or persistence of that presence as a point of failure for the vaccine will slightly artificially increase the efficacy or apparent efficacy of the vaccine since some of these HPV infections by high-risk oncogenic types are transient and clinically irrelevant, not important.

Even some in the face of cytologic slight abnormalities we know will regress over time. Using a marker that is more approximate rather than more distal from the actual invasive cervical cancer rather than more approximate will make the vaccine efficacy appear to be higher.

That is neither here nor there to a certain extent, but if one thinks about the scenario of what we're tying to treat which is either high-risk precursors or invasive cancer, we have to remember that the clientele that we are treating with the

vaccine are at least a decade younger than the average age of onset of high-risk precursor lesions and certainly much younger than the incident age of invasive disease.

The question arises here as to what the efficacy of the vaccine will be for those lesions later on a decade or so later. Problems with this that aren't part of the discussion today in the background that one has to keep in mind are that we know very little about the induction of mucosal immunity as compared to serologic markers of immunity induced by a vaccine.

We don't know whether memory in the mucosal immune system will be the same as the surrogate markers and serum for systemic infections. Ten to 15 years later when that 18 and 20-year-old is at greatest risk for the development of precancer or invasive disease, will this immunotherapeutic still apply? We don't know. It's outside of the discussion of this.

But if we use a more distal marker as a surrogate marker of efficacy, or even farther away from the endpoint that we ultimately want to prevent, I would think that is something that we have to think about in terms of discussing the surrogate endpoint.

DR. DAUM: Does the rigor of the definition of persistence matter with regard to your comments? In other words, if we take a one-year period and want four cultures or a two-year period and want six cultures, does that matter or the comment still stands?

DR. SHEETS: I think all it will do is enhance the apparent efficacy of the vaccine to a certain extent because you will be picking up on evidence of HPV positivity that may not be clinically relevant in the long run.

DR. DAUM: Dr. Reeves.

DR. REEVES: I think just one of the things that we are mixing some words and some concepts and you're hitting on it that we are still mixing these. As I understand it, CIN 2 and CIN 3, most of them, or some portion of them, are part of the actual natural history of the development of cervical cancer. CIN 2 leads to or results in CIN 3 in some proportion leads to or results in cervical cancer.

The same is not true for HPV. We're mixing the terms. We're often saying persistent HPV results in or leads to CIN. That's, in fact, not true. It's associated with it.

There's a rather major difference of being

associated within a small number of, as are all studies, flawed epidemiologic studies and selected groups, some in populations and some not. But an association is not causal and an association does not imply anything on a path or leading to or resulting in things.

DR. DAUM: That's helpful.

Dr. Felix and then Dr. Sheets. I'm sorry, Dr. Kohl was first. Dr. Kohl, Felix, and Sheets. Excuse me.

DR. KOHL: I just want to emphasize what Dr. Sheets said in terms of something we really haven't talked much about, although it was mentioned in the modeling -- sorry, it was mentioned yesterday -- restoration of protection.

We're talking about almost a life-long risk and, in certain situations, an increasing risk over time, although that seems to be possibly controversial. We heard very, very little about hypotheses of duration or protection.

I don't remember data on duration or protection and that's really a critical issue which I think could accrue in a lodge or a long-term study but I'm concerned whether we would see much of that in a short study with a surrogate that is closer to

infection versus closer to CIN 2/3.

DR. DAUM: Thank you for raising that point. We haven't talked it for a bit.

Dr. Felix, Dr. Sheets, Dr. Griffin.

DR. FELIX: I'll actually address two points quickly. Dr. Kohl brings obviously a very important point, duration of protection. But we have to remember that if you protect a woman very early on, that may be in itself even if the protection wanes an extraordinarily important protection because age at first coitus is an extremely important risk factor for the development of cervical cancer.

We don't know what it is about the transformation zone of a very young woman, but clearly woman who start sexual activity at the age of 16 or perhaps earlier have a relative risk that is much higher than woman who start first coitus after 18.

Obviously they are sexually naive. The initial age represents a tremendous increase in the relative risk. If you protect these woman at that age, even if immunity wanes, there is at least theoretical benefit of even those first two or three years of protection in lowering the relative risk of the population for acquiring basic carcinoma.

Immunity even of a transient, I think, is

something we ought to seek. Obviously it would be better if it persisted but that is maybe a very important parameter.

In response to Dr. Reeves, I think that the data suggesting that CIN 2 will progress to CIN 3 will progress to cervical cancer is robust. I think that currently there's almost as much data in the literature suggesting that persistence of high-risk viral types if you do it properly will result in the same effect.

Perhaps not at the same rates although very, very close because the rate of progression of CIN 2 is about 20 some odd percent. The rate of acquisition of the high-grade dysplasia from persistent HPV is around 26 to 28 percent also. The data is pretty robust. Both of them are associations but I think they are very equivalent.

DR. DAUM: Thank you very much.

Dr. Sheets, then Dr. Griffin and Katz.

DR. SHEETS: I think there are multiple issues on the table at this point in time for which we have no solid data to make statements one way or the other. I guess I would respectfully disagree with Dr. Felix in saying that stopping an apparent infection by the parameters that we have to test for that infection

today ultimately will definitely result in decrease invasive disease in the future. I don't know that.

My concern is that when we look at the epidemiology of invasive disease in America, we know that in the late teens, early 20's that these women are at great risk for oncogenic viral infection with subsequent cytologic abnormalities, perhaps even CIN 2/3 which may or may not be caught and treated at that point in time, but there is a large amount of regression through that decade.

We know that in the 30's and 40's slightly more mature individuals are the ones at risk for the reoccurrence or reestablishment of a high-risk lesion histologically that are at risk for the invasive disease that we're talking about.

We don't know what happens in that window. We don't know if the resolution spontaneously of a recursor lesion in their 20's leaves them at great risk for those women, those specific women for invasive disease.

We know epidemiologically that HPV infection is the greatest risk factor for preinvasive high-risk lesions and invasive disease sans sexual partners or age of first intercourse, but we don't have documentation of long epidemiologic studies over a

long period of time with no intervention what that biology might be.

If we add on top of that a vaccine which apparently decreases the "insipid shedding of HPV infection," is that the same as never being exposed or having a latent state?

We don't know because certainly there is a great deal of discussion right now in this country in mucosal immunology and HPV research that indicates there may be a latent phase for women who apparently were either treated or regressed their lesion in their 20's redeveloping that lesion later on. We just don't know that data.

In regards to HPV persistence in the development of high-risk histology later, that is well documented that may occur but, again, subject in the 20's, late teens and early 20's, to the same problems associated with spontaneous regression and clinical relevance of those lesions at that point in time. We just don't know what that translates into later than the 30's and 40's.

Some would say that CIN 2 is variable in regression rate whether it exist or not. Listening to Mark Schiffman talk about it maybe it's not even a lesion according to him. Some of us certainly deal

with it on a daily basis. That's for sure. It does regress at a fairly high rate compared to documented CIN 3 but that's outside the venue of this discussion.

DR. DAUM: Thank you very much.

Drs. Griffin, Katz, and Fleming.

DR. GRIFFIN: I guess I just wanted to reiterate one point, and that is that I think the data are excellent and nobody has really challenged them, that infection is a precursor -- becoming infected with one of these high-risk HPV types is a precursor to developing cervical carcinoma.

Granted we don't understand everything that's happening during those 20 years before you actually diagnose the disease. Therefore, it seems to me a priori that if you prevent that infection, you're going to prevent the cervical carcinoma.

Now, that doesn't mean that -- then duration becomes important, for how long you're protected. I don't think it means that if you use virus or infection with virus as a marker for the efficacy of the vaccine that you have overestimated.

If you prevent infection that you've overestimated the efficacy of the vaccine, what you've overestimated perhaps more likely is the efficacy for preventing cervical carcinoma but not the efficacy for

preventing infection which is usually what we're looking for in a vaccine.

So to me the big question then becomes it would be nice to understand all these things but also whether HPV types will come in and now may play a more prominent role, etc., in the cervical carcinoma that develops in those individuals. I think preventing infection is a very important goal and readout for these vaccines.

DR. DAUM: Thank you.

Drs. Katz and then Fleming.

DR. KATZ: I think Dr. Sheets and Dr. Griffin have helped me in my thinking. We're dealing with two different worlds. One of the gynecologic oncologist and then those of us who think of ourselves as vaccinologists. The terms have been used back and forth inappropriate perhaps.

We're not talking about a therapeutic vaccine. I assume we're talking about a prophylactic vaccine so we're preventing. That's what Diane commented on. Not that we're treating and applying a therapeutic intervention.

Although Dr. Wilkinson showed me wonderfully slides yesterday, I don't know enough about what goes on in the cervix. Are there lymphoid cells? Are

there the equivalent of M cells? What's there that provides -- Ellen was talking about mucosal immunity.

I know a lot about the GI track and the respiratory track. I don't know anything about mucosal immunity and what to expect as far as local host defense is concerned.

I agree that antibodies may be fine but what goes on locally may be even more important. Are there lymphoid follicles? Is there trafficking of lymphocytes from the cervix to other areas of where we have lymphoid deposits in the body? Can you help me with that at all?

DR. DAUM: Dr. Wilkinson, Dr. Sheets, go ahead.

DR. WILKINSON: I think Dr. Sheets probably has more to say on this than I do but I would say that although the cervix is not considered a molt organ specifically, it is richly endowed with immunologic base cells.

Often these cells are rallied in the face of, say, invasive carcinoma. You can appreciate that in many settings. In certain infections such as chlamydial infection it's not unusual to see aggregates of lymphocytes occurring, a condition referred to as pellicular cervicitis for example.

