Meeting Summary
AIDS Vaccine Trials:
Considerations for Phase III Trial Design and Endpoints

Dale and Betty Bumpers Vaccine Research Center
National Institute of Allergy and Infectious Diseases, National Institutes of Health
Bethesda, Maryland

November 16, 2001

Introduction

To address questions relevant to the design of efficacy trials for AIDS vaccines, the Vaccine Research Center of the NIAID, NIH, organized a meeting entitled, AIDS Vaccine Trials: Considerations for Phase III Trial Design and Endpoints," to focus on issues related to virologic, immunologic and clinical assessment of vaccine efficacy. A group of investigators from academia, industry and government, including the NIH and the U.S. Food and Drug Administration (FDA), were brought together to consider these important issues. The main goal of the meeting was to provide guidance concerning the design of phase III efficacy trials of an AIDS vaccine.

Background Presentations and Roundtable Discussions

The meeting was organized as a series of plenary sessions and roundtable discussions. Session topics included, "Perspectives on Vaccine Licensure: Past Experience and Current Issues," "Primate Studies: Immune Correlates of Protection and Clinical Endpoints," and "Ongoing and Planned Efficacy Trials." The roundtable topics included, " Predictive Value of Virologic and Immunologic Measures in HIV Infection," and a combined roundtable on "Endpoints for Efficacy Trials: Clinical, Virologic and Immunologic Considerations" and "Phase III Efficacy Trials: Study Design, Immune Assays/Correlates and Statistical Considerations." A portion of the meeting was devoted to "Recommendations and Action Items." An agenda, including lists of the presenters, panel members, and attendees are appended to this summary report.

Main Points from Presentations and Discussions

Vaccine Licensure: Past Experience and Current Perspectives.

Drs. Gordon Douglas and Karen Goldenthal reviewed vaccine licensure issues from the perspective of industry and the FDA, respectively. Pharmaceutical companies consider vaccine licensure requirements from early in the process of vaccine development. Issues such as the manufacturing process, vaccine formulation and target population are considered prior to the design of pivotal efficacy trials. A lack of consideration of these variables can delay development of the data required to achieve product licensure. The FDA's role in licensure is defined by legislation and by various sections of the Code of Federal Regulations. Approval of vaccines for licensure involves a series of formalized steps including input from FDA advisory committees. Decisions are based on clinical, manufacturing, and other relevant product data presented to the FDA. Safety data are of paramount concern and one trial alone may not provide sufficient data demonstrating that a product is safe and effective. However, unlike the licensure of most therapeutic drugs, some vaccines have been licensed after a single well-designed efficacy trial. An important factor determining whether one efficacy trial will be adequate is the level of efficacy. Licensure of an HIV vaccine poses some unique challenges such as determining the appropriate endpoints that will be measured in a phase III trial. This issue was considered in detail in the roundtable discussions.

Primate Studies: Immune Correlates of Protection and Clinical Endpoints

Drs. Vanessa Hirsch and Norman Letvin reviewed the current status of HIV/SIV vaccine studies in non-human primates. Studies using SIV and chimeric HIV/SIV (SHIV) have shown protection by several

candidate vaccines. These animal model experiments have demonstrated that some experimental vaccine approaches can decrease viremia, preserve CD4 T-cells, prevent the development of AIDS and extend life. Several SIV and SHIV models have been used and these experiments have consistently demonstrated a correlation between vaccine-induced HIV-1 specific CD8 T-cell responses and (partial) protection. Based on these and other data from human studies of HIV-1 pathogenesis, it has been hypothesized that an HIV vaccine that elicits broad and potent cellular immunity should protect against the progression of HIV disease rather than against infection. This influences the design of the phase III trials that can be powered to demonstrate the significance of associations between specific immune responses, reductions in viral load and clinical benefit.

Roundtable Discussions: Vaccine Endpoints and Study Design:

There was extensive discussion of the appropriate endpoints for phase III efficacy trials of AIDS vaccine candidates. For most infectious diseases, effective vaccines prevent the signs and symptoms of the disease (e.g., polio, measles) and enable the host to eliminate the infectious agent. Because HIV is a persistent infection rather than an acute self-limiting one, clinical endpoints demonstrating lack of disease (i.e., progression to AIDS) would take many years to occur and to assess. Therefore, if an HIV vaccine cannot prevent infection, it will be critical to determine the most expeditious methods for evaluating the efficacy of HIV candidate vaccines.

The prevention of persistent HIV infection is often referred to as "sterile protection." The only ongoing phase III trial of an AIDS vaccine (AIDSVAX, VaxGen) uses HIV infection as the primary endpoint. However, prevention of infection may not be achieved and there are, therefore, other outcomes of immunization that could be beneficial to the host and could also have a positive impact on the AIDS epidemic. Given these issues, it was recognized that it is important to establish alternate virologic, immunologic and clinical endpoints that could be applied to HIV vaccine efficacy trials. For this discussion, endpoints other than prevention of HIV infection will be termed "surrogate endpoints" because they are substitutes for the goal of prevention of HIV-1 associated clinical disease.

The surrogate clinical endpoints and their evaluation criteria were categorized as follows: 1) virologic, 2) immunologic, 3) clinical, and 4) epidemiological.