The cervix also has secretory IgA and so forth. It's quite a complex organ and probably should be ranked among the molt organs but, in fact, is not.

DR. KATZ: So that leads to a little more optimism about preventing infection or reinfection.

DR. KATZ: I want to stay focused in this issue before we go on. When we go on, we'll go to Dr. Fleming next. Dr. Sheets and then Dr. Felix wanted to speak to this very issue.

DR. SHEETS: I think in published data that is currently available in therapeutic vaccines we know that we can give a systemic injection and have cells that were destined -- T cells that were destined for mucosal immunity in the cervix to be exposed to that therapeutic systemically and then track back to the cervix or home back.

We know T cell immunity does happen although at a much lower rate than it would happen necessarily systemically since the dose is given systemically and there's a great discussion of therapeutic vaccines, whether they should be given transmucosally much like the GI tract, etc.

In terms of IgA, IGG secretion, antibody secretion, there's no doubt that the cervix and its mucus has a fair amount of antibody occurring there.

I am aware that there are efforts to create the same type of immunologic evaluation that's going on in the cirri that we've heard previously prevented in closed session to do transvaginally to look at that neutralizing antibody from the cervical mucus.

There have been assays set up to do that. The problem is we don't know a lot about the relationship between that mucosal immune system, just as we don't know about certain things in the GI tract compared to the systemic.

We don't know about durability and we don't know about level to a certain extent. This is not known. This is all very new. That's what I was pointing out.

DR. DAUM: Thank you very much.

Dr. Felix, this issue.

DR. FELIX: She presented it.

DR. DAUM: Excellent. Let's move on then. Dr. Fleming.

DR. FLEMING: I'd like to go back to Dr. Kohl, Dr. Sheet, and Dr. Griffin who have brought up a set of issues that have really been troubling me and I was delighted to see that they have pursued this.

I guess I could cast them in the broad sense of what are the durability. What is the durability of

effects. What are the long-term protective effects. I think of this in at least two dimensions.

One is what is the long-term protective effect from initial HPV infection that would relate to waning of immunologic response. But the other is what is the long-term impact on rate of progressive disease in those people who are infected.

Dr. Griffin, you had mentioned that the goal of a vaccine is to prevent the infection. My understanding is that with some vaccines the actual true clinical benefit may be achieved by the impact on the immune system in being able to control infection once infection has occurred and what do we know about that in this setting, about long-term impact on the immune system.

I would also say that whereas the effect of the vaccine may be to prevent infection or, in fact, it may be to prevent the sequelae, in essence what to my way of thinking really motivates any intervention is to prevent something that is clinically tangible or meaningful.

In this sense what we've really focused on is cervical cancer. It seems to me entirely likely based on the epidemiology that large numbers of people become infected and the immune system is already

capable of clearing the infection in a manner that there are no sequelae.

What I worry about is just because there is this association and it may be causal. If we provide protection in 80 percent or 90 percent, it may be that those are the very people whose immune system was already capable of clearing the infection and, hence, preventing the clinical sequelae.

I think this does become inherently very complex and I think these issues of long-term impact are important not just from the perspective of what's the ability because this is a chronic risk situation. A 20-year-old woman will be at chronic risk for infection.

Beyond that even when you do become infected, what is the overall impact of the vaccine induced immune response on progressive disease, not only over the short-term but also the long-term. These are a lot of questions that I'm very uncertain about.

DR. DAUM: Thank you, Dr. Fleming.

Dr. Snider, then Dr. Katz.

DR. SNIDER: With regard to the issue -- continuing with the issue of preventing infection, I'm still having some mixed feelings about that.

I mean, certainly with hepatitis B, for example, if we had said the most severe consequence of hepatitis B is cirrhosis and hepatic carcinoma and we want to establish a trial to show reduction in cirrhosis and hepatic carcinoma, the size of that trial would have been tremendous and it would have taken a very, very long period of time.

Then the issue of preventing infections that are trivial. We've dealt with this before. I mean, as everybody knows, what are the numbers, Sam? I mean you prevent 100 infections or is it more for every clinical case that occurs.

Right now we don't know how to pick out who is going to develop paralytic polio so we prevent a lot of infections with polio virus that are going to be trivial. It seems to me that -- I understand that the question has to do with intended to prevent cervical cancer and that this is perhaps a little bit off the mark in terms of addressing the questions.

I guess I'm still wondering with Diane if there is not enough evidence to suggest that preventing infections may be something that is quite useful, particularly when I hear that persistent infections are likely to result in maybe not therapy but in terms of additional interventions which I

understand the cost of those can't be -- the dollar cost can't be weighed in this discussion but performing these procedures do inconvenience people.

They result occasionally in certain morbidity. Then dealing with some of the lesions that will not apparently result in cervical cancer there is not only morbidity but some low-level of mortality from complications.

I guess all I'm trying to say is that I see some societal benefits perhaps of preventing infection which doesn't mean I would give up in any trial design in trying to get a trial design that would also show that there was a reduction in the higher grade lesions.

I don't think we're going to be able to use -- I mean reveal right now cervical carcinoma as an endpoint. I don't think ethnically that's justifiable. Nevertheless, as intermediate endpoints it seems to me those are very worthwhile. The question becomes whether that would be sufficient information to recommend a general use of the vaccine or not.

DR. DAUM: There are three people who want to commend on what Dixie said before we go to Dr. Katz next. First is Karen Goldenthal and then Tom Fleming.

DR. GOLDENTHAL: I just wanted to make a comment about endpoints for vaccine clinical trials. It seems that for most of them, in fact, there has been some type of clinical case definition associated with it. I mean, for example, in polio in the Francis trial, the Francis Field trial, it was really paralytic polio was the endpoint.

With regard to hepatitis, I keep hearing about hepatitis and infection was the endpoint. Certainly in the FDA label it says that the vaccine is indicated for the prevention of hepatitis B infection.

But all this talk about hepatitis B also prompted me to go back and look at the smuness and don Francis efficacy trials. In both of those trials there was actually -- they did show a prevention of infection, but they also showed a prevention of hepatitis that was significant between the vaccine and the placebo group. I just wanted to make that point clear.

DR. DAUM: Thank you.

Dr. Fleming. We are going to stay on this very point for a minute.

DR. KATZ: It relates to exactly what Karen has said.

DR. DAUM: Go ahead. But Dr. Fleming is

next.

DR. FLEMING: I yield the floor.

DR. KATZ: I hate to disagree with you but the very data you're quoting you do not prevent infection. They showed very well that with hepatitis B vaccine you could have infection as shown by the fact that individuals developed anti-core antibodies.

DR. GOLDENTHAL: And certainly some of them did.

DR. KATZ: So you prevent hepatitis but you don't prevent infection and that's why what Tom was saying I think is to me -- again, I apologize. I'm the vaccine person. I'm not the gynecologist. With most vaccines you do not prevent infection. You abort infection and you use polio as an example.

If you take individuals who have been immunized and don't get paralytic polio, they will shed virus. If they are exposed to enough virus, they'll shed virus for an abbreviated period of time in contrast to the naive individual who has never seen it before. I think the concept that you prevent infection is looking for too stringent a criteria. You abort infection and prevent persistent infection.

DR. DAUM: Thank you, Dr. Katz.

DR. KATZ: Sorry.

DR. DAUM: No problem. There was light shed on issues.

DR. FLEMING: I'm delighted to hear it. I concur.

Dixie, I want to just follow up on your thought about if you prevent the infections. We have considerable evidence. It is association evidence but there's considerable evidence that there is a necessity here. HPV infection is a necessity in the overall causal process that leads to cervical cancer.

What I've been struggling with all along is this issue of sufficiency. You had used as an example, and it's probably a very reasonable approximation, maybe for every 100 infections that you would prevent, you would prevent one case of cervical cancer.

If I knew that if I prevented those 100, I would prevent the one case of cervical cancer, I would be persuaded that I'm achieving something very important. I'm not of the perspective that I have to know if I prevent 100 infections that I'm preventing 100 bad things.

My big concern is that I may prevent -- if, in fact, I have 100 percent efficacy as a result, then I can be confident that when I'm preventing all 100 of

the infections with my 100 percent efficacy that I am preventing those 1 percent of the cases of cervical cancer that will follow.

My concern is if I prevent 80 of the 100, I may well be missing the one, in fact, that would have resulted in cervical cancer. If I have 80 percent efficacy or 90 percent efficacy even, I may have almost no efficacy against what I really care about.

It's the sufficiency issue that I keep saying. It seems to me that because this is a setting where the numbers suggest that it's something on the order of 50 or 100 people who will have HPV infection for everyone one that eventually will over their lifetime have cervical cancer, this is clearly a situation where it's far more complex than simply saying is the vaccine going to prevent the initial infection.

What I'm struggling with here is what is it that we have to achieve in order to be confident that we are actually having a meaningful impact on what we really care about which is reducing the rate of occurrence of clinical events.

Now, we focused on those clinical events being primarily cervical cancer. I would, however, accept a broader sense of clinical events, i.e., if we

believe that we are also achieving a reducing in the need for invasive surgical interventions, etc., that's part of the overall benefit as well, although I think our highest priority clinical event here is preventing cervical cancer

So the bottom line is we acknowledge we're preventing many more cases of infection than we are clinical sequelae, important clinical sequelae. I just want to know that when we do get this reduction it translates into a meaningful reduction in cervical cancer.

DR. SNIDER: Could I just quickly respond and say, Tom, I think you and I are in agreement. All I'm saying is that if we don't look at persistent infection as one of the endpoints, it seems to me that would be a shame because we're not preventing persistent infection. I'm not optimistic that CIN 2 and 3 are going to be prevented.

DR. FLEMING: So you're saying that's in your vision of what the markers would have to be. That's one of the necessary components that has to be impacted.

DR. SNIDER: Right.

DR. FLEMING: I'm very willing to accept that. I'm struggling with what are the other elements

that give me a sufficiency condition here such that when I see persistent infection and what else, is this going to be adequate to be reasonably confident I'm having an impact on cervical cancer rates.

DR. DAUM: Okay. We're going to stay on this issue before we go on so people who want to talk to this very issue. Dr. Reeves, Dr. Felix, Dr. Kohl.

DR. REEVES: Just a quickie of something that I would have liked to have heard and I don't see any of the NCI people that can give the answer. I think this vaccine to prevent cervical cancer is going to be unique among vaccines. Diphtheria, influenza, and many of the vaccines I'm aware of work very quickly.

Rolando Herrera, I believe, two years ago presented some very elegant modeling studies of the effect of vaccination on the rates of cervical cancer world wide which, again, is the end disease we're trying to deal with.

In essence he showed that it was going to be approximately two decades before any effect was seen. I think this rather important information, something to take into consideration both in looking at whether we're going to approve or recommend approval for accelerated licensure. But two to three decades is a

long time to actually see an effect from something.

I suspect that the actual effect on surgical procedures for high-grade dysplasia or CIN 3 with the actual public health effect and efficacy of this is probably going to be in terms of decades as well. I think some kind of presentation of that kind of information would have been very helpful.

DR. DAUM: Dr. Felix and Dr. Kohl, this very issue we're on.

DR. FELIX: I appreciate the concerns that Fleming has. I have the identical concerns. However, if you're proposing that by producing 80 percent or 90 percent of the HPV you may not be reducing the 10 percent that will proceed to cancer. The same identical argument can be used for the more distal surrogate endpoint which would be high-grade dysplasia or CIN 2, CIN 3.

If you prevent 90 percent of CIN 2, CIN 3 it is perhaps that 10 percent that you don't progress that you don't protect for that will progress to cervical cancer. I don't think it is reasonable to expect a trial with an endpoint of cervical cancer. I don't think it will happen if that's the case.

I think Dixie was correct. I think we need to keep assurances that all of the reasonable

endpoints will be looked at, that we're going to look at persistent virology, and the issue that I'm most concerned with that I hope we are going to address very soon, the issue of what interval does persistence truly become meaningful.

Then have relative assurance that we are going to see CIN 2, CIN 3 data. It is, I think, within the realm of this committee to insist that the trial for the latter be finished by the time the accelerated approval for the virological endpoints come out so that we could guarantee that the second trial or the second observation would happen.

I don't think that it is reasonable to expect anymore than the surrogates that are still going to leave doubt as to the efficacy of the vaccine.

DR. DAUM: I think in our own way we are starting to build consensus.

Dr. Kohl next. This very issue. We're still there. Then Dr. Unger, Katz, and Sheets.

DR. KOHL: I'm feeling a consensus also hopefully, what I'm thinking is the consensus as the same thing other people are thinking.

DR. DAUM: We'll find out.

DR. KOHL: Being at this end of the table,

all the way at the end, this is the Dixie memorial seat down here, I'm trying to think as a virologist now. We are dealing with a virus but a virus that has an interesting effect, namely cancer.

I'm trying to think what we know about -- at least what we've been presented about the immunology or the protection against first infection. Perhaps more importantly the immunology against cancer, the prevention of cancer.

I don't think we've heard much to anything about the immunology or the prevention of cancer. Most of what's in the literature, that I'm familiar with at least, regarding the viral like particles is the elicitation of neutralizing antibody.

Yet, we know that the -- or we think we know that what causes cancer are the E6/E7 transforming elements. Then there's the whole issue of latency.

What I want to get around to in a sort of sequitious way is following some of what Dr. Fleming is talking about. What if we have that heterogenetic population where a small percentage, because of immunological aspect we don't understand, is very susceptible.

And what if paradoxically neutralizing antibody doesn't have a positive effect but has a

negative effect? It's wild. It's outside the box, but it's one of those things we just don't know about. I think all these uncertainties would push me towards a more rigorous endpoint as we think about surrogate endpoints.

DR. DAUM: Thank you.

Dr. Unger.

DR. UNGER: I just want to remind everybody about the difficulty in the assays in talking about infection and persistent infection.

DR. DAUM: Talk right into the microphone.

DR. UNGER: Okay.

DR. DAUM: Thanks. Sorry.

DR. UNGER: I'll start again. I just want to remind everybody about the difficulty of establishing infection, the difficulty both in the assays and the sample. I think that we need to be sure that the sample is taken appropriately and the appropriate amount of the sample is put into the assay.

You can have the most eloquent and sensitive assay in the world but if the sample is not the appropriate sample and enough is not put in, it's going to make your definition of endpoint and infection a moot.

I think that the literature is very clear that the assays and the sampling will muddy the kind of pictures that you see. We need to be clear on what kind of documentation we want to see or should be part of looking at this kind of persistent infection.

I think that the better the assays have become and the more standardized the sampling has become, the clearer the picture is as to what the situation -- not that it's clear now but there is starting to be some consensus.

I think part of the confusion is the definition of persistent infection and the timing that should be required in order to say what persistent is versus a normal endpoint of clearing of an infection that would go away on its own.

DR. DAUM: Dr. Katz at last.

DR. KATZ: I would like to go back again to what Dixie has said and what Karen has said. Viruses are all different and it's very inappropriate to make generalizations because this virus does this, that virus does that.

But the example that's been used is a reasonable one of hepatitis B. Why did they start looking for hepatitis B vaccines? Not just to prevent acute disease but because Palmer Beasley showed in

Taiwan where they had a high incidence of hepatocellular carcinoma and that hepatitis B infection led to hepatocellular carcinoma.

The studies that have gone on there over the years now have shown they markedly reduced hepatocellular carcinoma to a rare disease in Taiwan because they gave vaccine to young people.

Now, it does prevent hepatitis over disease but it doesn't prevent occult infection and you may have occult abbreviated infection. This, as I mentioned in response to Karen, is shown by the fact that the vaccine only gives you antibodies to one antigen, the surface antigen.

You can show that vaccinated people, though they don't have the disease, develop antibodies to the core antigen which indicates they have not only been infected but they have been infected sufficiently to arouse an immune response.

Those people who have totally lost detectable antibody to the surface antigen nevertheless resist developing clinical disease or chemical disease. We have a model which is not a perfect paradigm, but I think we do have a model, at least, of where preventing an infection from developing beyond an abortive state does prevent the

development of cancer.

I think the long-term effects of this can be in some ways analogous, if you will. Not a perfect one but I'm encouraged that if you can prevent infection with these oncogenic papilloma viruses you may well prevent cancer.

DR. DAUM: Thank you, Dr. Katz.

Dr. Sheets.

DR. SHEETS: I guess I'm simply a gynecologic oncologist. Not a virologist nor immunologist, nor a vaccinologist. When I think of human papilloma virus infection, I think of the transvaginal infection that may or may not ever be systemically manifested. Even invasive cancer you may or may not show systemic antibodies to E6/E7 my understanding is.

When we think about this vaccine and we think about this vaccine and we think about proximate surrogates or distal surrogates as to what that might eventually prevent invasive cancer, we have to think about what's happening with the mucosal barrier.

The vaccine is supposed to prevent infection by neutralizing antibodies being present in cervical mucosal discharge that keeps the virus from infecting the epithelium. That's my understanding of what the

vaccine is supposed to do.

We don't know, and I think hepatitis is certainly a good surrogate systemic infection to look at for the development of a cancer. But what we don't know is the latency issues of HPV. We don't know that.

You are discussing the fact that latent virus associated with hepatitis B may cause -- does cause hepatocellular cancer. Eradicating that virus you may get infected but having the antibody potential systemically to kill that viral infection does preventing the latent state leading to hepatocellular cancer is a surrogate marker for HPV infection.

I simply don't know that. I don't know if that's true, but I think it's out of the venue of this discussion to decide whether we're going to move forward with a fast track for this vaccine or not.

I think what it underscores is the fact that we don't know how HPV induces ultimately cervical cancer in the epithelium and what the immune response plays in that role for therapeutic interventions or prophylactic interventions.

But we have to assume that the stuff the vaccine is causing is simply to block the infection itself and may have secondary effects of T cell

responses, etc., etc., should there be a small amount of virus that penetrates the epithelium and causes a T cell response and we do get efficacy in that system. We don't know that yet.

Maybe the NCI knows that but I don't at this point in time. I think we have to look at the data that's here and the decision that we have to make is one step away from cervical cancer. The question is how many steps away will we allow. If we allow it to be too far away, will we ever know the real answer.

My concern ultimately, and it's a step beyond what we're talking about now, is the apparent efficacy of the vaccine is so great for preventing infection will we ever be able to carry a placebo group forward.

DR. DAUM: Can you help me with one more expansion of your comments?

DR. SHEETS: Maybe.

DR. DAUM: Are you suggesting that there is a scenario -- supposing we had a crystal ball here and we knew that this vaccine was being universally used now and it meant that HPV infection was efficacy 100 percent prevented. Can you imagine a scenario with that being true where it would not have an impact on cervical cancer?

DR. SHEETS: 100 percent efficacy for both male and female?

DR. DAUM: Yeah.

DR. SHEETS: So that you're not re-exposing them chronically to the virus?

DR. DAUM: Yes. Let's go whole hog.

DR. SHEETS: How could it not? If you eradicate HPV it would impact. No doubt.