> Virologic endpoints: a) Decreased plasma viral load set-point (e.g., 1-2 $\log_{10}$ RNA copies/mL), or b) decreased plasma viral load below some biologically significant set-point (e.g., 10^3 RNA copies/mL) and, in addition, increased duration of the effect for a meaningful time period (e.g., more than one year). This discussion also focused on the frequency of endpoint measurements during a phase III trial. Of note, the FDA has approved some antiretroviral drugs based primarily on their effects on the plasma viral load. However, this was done after prospective studies confirmed that the effect on viral load provided a substantial clinical benefit. In contrast, the clinical benefit of a vaccine-induced decrement in viral load is not known because no phase III vaccine trials have been completed.
>
> Immunologic endpoints: a) Maintenance of the CD4 T-cell count (e.g., >350 cells/μL), or b) decreased rate of CD4 T-cell decline. A declining peripheral CD4 T-cell count is a well-established marker for progression to AIDS. In the context of a vaccine trial, it is not clear whether CD4 T-cell counts during the first year after infection will be predictive of a long-term decrement in the CD4 T-cell count. Also, several discussants noted that HIV-specific CD4 and CD8 T-cell responses are deficient in HIV- infected patients, and that this is thought to be part of the pathogenesis of HIV disease. Patients treated with potent antiretroviral drugs during acute HIV infection appear to be able to maintain T-cell responses and control viral load. Therefore, vaccine-induced HIV-specific T-cell responses that persist during HIV-1 infection may be biomarkers indicative of protection against HIV-associated disease.

Clinical endpoints: a) Decrement in the number of HIV-infected vaccinated subjects requiring antiretroviral treatment, or b) increment in the time interval from infection to initiation of antiretroviral treatment. In the absence of a positive effect on the viral load and the CD4 T-cell count, it may be unlikely that such endpoints would, independently, be predictive of clinical benefits. Changes in antiretroviral treatment recommendations during a trial could complicate the assessment and interpretation of the clinical endpoints. Additional discussion of antiretroviral treatment is summarized below.

Epidemiological endpoints: a) Decrement in sexual transmission rates by vaccinated subjects who become HIV-infected subsequent to vaccination, or b) decrement in maternal-infant transmission rates for women who become HIV-infected subsequent to vaccination. In these situations, the clinical benefit may be to others rather than to the vaccinated subject. These phase III trials should be specifically designed and powered to measure such post-vaccination effects.

Most of the discussions of surrogate endpoints focused on the value of markers such as the plasma virus load and the peripheral CD4 T-cell count. These markers have predictive value in natural HIV-1 disease and have been previously used to grant licensure of antiretroviral drugs. There was general agreement that these markers have biological significance, but the validity of such markers for evaluating the efficacy of an AIDS vaccine remains to be established. There was also discussion of the effect of antiretroviral treatments on each of the surrogate endpoints. Long-term clinical follow-up of vaccine trial participants will be required to optimally elucidate the mechanisms of vaccine efficacy and to validate the surrogate endpoint markers. Interpretation of the surrogate endpoint data will be complicated by the initiation of antiretroviral treatment in some HIV-infected participants. Recommendations and standards of care for initiation of treatment are evolving and may not be consistent throughout the course of a clinical trial. Also, the availability and use of antiretroviral drugs worldwide will vary by country. Similar issues will complicate the use and interpretation of the time interval from infection to initiation of treatment as a reliable marker for the surrogate endpoints.

The potential short-term outcomes of Phase III trials were summarized as follows:

1) A highly effective vaccine that prevents establishment of persistent HIV infection in a significant proportion of vaccinated subjects;
2) An ineffective vaccine that has no statistically significant effect on either the incidence of infection or on surrogate endpoints;
3) A vaccine that has no effect on the incidence of infection, but has some measurable effect on surrogate endpoints such as the viral load and the CD4 T-cell count;
4) A vaccine that has some statistically significant effect (or an effect that approaches significance) on the incidence of HIV infection and also has some positive (beneficial) effect on surrogate endpoints.

There was general agreement that number 3 and 4 (above) are likely outcomes. While prevention of persistent infection is the most desirable outcome, a vaccine could have a small, but measurable, positive effect on the incidence of HIV infection, and/or a beneficial effect on the course of HIV disease. There was also general agreement that there would be increased confidence in the biological significance of surrogate endpoints if these were associated with a statistically significant decrement in the incidence of HIV infection. Optimal criteria for surrogate endpoints will evolve as knowledge is gained during the conduct of vaccine efficacy trials in humans. Nevertheless, clearly defined specific surrogate endpoint criteria are needed to design phase III trials of candidate vaccines.

Towards this goal, most participants agreed that it would be reasonable to design a phase III efficacy trial based on assumptions that a vaccine would have a modest effect on the incidence of infection and/or an effect on surrogate endpoints. For example, a vaccine could be considered for licensure if it produced a decrement in the incidence of infection (e.g., lower bound on the 95% confidence interval of 30%), or if it produced a decrement in the viral load set point (1-2 $\log_{10}$ RNA copies /mL) in vaccinated subjects subsequently infected with HIV. Of note, the FDA has already made a determination that a vaccine that

prevents infection with a lower bound on the 95% confidence interval of 30% is potentially licensable. However, in this case, the sponsor is conducting two efficacy trials.

Additional specific examples of surrogate endpoint criteria were discussed. These included: a) decrement in the plasma viral load set-point of less than 10^3 RNA copies/mL, b) maintenance of the CD4 T-cell count above 350 cells/μL, c) decrement in the number of vaccinated subjects subsequently infected with HIV requiring antiretroviral treatment, and d) increment in the time interval from HIV infection to initiation of antiretroviral treatment. It was noted that the effects of antiretroviral treatments on surrogate endpoints may vary between countries and even between clinics within the same country.