DR. DAUM: Okay. Good.

DR. REEVES: It would be next on the list behind measles.

DR. FLEMING: Let me just make sure your question is clarified. When you say 100 percent that suggest to me that you mean 100 percent across all types and 100 percent across all time. Then if that is the case, then I'm happy to say yes, too. There's a lot to that question.

DR. DAUM: Let me clarify. Let me say all time, yes, but all types, no, only the types in the vaccine. Yes, 100 percent against all the types.

I'm trying to get a sense from people who really understand the subject which does not include me, whether or not it is conceivably possible to prevent HPV infection completely and at the same time not assume that cancer is prevented also. That's what

I'm trying to understand. Is there such a scenario?

Does anyone want to speak to this? Diane.

DR. GRIFFIN: No. If you're talking about HPV 16 induced cancer, if you prevent all infections, you will prevent HPV 16 induced cancer. I also want -- I mean, I think the links are extraordinarily strong and we certainly understand a whole lot more about how HPV induces cancer than about how hepatitis induces cancer which, as far as I understand, we have relatively little understanding of that pathway.

We understand that much better for the HPV. We don't have a perfect understanding of that but it does require infection and it does require infection that is over some period of time and I don't know what that period of time is.

I think you are ignoring a lot of virologic data that has come in for a long period of time about these links and about the pathogenesis of this process.

DR. DAUM: I'm going to try and maintain some sense of order here. I wrote the rules myself and jumped in, but I have Dr. O'Connor first, then Dr. Felix, Ms. Fisher, Drs. Reeves, Katz, Kohl.

DR. O'CONNOR: I get the impression there are a lot of topics floating around here. I wanted to

go back and address endpoints for just a minute and say very quickly that I agree with both Dixie and Juan as far as the endpoints go.

I think there is enough evidence to indicate that persistent papilloma virus infection is associated with CIN to the point that it can be considered a vaccine failure, surrogate or not. Certainly identification of it is accelerated enough that it might be considered surrogate.

I think there is excellent evidence to indicate that CIN 3 is associated with cervical cancer, although the information regarding CIN 2 is not as clear because criteria for diagnosis are not that reproducible. I think there's enough there to say that CIN 2 should be lumped in with CIN 3. CIN 1 doesn't work just because it's a polyglot and the diagnosis is extremely irreproducable.

The last thing I want to say is that we're talking really about histologic diagnoses and not cytologic diagnoses. You need to be clear on that. Even though the specificity of cytology gets better as the abnormality gets worse, you still have a significant number of HSILs, and I'm talking about cytology, that will have no dysplasia or low-grade dysplasia on biopsy.

I think it's best to leave that as a screen test. When you're talking about endpoints talk about a directed biopsy or excision procedure that will give you a histologic diagnosis.

DR. DAUM: Thank you, Dr. O'Connor.

Dr. Felix.

DR. FELIX: I am going to have to politely reverse Dr. Sheets' disagreement with me and disagree with her. I don't think that necessarily the function of the vaccine is to prevent infection. I think that you can have an extremely efficacious HPV vaccine if you abort infection early.

In other words, induce regression at an accelerated rate. We know that regression results in prevention of cervical cancer. I don't think that you necessarily have to prevent infection in order to make an effective vaccine. Obviously the examples have been brought forth for hepatitis B.

I think that it's a very reasonable analogy to make at this point. I think if you have cellular immunity that will act in aborting a lesion early on, you can, in fact, enhance prevention of cervical cancer.

DR. DAUM: Thank you very much.

I have Ms. Fisher, then Drs. Reeves, Katz,

Kohl, Palese, and Kim.

MS. FISHER: In terms of the idea of eradicating HPV infection by vaccinating all women and men, how do you know you're not going to put pressure on an organism to change into a vaccine resistant form when you're only using certain types such as HPV 16 and 18?

DR. DAUM: That's a provocative question. I don't think we do know.

DR. GRIFFIN: You won't change those into new types but you may have the opportunity for other types to now fill those niches and we're not going to know that until we do the studies. That's the reason one of the things that needs to be incorporated into the studies is looking at these other types.

DR. DAUM: People would have to be mind of those things, I would think.

Dr. Reeves.

DR. REEVES: I had a couple of points and they kind of go back a bit. I disagree completely that if we eradicated HPV from the face of the earth, all types of infected genital mucosal, that we would necessarily prevent cervical cancer.

If, for example, we eradicated hepatitis B with a vaccine program and we eradicated hepatitis C,

we would not, in fact, eradicate hepatocellular carcinoma or cirrhosis.

DR. DAUM: Due to those agents?

DR. REEVES: I'm talking about the disease because the disease is a complex multi-factorial disease of which HPV is currently the most important associated risk factor.

Unfortunately, I remember in the old days, and I think same probably remembers this, too, when herpes II caused this disease. It is not necessarily a simple disease. We have an ideologic agent highly associated with the disease and vaccine will probably have a major effect on it.

I go back to hepatitis B. The timing of the vaccine, as I recall, was very important in the prevention of hepatocellular carcinoma. It was infections of young children I think more associated around the time of delivery or transplacental transmission that was important. The timing in which this vaccine is given is very important. We talk about naive women, women who have not been infected with the agent before, that's probably not the group that's going to be vaccinated. I don't think we always know what naive means in terms of this agent.

Finally, there is at least one agent that I

am aware of, unless it has changed, respiratory censishal virus, an apparently very good vaccine made worse. That possibility --

DR. KATZ: It wasn't a good vaccine. That's not fair.

DR. DAUM: Can you clarify one thing that you said? If you prevented, let's say, two serotypes of HPV, would you prevent an infection by those two viruses? Would you prevent cancer caused by those two viruses?

DR. REEVES: I think what we want to do is prevent the affects of the infection, so preventing the affects or ameliorating the affects of the infection. Preventing the infection would obviously do that but one would not have to prevent the infection to ameliorate the affects of that infection if that involves integration, over expression of E6/E7, etc. I think obviously preventing the infection would prevent the disease that resulted from that infection, yes.

DR. DAUM: Thank you. Thanks very helpful.

Dr. Kohl, Dr. Palese, Dr. Kim.

DR. KOHL: I want to genteelly object to one of my chairman's constructs.

DR. DAUM: For the first time.

DR. KOHL: Absolutely. He proposed the possibility of 100 percent prevention of an infection and then the resultant 100 percent prevention of a disease associated with that infection, namely, prevention, let's say, HPV 16 and then prevention of HPV 16 associated cancer. I would agree that is probable.

But I think as one of my favorite people, Ross Perot, said, "The devil is in the details." He's not really one of my favorite people. I can't think of any vaccine -- any vaccine, let alone a mucosal vaccine, that is capable of preventing 100 percent of infection. I can't think of that as a possible scenario.

Therefore, I'm left with some finite percentage of people in whom the prevention won't be complete, who will still get infected. It's that small percentage, because they have some unknown immunological situation that Barbara Fisher alluded to yesterday, that causes some people to progress who I'm most concerned about.

Do they have latent infection of some kind? Does antibody make that worse? I don't know. It's that little group of people, 5 percent, 10 percent, 15 percent, that I'm concerned about and that's a big

unknown with this vaccine.

DR. DAUM: Steve, my comments were by way of requesting information from experts to try and get at the solidness of the link between infection and the consequences. Of course, it can't be 100 percent effective but in hemophilus there are some people who are clearly still at risk of disease because we still have a few cases occurring despite full immunization.

DR. KOHL: In some of them we know why.

DR. DAUM: The 100 percent was a hypothetical discussion.

DR. KOHL: But it muddies the water, I think, because it leaves out that 5 or 10 percent who will still be infected for sure and whom we know very little about why that's the case and what a vaccine will particularly do in that setting in those people.

DR. DAUM: Thank you.

Dr. Palese.

DR. PALESE: I just want to raise the question about the safety of the preparations which are being discussed right now. These are, if I understand it right, inactivated so they are viral like particles.

I want to ask whether there is any evidence that they have any unacceptable side effects, or that

there were any exacerbations of any kind of disease associated with giving this experimental preparation.

Is anything known and what is the longest time period that we can consider here so we can have the earliest preparations being administered? Is there anything known? Have we heard anything?

DR. DAUM: I'm going to call on Dr. Goldenthal because my sense is that although safety is crucial to any plan to go forward with the deployment of this vaccine, it hasn't been among the things that we've been asked to consider today, at least head on. How would you like us to take up this question of safety, Dr. Goldenthal?

DR. GOLDENTHAL: Well, I think that it's a reasonable topic for discussion, especially when we get to question No. 2 because one of the issues there would be potentially the amount of safety data that we would have prior to licensure. I think it's a legitimate thing.

In answer to your question, I think I can say in general there's been maybe three years or so of follow-up on individuals who have received VLPs in various trials. The numbers are fairly limited at this point. Maybe a few thousand at most.

It would be hard based to make, you know,

based on -- while there's nothing that's been troubling that I'm aware of, it also would be hard to make a lot of conclusions at this point.

DR. DAUM: I think when we focus more on this accelerated approval question and I think we need to return to this issue, at least only to state what we believe would need to be done before we would be comfortable.

Dr. Kim.

DR. KIM: Well, we heard a lot about some aspects of HPV infection and how infection would either regress or persist. Again, we also talk a lot on the issues of a persistent infection which has been very arbitrarily defined and interpreted amongst all of us.

I have not got the concept yet. What is the biological relevance of persistent infection, particularly as it relates to CIN 2 and 3, not cervical cancer at this juncture?

DR. DAUM: Thank you.

Dr. Goldberg.