Because the clinical endpoint of progression to AIDS would likely take many years to evaluate, there was discussion regarding the possibility of accelerating vaccine approval based on surrogate endpoints. Final vaccine licensure using traditional approval criteria could be based on development of clinical endpoint data from controlled confirmatory trials. In this scenario, a phase III trial would measure specific surrogate endpoints and a licensure application would be considered while clinical follow-up was in progress. This approach may accelerate the time to licensure of a safe and potentially effective AIDS vaccine. Of note, long-term follow-up could also demonstrate the lack of efficacy of a vaccine granted accelerated licensure.

Issues related to International Trials and Vaccine Licensure

FDA approval for licensure pertains to the U.S. alone. Approval and use of vaccines in other countries is guided by national regulatory bodies in those nations, often in consultation with the World Health Organization (WHO). Dr. Jose Esparza noted that few developing nations have a regulatory process comparable to that of the U.S. FDA, and many choose to rely on the U.S. FDA's approvals as guidance for their national decisions.

FDA staff participation in a number of international forums, especially WHO, will undoubtedly provide valuable information to the international vaccine community concerning approval of vaccines.

The FDA considers the risk/benefit in U.S. populations primarily, but will also consider data developed in other countries for product licensure. The risk/benefit ratio and the acceptable level of efficacy for an AIDS vaccine may vary between countries.

Summary and Recommendations

- Non-human primate studies suggest that an AIDS vaccine is possible. Non-human primate studies have demonstrated partial vaccine-induced protection measured by surrogate endpoints such as decrements in the plasma viral load and the CD4 T-cell decline. In animal models, these effects are associated with decreased progression to AIDS. This suggests that such surrogate endpoints may be valid for the design of phase III efficacy trials.

- The efficacy of current and future candidate vaccines will have to be determined in well-designed phase III trials. Such trials will likely require international collaborations among several organizations and the endpoints measured will require careful consideration.

- Following the completion of the relevant phase II studies, the sponsoring organization will submit a written summary of the trial(s) to the FDA. This report should include the draft phase III efficacy trial protocol and supporting data. Subsequently, the sponsor will also present these data to the FDA Vaccines and Related Biological Products Advisory Committee. Information on the viral loads and CD4 T-cell counts of study subjects who developed HIV infections during phase I/II trials will likely be considered.

- An ideal HIV vaccine will prevent AIDS by preventing establishment of persistent HIV-infection. This endpoint can be readily measured by a combination of well-established serologic and/or molecular methods.

- Meeting participants expressed the belief that an AIDS vaccine could be considered effective if it provided protection against progression to AIDS. Such a vaccine is expected to produce changes in the virologic or immunologic markers of HIV-1 disease such as the plasma viral load and the CD4 T-cell count. Although not yet validated in the context of vaccine studies, such markers are biologically plausible and may be useful for supporting FDA applications for accelerated approval, pending positive clinical endpoint data from controlled confirmatory trials.

- Reasonable criteria for a successful phase III trial include demonstration of an effect on incidence of infection, and/or an effect on specific surrogate endpoints. For example, many participants thought that a vaccine should be considered for licensure if it produced a modest effect on the incidence of HIV infection (e.g. the lower bound on the 95% confidence interval of 30%) or if it produced a sustained decrement in the viral load set point (1-2 $\log_{10}$ RNA copies /mL) in vaccinated subjects who were subsequently infected with HIV. Additional specific examples of surrogate endpoint criteria are plasma viral load set-point of less than 10^3 RNA copies/mL and the maintenance of CD4 T-cell counts above 350 cells/μL.

- There would be increased confidence in the validity of surrogate endpoints if a vaccine also produced a statistically significant decrement in the incidence of HIV infection. Thus, a small measurable decrease in the incidence of HIV infection coupled with a positive effect on a surrogate endpoint (e.g., viral load) could be the basis for vaccine licensure.

- There should be further consideration of methods to measure clinical correlates of disease progression such as the length of time from HIV infection to the initiation of antiretroviral treatment. Such treatment-related endpoints could be integrated with immunologic and virologic endpoints. Many discussants believed that treatment outcomes may be highly correlated with the virologic and immunologic markers but may not, independently, be predictive of vaccine efficacy. It may be difficult to standardize and compare the treatment outcomes of different populations.

- If appropriate, accelerated vaccine approval may substantially decrease the time to availability of a safe and potentially effective AIDS vaccine. Because the clinical endpoint of progression to AIDS would take many years to recognize, accelerated approval could be based on surrogate endpoints. Subsequent vaccine licensure by traditional approval criteria could be based on the development of positive

confirmatory clinical endpoint data. In this scenario, a phase III trial would measure specific effects on surrogate endpoints and a licensure application would be considered while clinical follow-up was in progress. It is acknowledged that clinical information validating the use of surrogate endpoints will only accrue from well-designed controlled efficacy trials.

- If surrogate endpoints are used, careful consideration should be given to the methods for long-term clinical follow-up to demonstrate the effect of such markers on HIV-1 disease progression. This could accelerate future vaccine trials.

- Valuable information towards the design of future AIDS vaccines can be obtained from well-designed efficacy trials of (even modestly) effective vaccines.

Concluding Comments

The carefully considered use of surrogate endpoints in AIDS vaccine trials could substantially accelerate the licensure of an AIDS vaccine, but no such endpoints have yet been validated in the context of vaccine trials. Clinical information validating the use of such surrogate endpoints can accrue from well-designed efficacy trials and this information can be applied to the design of future trials. Following the completion of relevant phase II studies, sponsoring organizations will present proposed efficacy trial protocols and supporting preclinical, human safety and immunogenicity data to the FDA Vaccines and Related Biological Products Advisory Committee.