DR. GOLDBERG: My question -- it's a comment really. We saw a lot of data on different intervals for defining persistence, the time between the two successive observations.

It seems to me that a study such as the one we heard from the NCI yesterday should allow us to be able to look at the distribution of lengths of persistence in a large population and then relate back to later events.

I would like to see that kind of thinking incorporated into the trials that are designed regardless of what endpoints we choose because I think this will be relevant as we go forward.

DR. DAUM: Dr. Sheets is scheduled to speak next and maybe I would ask before you make what comment you wish, could you address Dr. Goldberg's question in that if persistence is going to be used as an endpoint, vis-a-vis question 1b, then what definition does a real expert in this recommend that we use? Clarify your question first.

DR. GOLDBERG: Okay. I'm not convinced that I saw anything that would give me great comfort in any of the definitions. What I'm suggesting is that as we design trials going forward that we incorporate the ability to look at the distributions of the lengths of time between the successive positive tests for HPV.

I think particularly the information from the control groups will inform out thinking with regard to the influence of this on the later endpoints

such as CIN 2 and 3. What I'm thinking is that if you cut that interval too short, you're taking away all the cases.

You're using cases that would have resolved by themselves that will have no impact. If the interval is too long, you may be practically there. I think you can get some information.

I think the NCI trial that we heard yesterday, if I understand the data correctly, and if the remainder of the cohort other than the ones that were positive at entry are examined over time and you may get some important information.

It's sort of like developing a receiver operating characteristic curve on different cut points for the definition of what the interval between successive positive HPV tests are that would be meaningful later.

DR. DAUM: Now, Dr. Sheets. Thank you.

DR. SHEETS: I don't think I can speak specifically to the NCI close session data talked about yesterday.

DR. DAUM: Nor do we really want you to.

DR. SHEETS: But I do think it's relevant to say at this point in time in 2001 that we don't know the answer to your question in regards to what

represents a persistent infection that's clinically relevant, or if that is even important depending on your time point or endpoint or what you want to prevent.

Ultimately we want to prevent invasive cervical cancer, both adeno and squamose. That's the goal here. We don't know whether we can translate HPV presence, high-risk oncogenic presence, specific to the viral type being vaccinated against as being a surrogate for that or not. That's the discussion I think is on the table.

I'm not an expert in that in terms of virology persistence, but I would say that I don't know yet from the data that I've seen in the world's literature, nor heard in closed session that I can make that statement. It should be incorporated into whatever trial we decide is endpoints.

I guess within the bounds of what can be presented here in open session compared to closed, I would like to hear from Doug Lowy his point of view in terms of what this vaccine or vaccines in general that are prophylactic would probably be the best way to phrase this. A prophylactic vaccine using VLPs theoretically should be doing for us in terms of how it interrupts the HPV cycle or if we know that at all

in this point in time because I think it's an important consideration in answering Dr. Felix's disagreement with me, disagreeing with me over what we're agreeing as to whether you actually do get an infection, yet dissipate that infection so it doesn't become clinically relevant and the vaccine does do that for us.

My concern is that we're using a systemic system both across the table and over here, an hepatocellular infection that is not necessarily the same as what we're talking about here today in the mucosal immune system. I'm just interested in hearing what Dr. Lowy could point out in that. Is that possible?

DR. DAUM: Is Dr. Lowy here?

PARTICIPANT: Yeah. Right there.

DR. DAUM: Do you care to comment on this? You're not obliged to.

DR. LOWY: Ellen, thank you very much. I think that the issues that are being raised are very pertinent and relevant to the discussion. My colleague, John Schiller, may want to amplify on some of my comments.

My sense of the VLP vaccine is that it is going to be doing -- it is basically going to reduce

the inoculum. We haven't talked much about viral inoculum but with most infectious diseases the size of the inoculum has a very important impact on disease downstream.

By reducing the inoculum there should be one of two outcomes. One is that you would completely prevent infection, and the other would be that you would reduce the number of infectious hits.

There also is a possibility it's ambiguous whether the target, which is the transition zone of the cervix, is the immediate site of infection or whether there might be a remote site distant from that.

You could imagine that antibodies might have a further impact on reduction of going to the site of the target, if you will, analogous to the hepatitis situation where you get infection but it doesn't get in sufficient numbers to the target. I think it's ambiguous which way that would work. In the best case scenario it would be a complete prevention of infection but I certainly wouldn't expect it to do that in all individuals.

In terms of the long-term persistence of antibodies, I suppose it's hypothetically possible that might have an adverse impact, but there is no

theoretical reason to believe that you are going to be -- that it would have such an impact.

We haven't seen in the limited trials that we have done which involves maybe 100 individuals, we haven't seen a group of people who are particularly resistant to responding in terms of immunity or particularly susceptible when we look at the bell-shaped curve.

The concern of Dr. Kohl that maybe you're picking out a particular group of people, I think while it's hypothetically possible, I don't think we have a coherent notion that the latent infection would be more likely to be more serious because of antibodies being present, although I think hypothetically that might be a possibility.

With regard to persistent infection, I think that Dr. Fleming is, of course, raising a very important issue about the duration of infection.

It's one of the reasons why when one picks persistent you would like to have a relatively long period of time, thereby increasing the probability that by reducing those persistent infections that you really would be having an impact on the clinically important downstream events.

The precise number whether it should be six

months, 12 months, 24 months is going to be somewhat arbitrary which is what Mark was trying to point out yesterday. There are some data now, and there will be better data.

Even when you get the better data it's going to be a balancing act. I guess with Dr. Wilkinson, I think that he raises a very important issue of the question of referring people for colposcopy.

My question for Dr. Wilkinson would be if you get referred to for colposcopy, what's the likelihood that you would be biopsied? Because if you were going to be biopsied, then you presumably would be out of a clinical trial.

DR. DAUM: Having said all that and being practically oriented, given all your expertise and given the arbitrary nature of the decision that I'm about to ask you for, if you were to pick, and emphasis on the word "if," persistent infection as an endpoint, what definition would you use for that?

DR. LOWY: I really am relying on Mark because he is our expert. He is our medical epidemiologist. He feels that an appropriate balance would be a year, that you will be clearing out most of the, if you will, clinically irrelevant infections and it will have a high predictive value of preventing

significant proportion of the downstream events.

DR. DAUM: One year. Thank you very much.

Okay. The next people to speak are Drs. Snider and Myers. Are these clarifications of this very issue?

DR. SNIDER: Yes.

DR. DAUM: Okay. Then Drs. Griffin and Snider. Dr. Snider, you're next anyway. Why don't you go first and then Dr. Griffin on this very issue. Then we'll go on to Dr. Myers next.

DR. SNIDER: I would like to just pick up on the comments that were just made. The trade off, as I understand it, is even more profound in the sense that it's not just specificity of the study endpoints, but there are some clinical implications, some ethical implications in terms of the intervals you choose.

If you choose a shorter interval, of course, then you have the possibility that's already been mentioned or the certainty that's already been mentioned, that you'll be calling a lot of endpoints, significant endpoints which are not significant in the sense that they will regress.

There also is a clinical corla in the sense that it sounds as if whatever interval is chosen, there will be some interventions that again will have

some not only economic cost but some morbidity and at least psychological morbidity and physical morbidity associated with them.

The longer you go the more specificity you get, but then if I understood correctly, for two reasons you may wind up with more cancers. One is because there are a few women who would rapidly progress. If you went to two years, for example, there are a few women that I think he said you would lose. I think he said you would lose but I think what he meant was they would progress quite rapidly to cancer.

The other, of course, is this whole issue of compliance in clinical trials. The longer you wait, the more you signal that this is not all that important and women start dropping out and they don't come in for that two-year visit.

Again, you run the risk of having these very serious outcomes that have more morbidity and perhaps even mortality associated with it. It is a delegate balancing act.

I just wanted to at least indicate some of my understanding about some of the value judgements and some of the ethical and other implications of making that choice. There is no exactly right answer

right now.

The other thing that has to do with persistent infection in terms of how you define it is not just the interval but it has to do with how many specimens you want. Also, as has been pointed out, how you obtain those specimens and what assay you use.

These are all critical issues in terms of defining persistence to have to be looked at very carefully. I'm not sure this committee can get into all of those details but there are some general principles, I think, we could probably articulate about what we would like to see with regard to the intensity in which one investigates and the characteristics of the test.

DR. DAUM: Thank you, Dixie.

I have Drs. Griffin, Myers, Freeman, Pagliusi, and Kohl.

DR. GRIFFIN: I just wanted to comment on and get Doug to expand on the reason that persistent infection is such an important part of the pathogenic process that we are trying to prevent and also examine in these women.

It's my understanding that the longer the virus continues to replicate in its site, the increased likelihood that you'll get integration,

which is a random event, and other oncogenic changes in those cells that will then eventually result in carcinoma.

That is sort of the biologic principles under which one becomes interested in persistent infection and the length of persistent infection. But I would like Doug's comment on that.

DR. LOWY: This is a series of genetic changes presumably and the more opportunity you have in terms of chronologically, the more likely it is to happen.

DR. DAUM: Thank you.

Dr. Myers, please.

DR. MYERS: I'm not a papilloma virologist but I think we need to be careful about some of the terms we're using like inoculum and persistence and latency and replication because we really don't know how to measure those in the circumstances that we're talking about.

I guess the question is, to go back to the comment that you made, the reducing inoculum. Is that really the intent or is what we're trying to do is alter the natural history of persistent outcome? I think that's important if you go back to Dr. Reeves' comment earlier.

This vaccine is not going to just be given to naive individuals. I think we need to explore -- and we haven't really talked much about this but we really need to explore the intent to immunize the outcome from the intent to immunize.