AIDS VACCINE TRIALS: CONSIDERATIONS FOR PHASE III TRIAL DESIGN AND ENDPOINTS
NOVEMBER 16, 2001
Agenda

MORNING SESSIONS

8:15 a.m. – 8:30 a.m. **Introductory Remarks**
Gary Nabel, Kathryn Zoon

PRESENTATIONS

8:30 a.m. – 9:15 am. **Perspectives on Vaccine Licensure: Past Experience and Current Issues**

Chair: William Egan
Gordon Douglas
Karen Goldenthal

9:20 a.m. – 10:00 a.m. **Primate Studies: Immune Correlates of Protection and Clinical Endpoints**

Chair*:* John Mascola
Vanessa Hirsch
Norman Letvin

10:00 a.m. – 10:20 a.m. **Break**

ROUND TABLE DISCUSSION

10:20 a.m. – 11:45 a.m. **Predictive Value of Virologic and Immunologic Measures in HIV Infection**

Chair: George Shaw

Larry Corey
Barney Graham
Harriet Robinson
John Coffin
Carol Weiss
Jeff Murray

PRESENTATIONS

11:45 a.m. – 12:30 p.m. Ongoing and Planned Efficacy Trials

Introduction - Barney Graham (Chair)

Ongoing VaxGen phase III trial - Vladimir Popovic

Plans for Walter Reed-sponsored phase III trial in Thailand - Jerome Kim

Plans for VTN-sponsored phase III trial - Larry Corey

12:30 p.m. – 1:30 p.m. Lunch

ROUND TABLE DISCUSSION

1:30 p.m. – 3:00 p.m. Endpoints for Efficacy Trials: Clinical, Virologic and Immunologic Considerations

Chair: Larry Corey – Joining by conference call

Steve Self	Michel Klein
Susan Ellenberg	Barney Graham
Hana Golding	Jerry Sadoff

3:00 p.m. – 3:30 p.m. Break

ROUND TABLE DISCUSSION

3:30p.m. – 5:00 p.m. Phase III Efficacy Trials: Study Design, Immune Assays/Correlates and Statistical Considerations

Chair: Jose Esparza

Wasima Rida	Tim Mastro
Don Stablein	Victor De Gruttola
Karen Goldenthal	Sanjay Gurunathan
Bill Snow – Joining by conference call	Jerome Kim

5:00 p.m. – 5:45 p.m. Recommendations and Action Items

Chairs: Gary Nabel, Karen Midthun

PRELIMINARY LIST OF QUESTIONS:

Primate Studies: Immune Correlates of Protection and Clinical Endpoints

(To be addressed by both presenters in this session)

What have SIV and SHIV studies taught us about cellular correlates of protection?
What have SIV and SHIV studies taught us about humoral correlates of protection?
Can virologic endpoints (e.g., plasma viremia) be used as a marker of vaccine induced protection? If so, how does this correlate with clinical outcome.
Do SIV studies of early intervention with HAART teach us something about possible vaccine induced protection?

Predictive Value of Virologic and Immunologic Measures in HIV Infection

What virologic marker best predicts clinical outcome (i.e., development of AIDS)?
What reduction in plasma viremia correlates with clinical benefit?
What is known about predictive value of peak viremia vs. set point?
How long after primary infection does it take to attain viral set point?
What is the predictive value of quantitation of the number of PBLs containing viral DNA?
Are any early immunologic markers (i.e., CD4 cell number) predictive of clinical outcome?

Endpoints for Efficacy trials: Clinical, Virologic and Immunologic Considerations

How will the primary endpoint of HIV-1 infection be measured; i.e., serologic or virologic endpoint (e.g., PCR)?
Can control of viremia (plasma viral RNA) be used as a primary endpoint?
Primary Endpoints: e.g., Plasma Viral Load

If control of plasma viremia is one of the primary endpoints:

- when and how many measurements will be required?
- what will be measured: peak viremia, viral set point?
- what decrease in viral load set point can be detected in a phase III trial
- what statistical methods can be applied to such endpoint measurements
- how will initiation of antiretroviral treatment affect this endpoint

Secondary Endpoints: Immunologic Parameters

- how will correlates of protection be evaluated and validated
- how can quantitative immune assay data (e.g., #'s of Elispots) be considered in addition to qualitative (yes/no) responses
- what statistical methods can be applied to correlate immune markers with trial endpoints

Clinical Considerations: Antiretroviral Treatment

Regarding antiretroviral treatment of confirmed HIV-infected volunteers:

- when should antiretroviral treatment be initiated (viral load, CD4 count)

- could the time to initiation of antiretroviral mediation be used as an endpoint in a phase III trial

---

Phase III Efficacy Trials: Study design, Immune Assays/Correlates and Statistical Considerations

If viral load is a primary endpoint:

- how will this affect the design and size of the trial
- what differences in viral load set point can we expect to detect
- how will frequency of blood draws affect the ability to use viral load as an endpoint

If protection is measured as control of viremia:

- will clinical endpoints be required in some subset of patients in order to validate viremia as an endpoint and, if so, should this be part of phase III trials, or part of post-licensure follow up (phase IV)?

What type of studies should be built into future vaccine licensure applications to insure validation of the endpoints used during the efficacy trails?

What are the licensure ramifications of a low/moderate efficacy result?

What is the minimal safety database to support a successful BLA?

Should efficacy trials be designed to evaluate homotypic versus heterotypic protection?

How would phase III trials be designed once there is an effective or licensed HIV vaccine?

Clinical endpoints: a) Decrement in the number of HIV-infected vaccinated subjects requiring antiretroviral treatment, or b) increment in the time interval from infection to initiation of antiretroviral treatment. In the absence of a positive effect on the viral load and the CD4 T-cell count, it may be unlikely that such endpoints would, independently, be predictive of clinical benefits. Changes in antiretroviral treatment recommendations during a trial could complicate the assessment and interpretation of the clinical endpoints. Additional discussion of antiretroviral treatment is summarized below.

Epidemiological endpoints: a) Decrement in sexual transmission rates by vaccinated subjects who become HIV-infected subsequent to vaccination, or b) decrement in maternal-infant transmission rates for women who become HIV-infected subsequent to vaccination. In these situations, the clinical benefit may be to others rather than to the vaccinated subject. These phase III trials should be specifically designed and powered to measure such post-vaccination effects.

Most of the discussions of surrogate endpoints focused on the value of markers such as the plasma virus load and the peripheral CD4 T-cell count. These markers have predictive value in natural HIV-1 disease and have been previously used to grant licensure of antiretroviral drugs. There was general agreement that these markers have biological significance, but the validity of such markers for evaluating the efficacy of an AIDS vaccine remains to be established. There was also discussion of the effect of antiretroviral treatments on each of the surrogate endpoints. Long-term clinical follow-up of vaccine trial participants will be required to optimally elucidate the mechanisms of vaccine efficacy and to validate the surrogate endpoint markers. Interpretation of the surrogate endpoint data will be complicated by the initiation of antiretroviral treatment in some HIV-infected participants. Recommendations and standards of care for initiation of treatment are evolving and may not be consistent throughout the course of a clinical trial. Also, the availability and use of antiretroviral drugs worldwide will vary by country. Similar issues will complicate the use and interpretation of the time interval from infection to initiation of treatment as a reliable marker for the surrogate endpoints.

The potential short-term outcomes of Phase III trials were summarized as follows:

1) A highly effective vaccine that prevents establishment of persistent HIV infection in a significant proportion of vaccinated subjects;
2) An ineffective vaccine that has no statistically significant effect on either the incidence of infection or on surrogate endpoints;
3) A vaccine that has no effect on the incidence of infection, but has some measurable effect on surrogate endpoints such as the viral load and the CD4 T-cell count;
4) A vaccine that has some statistically significant effect (or an effect that approaches significance) on the incidence of HIV infection and also has some positive (beneficial) effect on surrogate endpoints.

There was general agreement that number 3 and 4 (above) are likely outcomes. While prevention of persistent infection is the most desirable outcome, a vaccine could have a small, but measurable, positive effect on the incidence of HIV infection, and/or a beneficial effect on the course of HIV disease. There was also general agreement that there would be increased confidence in the biological significance of surrogate endpoints if these were associated with a statistically significant decrement in the incidence of HIV infection. Optimal criteria for surrogate endpoints will evolve as knowledge is gained during the conduct of vaccine efficacy trials in humans. Nevertheless, clearly defined specific surrogate endpoint criteria are needed to design phase III trials of candidate vaccines.

Towards this goal, most participants agreed that it would be reasonable to design a phase III efficacy trial based on assumptions that a vaccine would have a modest effect on the incidence of infection and/or an effect on surrogate endpoints. For example, a vaccine could be considered for licensure if it produced a decrement in the incidence of infection (e.g., lower bound on the 95% confidence interval of 30%), or if it produced a decrement in the viral load set point (1-2 $\log_{10}$ RNA copies /mL) in vaccinated subjects subsequently infected with HIV. Of note, the FDA has already made a determination that a vaccine that

prevents infection with a lower bound on the 95% confidence interval of 30% is potentially licensable. However, in this case, the sponsor is conducting two efficacy trials.

Additional specific examples of surrogate endpoint criteria were discussed. These included: a) decrement in the plasma viral load set-point of less than 10^3 RNA copies/mL, b) maintenance of the CD4 T-cell count above 350 cells/μL, c) decrement in the number of vaccinated subjects subsequently infected with HIV requiring antiretroviral treatment, and d) increment in the time interval from HIV infection to initiation of antiretroviral treatment. It was noted that the effects of antiretroviral treatments on surrogate endpoints may vary between countries and even between clinics within the same country.

Because the clinical endpoint of progression to AIDS would likely take many years to evaluate, there was discussion regarding the possibility of accelerating vaccine approval based on surrogate endpoints. Final vaccine licensure using traditional approval criteria could be based on development of clinical endpoint data from controlled confirmatory trials. In this scenario, a phase III trial would measure specific surrogate endpoints and a licensure application would be considered while clinical follow-up was in progress. This approach may accelerate the time to licensure of a safe and potentially effective AIDS vaccine. Of note, long-term follow-up could also demonstrate the lack of efficacy of a vaccine granted accelerated licensure.

Issues related to International Trials and Vaccine Licensure

FDA approval for licensure pertains to the U.S. alone. Approval and use of vaccines in other countries is guided by national regulatory bodies in those nations, often in consultation with the World Health Organization (WHO). Dr. Jose Esparza noted that few developing nations have a regulatory process comparable to that of the U.S. FDA, and many choose to rely on the U.S. FDA's approvals as guidance for their national decisions.