When we're talking about persistence and when we're talking about high-grade disease, we need to address that in individuals that are both HPV 16 and 18 positive as well as naive because we really don't understand these virologic events in the natural history of the clinical setting. I think we've been skirting that issue.

DR. DAUM: Thank you, Dr. Myers.

Dr. Freeman.

DR. FREEMAN: I just wanted to make a brief comment that the choice of these endpoints and, in particular, the precision with which these endpoints can be determined, I think, are incorporated into a trial that would lead to an accelerated approval or further I think are very important.

Not just from the point of view of demonstrating that the vaccine works but in convincing the subjects who will eventually receive -- the males and females who will eventually receive this vaccine if this thing actually works.

I'm reminded of the comments of one of the advocacy groups from yesterday that if the vaccine is approved, it really has to be meaningful in order to get compliance and usage to do what it's supposed to do.

The other thing is the physicians who are going to administer the vaccine and monitor these patients safely have to have a good idea about the -- have to be convinced that the trial really demonstrated the efficacy of the vaccine in terms of the way they understand the disease process.

I'm not sure from all that I've heard, although I am convinced of the association that has been mentioned, the association between the HPV viruses and this disease. I'm not sure how easy it's going to be to rely on the HPV endpoints as indications for usage of the vaccine practically.

DR. DAUM: Thank you.

Dr. Pagliusi.

DR. PAGLIUSI: Thank you. I would like to come back to the persistence of infection to the balancing act. I would like to address a question to the experts. Maybe Doug Lowy could help me here.

If we would think of measuring persistent infection twice, three times, four times, what that

increase the confidence and the effectiveness of the vaccine or the efficacy of the vaccine?

DR. DAUM: I'm not sure I understood the question. May I ask you to clarify?

DR. PAGLIUSI: My question is addressing persistence of infection. Dr. Lowy proposed that one year may give us more confidence on the results. My question is now if within this one year we would see three positives or four positives.

DR. DAUM: Or two.

DR. PAGLIUSI: Or two, what are the balancing here?

DR. LOWY: Sonia, I think that certainly it would be preferable under ideal circumstances to sample more frequently and to have recurrent positive results. My impression is that if you had two positives separated by whatever interval it was, you could then go back and be quite sure that this was with the same variant or not with the same variant.

Then you could be quite sure that the individual was continually infected with the same virus or a different one. I think that would be adequate.

DR. DAUM: Thank you.

Dr. Kohl.

DR. KOHL: I was a little confused. Oh, Dixie's not here. I think Dixie was implying that different time periods, i.e., a 12-month persistence or 24-month persistence would some how affect and I think he used the words "lose some women."

I was not under the impression that the amount of time that was chosen for persistence would per se affect how woman are followed for cervical cancer screening and that women would still be followed according to standard of care no matter what the time period were for what was decided as persistence. Is that correct? So no matter what you pick as a definition you're not going to "lose people."

DR. DAUM: I think we're getting to a point where people are locking in their ideas about what would be the endpoint they most favor. But before we really start systematically debriefing everybody of those few points, I would like to ask people to consider this.

Is it possible, Karen, and I hope this is within the spirit of your first question. Is it possible to consider multiple endpoints? For example, is there a possibility of designing research, a clinical investigation, a vaccine trial if you will,

that looked at different endpoints in sequence with each other and had sort of separate analyses for these different endpoints and sequence? Is that a feasible way to think about this, or do we need to focus on just one?

Karen, I would like you to respond to that first and then maybe others.

DR. GOLDENTHAL: I believe you could design a trial that way. That isn't the way we have ordinarily proceeded for preventive vaccines, but I think it's theoretically possible obviously with rigorous prospective statistical analyses plans and designation of endpoints.

DR. DAUM: Does anyone want to comment on that thought or that idea?

Dr. Kim.

DR. KIM: I was given the information that somehow linkage has been not clearly delineated and some question. I support the concept that perhaps two endpoints can be incorporated. For example, the first one would be persistent infection but second would be truly translated into CIN 2 and 3 as secondary endpoint.

DR. DAUM: Okay. Thank you.

Dr. Decker. We haven't heard much from you

today.

DR. DECKER: Or yesterday.

DR. DAUM: Or yesterday. Here's your chance.

DR. DECKER: I'm glad you brought up a point you just did because I've been thinking about that. It seems to me that if it ends up being decided that the primary endpoint for a trial would be nonvirological.

Then I think it would be imperative that their be co-primary or strong secondary endpoints that were virological, if for no other reason than so that future trials would be guided by the understanding of the links between the virological and the clinical outcomes.

To me it almost goes without saying that it would be essential that there be virological surveillance and virological endpoints measured in any trial whose primary endpoint was clinical.

DR. DAUM: Thank you.

Dr. Snider, Dr. Fleming next.

DR. SNIDER: I's just like briefly to address that point, too, I think in view of the evolving knowledge base, the rapidly evolving knowledge base around this issue, having that kind of

a trial may be not only advantageous to the FDA, this committee, but to the manufacturer as well because it allows you in one trial to make adjustments as new information becomes available rather than going out and having to redesign the trial. There's a lower risk of having to redesign trials.

DR. DAUM: Dr. Fleming is next.

DR. FLEMING: Bob, I strongly endorse your thought. I think in this setting where there is such uncertainty, and I think Steve had mentioned it earlier, it certainly leads me to be more cautious. The benefits of looking at a multi-dimensional or multi-variate type of outcome certainly does give us chance of capturing a broader spectrum of the nature of what the effects are.

After we discuss this broad issue, in fact, I had two or three other specific issues that I was hoping to discuss that really relate to this, to two of the domains of what I would think of as what might be the dimensions of this surrogate.

DR. DAUM: Go ahead.

DR. FLEMING: Okay. Well, one of them is we've -- my understanding is we're going to be focusing predominately on vaccines that would target the HPV 16 and 18 types. Certainly as we look at

outcome marker surrogates, the ones that will be most sensitive to the effects of these vaccines will also be type specific.

At least as I'm thinking through my own formulation of what might be a surrogate or an accelerated approval measure versus what might be a full approval measure, it would be the distinction in accelerated approval of allowing focus more on those type specific outcomes but full approval on more validation of a global benefit.

My sense of how important that distinction is I have uncertainties. My understanding from the data that was presented yesterday is something on the order of 60 to 70 percent of CIN2/3 as associated with HPV 16/18.

Before you comment on that, you can confirm or refute that, but my more important question is what is the nature of the -- how much of cervical cancer is attributable to 16/18? Will there be an opportunistic influence here? If you essentially reduce to eliminate 16 to 18, what influence does that have? Could we expect that will have on the global rate of cervical cancer?

So there's two elements to this. The one element is in the current milieu of the mixture of

these types, what fraction of cervical cancer is attributable to 16/18 and if you eliminate that causal influence, are there opportunistic influences that would alter what the ultimate reduction in the rate of cervical cancer would be?

DR. GOLDENTHAL: Well, across studies I would say that about 60 percent of cervical cancers overall globally are due to 16 and 18. That's a rough approximation.

I would suspect that in the U.S., as I mentioned yesterday, the adenocarcinoma components is becoming of increasing importance so that the 18 component, in my mind, has a lot of importance here. In terms of CIN 2/3 I think somewhere in the range of 50 to 70 percent of CIN 2/3 may be attributed to type 16 and 18.

DR. FLEMING: So you are confirming the approximate CIN 2/3 numbers that I gave, around 60 to 70 percent. You're suggesting that under the current milieu that there is a corresponding comparable percentage of cervical cancer that can then be attributable to 16/18.

The third aspect of it was is there any sense if you eliminate that component, can we conclude that we'll be left with then 40 percent, or could

there be an opportunistic aspect here such that the actual reduction in the rate of cervical cancer may be less than that?

DR. GOLDENTHAL: I think what you're asking about in part is replacement. In other words, if you eliminated some types would you have replacement with others. I've actually looked in the literature for that very -- to address that very question.

I didn't see evidence from the literature that removing, let's say, type 16 would be more likely to cause persistence of other types. Again, none of this is in the context of a vaccine trial so that has to be kept in mind also.

DR. SNIDER: Thank you. Karen, on that particular point --

DR. DAUM: Dr. Snider, is this on this very point?

DR. SNIDER: Yes.

DR. DAUM: All right. Let's finish this point. Go ahead. People are waiting in line so please go ahead and finish this point.

DR. SNIDER: I just wanted to point out that in the mathematical model yesterday this was taken into account and they assumed the reason it was taken into account is because women get infected with

multiple genotypes of HPV so that just because you're infected with 16 or 18 and develop CIN 2 or 3 cervical cancer as a result of that doesn't mean you are immune to.

It means, in fact, you're not immune to some of the other oncogenic genotypes. There would be not so much a replacement but there would be cervical cancer in people who receive this vaccine as a result of their being infected with other oncogen types if I understood the model correctly. It's a small proportion but, I mean, it's there.

DR. GOLDENTHAL: I don't think I want to comment on that model.

DR. DAUM: Let's go on then. Finally, Dr. Reeves.

DR. SNIDER: I apologize.

DR. REEVES: I have two comments, one just a follow-up on this. I would agree with everything that Dr. Goldenthal said. I mean, I think there's not going to be a rush of other types to replace it. If it works, if there is an effect with 16 and 18 associated cancers, then that gives us more evidence to make better vaccines.

I would agree with two endpoints. Actually, I was unfortunately looking at the slide and I'm

wondering if we shouldn't discuss three. To me, CIN means histologically confirmed disease and high-grade squamous intraepithelial lesions means PAP smear diagnosed disease.