FDA staff participation in a number of international forums, especially WHO, will undoubtedly provide valuable information to the international vaccine community concerning approval of vaccines.

The FDA considers the risk/benefit in U.S. populations primarily, but will also consider data developed in other countries for product licensure. The risk/benefit ratio and the acceptable level of efficacy for an AIDS vaccine may vary between countries.

Summary and Recommendations

- Non-human primate studies suggest that an AIDS vaccine is possible. Non-human primate studies have demonstrated partial vaccine-induced protection measured by surrogate endpoints such as decrements in the plasma viral load and the CD4 T-cell decline. In animal models, these effects are associated with decreased progression to AIDS. This suggests that such surrogate endpoints may be valid for the design of phase III efficacy trials.

- The efficacy of current and future candidate vaccines will have to be determined in well-designed phase III trials. Such trials will likely require international collaborations among several organizations and the endpoints measured will require careful consideration.

- Following the completion of the relevant phase II studies, the sponsoring organization will submit a written summary of the trial(s) to the FDA. This report should include the draft phase III efficacy trial protocol and supporting data. Subsequently, the sponsor will also present these data to the FDA Vaccines and Related Biological Products Advisory Committee. Information on the viral loads and CD4 T-cell counts of study subjects who developed HIV infections during phase I/II trials will likely be considered.

- An ideal HIV vaccine will prevent AIDS by preventing establishment of persistent HIV-infection. This endpoint can be readily measured by a combination of well-established serologic and/or molecular methods.

- Meeting participants expressed the belief that an AIDS vaccine could be considered effective if it provided protection against progression to AIDS. Such a vaccine is expected to produce changes in the virologic or immunologic markers of HIV-1 disease such as the plasma viral load and the CD4 T-cell count. Although not yet validated in the context of vaccine studies, such markers are biologically plausible and may be useful for supporting FDA applications for accelerated approval, pending positive clinical endpoint data from controlled confirmatory trials.

- Reasonable criteria for a successful phase III trial include demonstration of an effect on incidence of infection, and/or an effect on specific surrogate endpoints. For example, many participants thought that a vaccine should be considered for licensure if it produced a modest effect on the incidence of HIV infection (e.g. the lower bound on the 95% confidence interval of 30%) or if it produced a sustained decrement in the viral load set point (1-2 $\log_{10}$ RNA copies /mL) in vaccinated subjects who were subsequently infected with HIV. Additional specific examples of surrogate endpoint criteria are plasma viral load set-point of less than 10^3 RNA copies/mL and the maintenance of CD4 T-cell counts above 350 cells/μL.

- There would be increased confidence in the validity of surrogate endpoints if a vaccine also produced a statistically significant decrement in the incidence of HIV infection. Thus, a small measurable decrease in the incidence of HIV infection coupled with a positive effect on a surrogate endpoint (e.g., viral load) could be the basis for vaccine licensure.

- There should be further consideration of methods to measure clinical correlates of disease progression such as the length of time from HIV infection to the initiation of antiretroviral treatment. Such treatment-related endpoints could be integrated with immunologic and virologic endpoints. Many discussants believed that treatment outcomes may be highly correlated with the virologic and immunologic markers but may not, independently, be predictive of vaccine efficacy. It may be difficult to standardize and compare the treatment outcomes of different populations.

- If appropriate, accelerated vaccine approval may substantially decrease the time to availability of a safe and potentially effective AIDS vaccine. Because the clinical endpoint of progression to AIDS would take many years to recognize, accelerated approval could be based on surrogate endpoints. Subsequent vaccine licensure by traditional approval criteria could be based on the development of positive

confirmatory clinical endpoint data. In this scenario, a phase III trial would measure specific effects on surrogate endpoints and a licensure application would be considered while clinical follow-up was in progress. It is acknowledged that clinical information validating the use of surrogate endpoints will only accrue from well-designed controlled efficacy trials.

- If surrogate endpoints are used, careful consideration should be given to the methods for long-term clinical follow-up to demonstrate the effect of such markers on HIV-1 disease progression. This could accelerate future vaccine trials.

- Valuable information towards the design of future AIDS vaccines can be obtained from well-designed efficacy trials of (even modestly) effective vaccines.

Concluding Comments

The carefully considered use of surrogate endpoints in AIDS vaccine trials could substantially accelerate the licensure of an AIDS vaccine, but no such endpoints have yet been validated in the context of vaccine trials. Clinical information validating the use of such surrogate endpoints can accrue from well-designed efficacy trials and this information can be applied to the design of future trials. Following the completion of relevant phase II studies, sponsoring organizations will present proposed efficacy trial protocols and supporting preclinical, human safety and immunogenicity data to the FDA Vaccines and Related Biological Products Advisory Committee.

AIDS VACCINE TRIALS: CONSIDERATIONS FOR PHASE III TRIAL DESIGN AND ENDPOINTS
NOVEMBER 16, 2001
Agenda

MORNING SESSIONS

8:15 a.m. – 8:30 a.m. **Introductory Remarks**
Gary Nabel, Kathryn Zoon

PRESENTATIONS

8:30 a.m. – 9:15 am. **Perspectives on Vaccine Licensure: Past Experience and Current Issues**

Chair: William Egan
Gordon Douglas
Karen Goldenthal

9:20 a.m. – 10:00 a.m. **Primate Studies: Immune Correlates of Protection and Clinical Endpoints**

Chair*:* John Mascola
Vanessa Hirsch
Norman Letvin

10:00 a.m. – 10:20 a.m. **Break**

ROUND TABLE DISCUSSION

10:20 a.m. – 11:45 a.m. **Predictive Value of Virologic and Immunologic Measures in HIV Infection**

Chair: George Shaw

Larry Corey	John Coffin
Barney Graham	Carol Weiss
Harriet Robinson	Jeff Murray

PRESENTATIONS

11:45 a.m. – 12:30 p.m. Ongoing and Planned Efficacy Trials

Introduction - Barney Graham (Chair)

Ongoing VaxGen phase III trial - Vladimir Popovic

Plans for Walter Reed-sponsored phase III trial in Thailand - Jerome Kim

Plans for VTN-sponsored phase III trial - Larry Corey

12:30 p.m. – 1:30 p.m. Lunch

ROUND TABLE DISCUSSION

1:30 p.m. – 3:00 p.m. Endpoints for Efficacy Trials: Clinical, Virologic and Immunologic Considerations

Chair: Larry Corey – Joining by conference call

Steve Self	Michel Klein
Susan Ellenberg	Barney Graham
Hana Golding	Jerry Sadoff

3:00 p.m. – 3:30 p.m. Break

ROUND TABLE DISCUSSION

3:30p.m. – 5:00 p.m. Phase III Efficacy Trials: Study Design, Immune Assays/Correlates and Statistical Considerations

Chair: Jose Esparza

Wasima Rida	Tim Mastro
Don Stablein	Victor De Gruttola
Karen Goldenthal	Sanjay Gurunathan
Bill Snow – Joining by conference call	Jerome Kim

5:00 p.m. – 5:45 p.m. Recommendations and Action Items

Chairs: Gary Nabel, Karen Midthun

PRELIMINARY LIST OF QUESTIONS:

Primate Studies: Immune Correlates of Protection and Clinical Endpoints

(To be addressed by both presenters in this session)

What have SIV and SHIV studies taught us about cellular correlates of protection?
What have SIV and SHIV studies taught us about humoral correlates of protection?
Can virologic endpoints (e.g., plasma viremia) be used as a marker of vaccine induced protection? If so, how does this correlate with clinical outcome.
Do SIV studies of early intervention with HAART teach us something about possible vaccine induced protection?

Predictive Value of Virologic and Immunologic Measures in HIV Infection

What virologic marker best predicts clinical outcome (i.e., development of AIDS)?
What reduction in plasma viremia correlates with clinical benefit?
What is known about predictive value of peak viremia vs. set point?
How long after primary infection does it take to attain viral set point?
What is the predictive value of quantitation of the number of PBLs containing viral DNA?
Are any early immunologic markers (i.e., CD4 cell number) predictive of clinical outcome?

Endpoints for Efficacy trials: Clinical, Virologic and Immunologic Considerations

How will the primary endpoint of HIV-1 infection be measured; i.e., serologic or virologic endpoint (e.g., PCR)?
Can control of viremia (plasma viral RNA) be used as a primary endpoint?
Primary Endpoints: e.g., Plasma Viral Load

If control of plasma viremia is one of the primary endpoints:

- when and how many measurements will be required?
- what will be measured: peak viremia, viral set point?
- what decrease in viral load set point can be detected in a phase III trial
- what statistical methods can be applied to such endpoint measurements
- how will initiation of antiretroviral treatment affect this endpoint

Secondary Endpoints: Immunologic Parameters

- how will correlates of protection be evaluated and validated
- how can quantitative immune assay data (e.g., #'s of Elispots) be considered in addition to qualitative (yes/no) responses
- what statistical methods can be applied to correlate immune markers with trial endpoints

Clinical Considerations: Antiretroviral Treatment

Regarding antiretroviral treatment of confirmed HIV-infected volunteers:

- when should antiretroviral treatment be initiated (viral load, CD4 count)
- could the time to initiation of antiretroviral mediation be used as an endpoint in a phase III trial

---

Phase III Efficacy Trials: Study design, Immune Assays/Correlates and Statistical Considerations

If viral load is a primary endpoint:

- how will this affect the design and size of the trial
- what differences in viral load set point can we expect to detect
- how will frequency of blood draws affect the ability to use viral load as an endpoint

If protection is measured as control of viremia:

- will clinical endpoints be required in some subset of patients in order to validate viremia as an endpoint and, if so, should this be part of phase III trials, or part of post-licensure follow up (phase IV)?

What type of studies should be built into future vaccine licensure applications to insure validation of the endpoints used during the efficacy trails?

What are the licensure ramifications of a low/moderate efficacy result?

What is the minimal safety database to support a successful BLA?

Should efficacy trials be designed to evaluate homotypic versus heterotypic protection?

How would phase III trials be designed once there is an effective or licensed HIV vaccine?

NATIONAL INSTITUTE OF ALLERGY AND INFECTIOUS DISEASES
VACCINE RESEARCH CENTER

AIDS Vaccine Trials: Considerations for Phase III Trial Design and Endpoints

NOVEMBER 16, 2001

Charla Andrews, Sc.M.
Regulatory Affairs
National Institutes of Health
National Institute of Allergy and Infectious Diseases
Vaccine Research Center
40 Convent Drive, MSC 3022
Building 40, Room 5508
Bethesda, MD 20893
Phone: 301-594-8488
Fax: 301-480-2651
E-mail: charlaandrews@nih.gov

Larry O. Arthur, Ph.D.
Principal Investigator, Operations &Technical Support Contract, SAIC
SAIC-Frederick, P.O. Box B, Bldg. 428, Rm 48
Frederick, MD 21702
Phone: 301-846-1154
Fax: 301-846-1089
E-mail: arthur@avpaxp1.ncifcrf.gov
Assistant: Diane Simmons