I'm wondering since PAP smears are what, in fact, women screen in on, are a relatively easy procedure to do rather than following women all the time with colposcopy and biopsy to get a CIN diagnosis whether, in fact, studies should not have a large PAP smear component and include obviously with colposcopic follow-up but include reduction in high-grade squamous intraephithelial lesions as well as reduction in CIN 2/3 as well as potentially a decrease in infection or persistence of shedding.

DR. DAUM: Thank you very much, Dr. Reeves. My sense is that we've really had a fairly thorough sort of go around in terms of issues that bear on question 1, the issue of endpoint choice.

So what I would like to do is take a short break. Then upon return to begin systematically polling not as a vote but systematically hearing from each member of the panel in terms of the endpoint question. It's 10:25 here in the eastern time zone, or 10:20 according to this green clock. We'll take a 15-minute break and reassemble at 10:35.

(Whereupon, at 10:22 a.m. off the record until 10:39 a.m.)

DR. DAUM: Would everybody take their seats and get ready? Thank you very much. We're missing a few people and that's out of the table I must say. Do you know where everybody is?

PARTICIPANT: No, but I'll go find them.

DR. DAUM: Okay. We are now going to sample opinions, so to speak, on question 1. Before we do that, Dr. Fleming has a couple of succinct unspoken points to raise.

Dr. Fleming.

DR. FLEMING: Thanks, Bob. I'll just keep this to one theme, and that theme is we heard some brief discussion at the beginning of this morning about as we're struggling with defining which of these markers are really the appropriate ones to use as surrogate or replacement endpoints in accelerated approval or, for that matter, even full approval we've noted that some of these markers, certainly CIN 2/3, maybe even persistent infection, influence how interventions or care is delivered.

There has been at least some uncertainty about how that then impacts our view of the appropriateness of those markers as surrogates.

I guess the point I want to make is it's not uncommon in clinical practice in many disease settings for markers to be used and their use can be in several different ways.

Markers can be used as prognostic factors to guide patients and caregivers on risk of outcomes. They can be used as triggers for when and how to intervene. They can be used as surrogate endpoints which by definition we should mean as endpoints that serve as replacements for other ultimate more important clinical endpoints.

The point that I want to make here is that those are three distinct purposes and it may be that some markers are appropriate for some purposes and not others.

As a quick example, in the HIV world where we're looking at interventions to prevent transmission of HIV, it's clearly known that STDs are a prognostic factor indicating higher risk for transmission of HIV. But that doesn't mean that even though they are clearly prognostic markers that they are appropriate surrogate markers.

A couple simple examples of this, there were a couple of major trials done of STD inventions in developing countries to look at whether we could

prevent transmission of HIV by preventing STDs. In the RICAH trial with a mass intervention, we were successful in reducing STDs but we had no impact on HIV.

Conversely in the MELANZA trial with syndromic interventions we had no impact on a number of STDs but we reduced HIV. You can readily have a prognostic factor. Because it's a prognostic factor, that doesn't mean that it's specifically a replacement endpoint or surrogate endpoint.

It can also trigger an intervention. Classic example, in cardiovascular diseases we know that arrhythmias are risk factor for sudden death. It's clearly a prognostic factor. For that reason, it triggered many people to then use anti-arrhythmic interventions, echinide and flecunide, for example, to reduce arrhythmias which they do do with the intention of reducing sudden death.

Two hundred to 500,000 Americans a year were using them on this premise. Ultimately a placebo controlled trial was done that showed that they actually did reduce arrhythmias but they tripled the death rate.

A marker that is clearly prognostic that may trigger a physicians use to intervene doesn't

necessarily mean it's a reliable replacement measure to ultimately judge the effect of the intervention on the clinical endpoint.

The final example that I might give is early HIV infection. We can treat early HIV infection using HIV levels as a guide for how to tailor the intervention and that may well be an appropriate strategy.

If you want to mix the types of anti-virals we're using to achieve undetectable levels for an early infected HIV person, but that doesn't at all mean that reducing viral lows to undetectable levels in a certain manner is a clear surrogate endpoint for achieving prevention of long-term transmission of HIV, long-term occurrence of systematic disease and death.

Ultimately what is important is that when we consider markers in a case like this, which would be persistent infection, for example, or CIN 2/3 to distinguish the fact that they are clearly prognostic.

We know that they are prognostic. They may be used to trigger intervention. Certainly CIN 2/3 is. But whether that makes them -- it doesn't at all address whether the question that we're really interested in, which is whether they are appropriate replacement endpoints.

Although I will say -- certainly I will acknowledge that if CIN 2/3 is a trigger for an invasive surgical intervention, then a vaccine that would prevent the need for that invasive surgical intervention, that is a direct intrinsic value, but that doesn't also lead to the additional conclusion that we're doing anything specific relative to preventing cervical cancer.

DR. DAUM: Thank you very much. I think that is a very clarifying and helpful perspective.

Dr. Snider, you wanted to speak to this very issue?

DR. SNIDER: Actually, a very quick point that is a little different, and that is that it was mentioned to me at the break and sort of shamed me as an epidemiologist that I hadn't brought this up earlier. An FDA staff member by the name of Dr. Ellen Birch pointed out to me that in our discussion of concerns about eradicating HPV 16 and 18 infections in individuals.

We didn't think about the secondary effects of reducing the prevalence of those infections in the populations and, therefore, even if there were certain individuals who were not protected by the vaccine and got cervical cancer, if we were able to reduce HPV

prevalence in the population by 80 percent or so, that other people who were susceptible to cervical cancer from this infection may not even acquire it because the prevalence in the population had been reduced. I just felt that it was an important point that needed to be brought out in this consideration.

DR. DAUM: In other words, an effect in the transmission perhaps.

DR. SNIDER: Yes.

DR. DAUM: You're absolutely right. It hasn't been said and it sort of goes in the thinking of how vaccines work when deplored over a whole population.

DR. SNIDER: And Sam points out the magnitude of that would be greater if you gave it both to males and females. Still I think even if you gave it to females it would have some effect.

DR. DAUM: No, I think that it's good that it's been said. I'm sure it's been on many of our thoughts as we go through.

I would like to sort thicken the soup a little bit with raising one more issue. That is, this issue of accelerated approval. What I think we can do is have Karen Goldenthal remind us exactly what the agency means by that which she has agreed to do during

the break.

Then I think we can try going around and getting everyone to speak to these issues to incorporate this idea into your comments. I had thought initially we would go around twice but I don't think we need to. If that view needs to be reassessed, then I'm happy to reassess it.

I think that given your choice of endpoints, that you can also say how you would phase it in, how you would advise the agency to phase it in to their strategy for approving these vaccines.

In order to prepare us for this discussion, I'm going to call on Karen first to remind us in very precise succinct language, which she has agreed to do, what exactly is meant by accelerated approval and how it might phase into your choice of endpoints or multiple endpoint scenario.

DR. GOLDENTHAL: Thank you. I have a couple of points to make here. Accelerated approval is basically the use of a surrogate marker that's reasonably likely to predict clinical benefit as the basis for an approval, but that's not the end of it. You have to have a confirmatory trial that would need to be well controlled and well underway at the time of approval. I would even think at the time of a BOA or

license application submission for the accelerated approval endpoint.

Just a few things to keep in mind in that regard. This means that FDA would be asked to do an approval based on interim data with the accelerated approval application. That particular interim data would need to be presented to an advisory committee. You need to be thinking of how you would feel being an advisory committee member and having that particular accelerated approval endpoint to base your decision on.

Another critical thing pertains again to the timing of the confirmatory trial, particularly with regard to its completion. I think you need to think very carefully about whether randomized trial could realistically continue following an accelerated approval.

My suspicion is that at least in the U.S. that would be problematic. When I thought about applying accelerated approval, as I mentioned yesterday, I thought about the fact that it cuts about -- it would potentially make the vaccine available maybe a year earlier than it would be otherwise thinking of the FDA review and approval process.

DR. DAUM: Thank you, Karen.

Dr. Kohl, you have been placed at jeopardy by Dr. Stephens' departure. I'm sorry about that.

What I would like to do is to ask each person now, and we'll go around, to comment succinctly on the two questions, that's 1 and 2. I would like you to see if you could incorporate into your comments an issue that the agency has raised and asked for your comment, and that is the indication.

In other words -- I guess in other words, and Karen Goldenthal, correct me if I don't understand it, if there were an accelerated approval scenario where something were approved based on an interim indication, what would the approval indication say? I need you to sort of put that into your comments as well.

Dr. Kohl, let's start with you and we'll just get a feel for how this goes. We have a little over an hour to do this and I think we can get it done.

Not quite yet. Clarifying comment.

DR. GOLDENTHAL: Also the indication. Our question about what should the indication be also would apply to traditional approval.

DR. DAUM: Thank you, Karen. One more bit of food to swallow.

DR. PALESE: And this is not a vote, correct?

DR. DAUM: This is not a vote. This is your comment. They will be noted, recorded, and thought about, I can assure you, line by line.

Dr. Kohl.

DR. KOHL: We are being asked to consider endpoints for a vaccine that hopefully will provide long-term, possibly lifelong protection against cancer. The things that give me pause in terms of an early surrogate, and I'm not sure what is distal and what is proximal but in terms of a virological surrogate is we have no idea what the duration or protection is yet for any of these type vaccines.

There's a significant question about population heterogeneity and detection in different types of populations which I think needs to be addressed, or looked at, at least.

We don't have a clear definition of what persistence of viral infection is yet from the experts, although that may evolve in the next year or two possibly. The considerations for size obviously have to include what sample size and how long a duration would be necessary for safety as well as some kind of efficacy in terms of markers.

The last point that Karen brought up, early licensure, I think, will seriously preclude subsequent studies of this vaccine, the hypothetical vaccine, and, in fact, future vaccines for HPV prevention.

Bearing those issues in mind, what I would call for in terms of primary efficacy is a CIN 2/3 model. I would urge that this study be powered such that CIN 2/3 could be clearly defined in terms of efficacy, but it would include sequential virology yearly or every six months.

I'm not sure what is appropriate and what the best technique will be at the time that this study is undertaken. Right now it looks like it's PCR. I would include definition of all oncogenic HPVs, not just the ones that are in the vaccine so we can look at replacement.

And also would include immunological parameters that would allow us to determine what the correlates of protection are against both infection, persistent infection, and CIN 2/3.

Given that as question No. 1, then I come to is there something acceptable for me for accelerated licensure.

If this study were to proceed as I envision it, then for provisional licensure or accelerated

licensure I like something that Dr. Fleming suggested yesterday; namely, that my primary endpoint is going to be CIN 2/3 efficacy but accelerated could be a proof that there is a significant difference in CIN 2/3 between a placebo and a control.

That is, as soon an interim analysis shows a significant difference, accelerated approval might be asked for, but in that study will obviously come efficacy.

DR. DAUM: Thank you very much, Dr. Kohl. We're off and running. What you did that was really wonderful is you actually managed to address all the things I asked for and the agency asked for. If everybody could sort of make a little checklist in their minds as we go around to try and touch each of those points, I think we'll have a wonderful discussion.

DR. KOHL: The only thing I didn't address, I guess, would be what the package insert would say about what this prevented. I think it would say prevention against CIN 2/3 with probable effect on cervical cancer but not proven.

DR. DAUM: Thank you.

Dr. Griffin.

DR. GRIFFIN: Okay. With respect to

question 1, I guess my choices are A, B, and E. I think that I'm of the opinion that if you prevent A, incident infection, you will, therefore, by definition prevent persistent infection.

Now, whether you need then to -- and the main objection to saying preventing incident infection is what a criterion is for the efficacy of the vaccine and that may be much too stringent. As many people have brought up, you may get infection that is rapidly cleared and, therefore, preventing persistent infection would be a more realistic surrogate.

I think that data will just have to evolve so if you required prevention of persistent infection, you would accomplish that if you were also preventing incident infection. Therefore, I guess B would be the main virologic endpoint.

I guess I am most convinced by the one-year endpoint for persistence, definition of persistence, but, at the same time, realizing that this is a bell-shaped curve, about when the actual oncogenic activities for a virus infection would actually kick in for any individual person you can't predict.

In some people that's going to happen early and in some people that's going to happen late. In some people that's not going to happen at all. There

isn't going to be any way to predict for an individual.

Then, lastly, I think that the outcome that's most closely related to development of cervical cancer is the CIN 2/3 pathologic endpoint. What I would like to see in a trial is imbedded both outcomes, that you have two parameters.

Don't ask me how you would design this but I'm convinced that it's happening with other kinds of interventions with respect to HIV, etc., where you have early endpoints that then allow early accelerated approval, etc. But, at the same time, the same trial has enough individuals in it that you follow them for a longer period of time.

That's ongoing at the time that you're getting your early outcome data and you avoid the problem of then having to have a new trial with a vaccine that you've now got approval for and one would say you ought to be using. I would think that I would much favor a larger trial to start out with that you look at both of these, basically virologic and pathologic endpoint.

Embedded in that is then the fact that I can see accelerated approval using a virologic endpoint, i.e., persistent infection with the HPV types that are

in the vaccine. Then it's a little more problematic to say what you are preventing.

You're not going to be able to say in the package insert at that point that you are preventing cervical carcinoma or even that you are preventing CIN 2/3 if you have that data yet. You may or may not be able to say you are preventing infection depending on what the data show.

If you actually have prevented infection, you can say that with this oncogenic types. Otherwise, I guess you're stuck with saying you are preventing persistent infection if that's your outcome.

DR. DAUM: Diane, thank you very much.

Dixie, you're up.

DR. SNIDER: Thank you. First of all, I would just like to congratulate everybody who's been involved in all this work. I mean, it's really exciting to be sitting around the table talking about a vaccine that may prevent a cancer that globally and even in the United States is of great significance. I would express my appreciation to everybody in the academic community, NIH, FDA, pharmaceutical companies and so forth for getting us to this point.

As I expressed in my frustration yesterday,

it is a moving target and it does create a difficult situation in terms of making definitive recommendations but with the clarification that Karen gave us. I think it is possible for us to address these questions, at least as we view them today.

My recommendations are, I think, very similar to those who preceded me in that, at least at this point, I would be interested in designing one trial that would look at two endpoints, persistent infection and CIN 2/3. I'm assuming, of course, if you're looking at persistent infection, you're going to be looking at incident infection but that wouldn't be a primary endpoint.

I do have some concerns about persistent infection that others have already talked about as have I. How is it going to be defined not only in terms of the issues brought up there as it relates to the appropriate number of tests in the interval between tests, but the sampling methods and the assay methods and all of that needs to be carefully worked out to be sure that it's very highly sensitive in detecting the presence of infection.

Then there's the whole issue of whatever you want to call it, latent infection or an apparent infection using techniques that aren't highly rigorous

that concern me. Those are issues that have to be dealt with.

With regard to the labeling, I guess I would lean toward what Dr. Kohl, I think, has already mentioned, that the label would say if this endpoint was reached that the vaccine prevents CIN 2/3 which is associated in a high proportion with the development of cervical carcinoma.

I personally would not be inclined to support an accelerated approval approach right now. However, right now that is two important words because there is an evolving scientific database that might change my opinion and obviously the opinion of many other people if we got information.

We were able to get some information that, for example, identified subgroups of women who clearly had an extraordinarily high risk of cervical cancer or progression to CIN 2 and 3 with persistent infection. It's conceivable that somewhere along the way during this trial that an alternative could be revisited.

But, at this point in time, I think there are enough uncertainties about the significance of persistent infection and how you define it that I would be a little reticent to advise FDA and the manufacturer to proceed along those lines and bring

those data in. At least with the database we have right now, I think it might not lead to a happy outcome.

But if we were able to move to the point where we became convinced that persistent infections or, at least, persistent infections in certain identified populations, whether that's personal characteristics, viral loads, who knows what, really progressed to cancer, then the labeling would be of this sort that the vaccine prevents persistent infection with these particular types which is associated in some individuals, or maybe at that point in time it could be a high proportion of individuals, with progression to CIN 2 and 3 and cervical cancer.

DR. DAUM: Dixie, thank you very much.

Dr. Kim.

DR. KIM: I also support the concept that the trial can be designed large enough to address perhaps a minimum of two endpoints.

I guess this is in part that as we heard that there are many issues that are not only heterogenous but also answers are not in our hand at this time so that I think it is important to be able to monitor all the issues which have been addressed during this meeting as part of perhaps a trial so

that, again, going back to the specific questions would be my preference would be looking to a persistent HPV infection as a primary endpoint since the HPV infection per se can be difficult to predict whether you regress or you persist.

I would at least like to see that a vaccine has been shown to be beneficial in preventing persistent HPV infection due to vaccine types.

Then I guess the question which we do not have based on the discussion is whether that can be translated into the bottom line which is reduction in cervical cancer. I think it's because of that I would certainly like to see some data related to those issues as the study is coming along.

Particularly I would like to see the information on CIN 2 and 3. Again, I think cervical cancer would be very, very difficult to achieve as an endpoint so CIN 2 and 3 as a secondary endpoint as part of a trial.

So what that means, at least to me, is that when this vaccine can go through and then would be presented as an accelerated format, then I would like to see that vaccine has shown to be beneficial in significant reduction of persistent HPV infection due to serotypes.

Also, I would like to see that time of discussion, some information on a significant reduction on CIN 2 and 3 as a sort of assurance that, indeed, prevention of persistent infection has, indeed, a sort of right kind of target that we all want to see as part of this vaccine.

DR. DAUM: Thank you, Dr. Kim.

Dr. Katz.

DR. KATZ: I don't think I have any disagreement with what my preceding colleagues have stated. To me the most important issues or endpoints would be persistent infection and the CIN 2/3.

But I have several questions which perhaps are tangential but I would like to see some nested studies within the large trial and some nested studies that in a smaller cohort might be able to answer some of the questions we've tossed about to which we don't have answer about, the role of mucosal or secretory antibody, the role of salmeated infection and what could be done in looking at that along with virus cultures.

The other issue that concerns me is the way we've conducted conventional vaccine studies, and I would call this one somewhat unconventional, is once you've reached a point where you're comfortable that

you've achieved your goals, the controls then receive the vaccine that the original recipients have the benefit of.

I don't know when you would feel you've reached that point. If we accept the endpoints of persistent infection and CIN 2/3, then maybe that's the time that you would give the controls the vaccine.

But that wouldn't answer what Dr. Kim wants which is the next step which is cervical cancer. I think I would have to consider that in my overall format as I have put together the longitudinal protocol.

DR. DAUM: Thank you very much, Dr. Katz.

Dr. Faggett.

DR. FAGGETT: I disconnected my phone.

DR. DAUM: I'm very grateful..

DR. FAGGETT: I really learned a lot these past couple days. Just sitting next to Dr. Katz is always an hallucinating experience.

Really, I think more of us primary care providers need to hear this kind of very high-level discussion of the science of the vaccine approval process. I think it would make us better able to discuss it with our patients and encourage them to get the immunizations available.