Ira Berkower
Center for Biologics, Evaluation and Research
Food and Drug Administration
1401 Rockville Pike
Builing 29, Room 523, HFM-413
Rockville, MD 20852-1448
Phone: 301-496-1870
E-mail: ib3t@nih.gov

Jim Bradac, Ph.D.
Chief
Division of AIDS
National Institute of Allergy and Infectious Diseases
6700-B Rockledge Drive, MSC 7628
Rockville, MD 20892-7628
Phone: 301-435-3754
Fax: 301-402-3684
E-mail: jbradac@niaid.nih.gov

Susan Buchbinder, M.D.
San Francisco Department of Public Health
HIV Research Section
25 Van Ness Avenue, Suite 500
San Francisco, CA 94102
Phone: 415-554-4237
Fax: 415-621-0641
E-mail:
Susan_Buchbinder@dph.sf.ca.us
Assistant: Sarah Breveleri
E-mail:
Sarah_Breveleri@dph.sf.ca.us

Dennis R. Burton, Ph.D.
Scripps Research Institute
10550 North Torrey Pines Road
La Jolla, CA 92037
Phone: 858-784-9298
FAX: 858-784-8360
E-mail: burton@scripps.edu
Assistant: Ellen Klahn
(eklahn@scripps.edu)
Phone: 858-784-8104

John Coffin
NCI-Frederick
Building 535, Room 310
Frederick, MD 21702
Phone: 301-846-5944
Fax: 301-846-6013
E-Mail: jcoffin@ncifcrf.gov

Larry Corey, Ph.D.
Professor, Medicine and Laboratory Medicine
Head, Virology Division/University of Washington
Head, Program in Infectious Diseases
Fred Hutchinson Cancer Research Center
Principal Investigator, HIV Vaccine Trials Network
Phone: 206-667-6770
Fax: 206-667-4411
E-mail: lcorey@u.washington.edu

Therese Cvetkovich, M.D.
Medical Officer
Division of Antiviral Drug Products
Center for Drug, Evaluation and Research
Food and Drug Administration
1451 Rockville Pike
HFD-530
Rockville, MD 20852
Phone: 301- 827-2330
Fax: 301-827-2523
E-mail: cvetkovicht@cder.fda.gov

Veffa Franchini
NCI
41 Library Drive
Building 41, Room D804
Bethesda, MD 20892
Phone: 301-496-2389/4840
Fax: 301-496-8394
E-mail: franchig@mail.nih.gov

Mike Gilbreath
DAIDS/PRDB
E-mail: mgilbreath@niaid.nih.gov

Victor De Gruttola, D Sc.
Director, Adult Division
Center for Biostatistics in AIDS Research
Harvard School of Public Health
677 Huntington Avenue
Building 2, Room 459 A
Boston, MA 02115
Phone: 617-432-2820
Fax: 617-432-1869
E-Mail: victor@sdac.harvard.edu
Assistant: Nick Stenzel
E-mail: nstenzel@sdac.harvard.edu

Dennis O. Dixon, Ph.D.
Chief, Biostatistics Research Branch
NIH, NIAID, DAIDS
Room 4115
6700-B Rockledge Dr. MSC 7620
Bethesda, MD 20892-7620
Phone: 301-402-2306
Fax: 301-402-0145
E-mail dd23a@nih.gov

Daniel Douek, M.D., Ph.D
National Institutes of Health
Vaccine Research Center
40 Convent Drive
Building. 40, Room 3509
Bethesda, MD 20892-3005
Phone: 301-594-8484
Fax: 301-480-2779
E-mail: ddouek@nih.gov

R. Gordon Douglas M.D.
8 Windermere Way
Princeton, NJ, 08540
Phone: 609-921-8530
Fax: 609-921-7091
Email: gordon_douglas@prodigy.net

William M. Egan, Ph.D.
Deputy Director
Office of Vaccines Research and Review
Center for Biologics Evaluation and Review
Food and Drug Administration
1401 Rockville Pike
Rockville, MD 20852
Phone: 301-827-0652
Fax: 301-827-0448
E-mail: Egan@cber.fda.gov

Susan Ellenberg
HFM-210, WOC1
DHHS/FDA/CBER/OBE
1401 Rockville Pike
Rockville, MD 20852
Phone: 301-827-3070
Fax: 301-827-3075
E-mail: ellenberg@cber.fda.gov

Jose Esparza MD, Ph.D.
Coordinator
WHO-UNAIDS HIV Vaccine Initiative (HVI)
Initiative for Vaccine Research (IVR)
Health Technology and Pharmaceuticals (HTP)
World Health Organization (WHO)
20 Avenue Appia
1211 Geneva 27
Switzerland
Phone: 41-22-791-4392
Fax: 41-22-791-4865
E-mail: esparzaj@who.ch

Anthony S. Fauci M. D.
Director
NIH/NIAID
31 Center Drive Room 7A03
Bethesda, MD 20892-2520
Phone: 301-496-2263
Fax: 301-496-4409
E-mail: af10r@nih.gov

Jorge Flores
Chief, Development Branch
Vaccine & Prevention Research Program
National Institute of Allergy and Infectious Diseases
6700B Rockledge Drive, Room 4154
MSC7628
Bethesda, MD 20892
Phone: 301-435-3758
Fax: 301-402-3684
E-mail: jflores@niaid.nih.gov

Sarah Frankel, M.D.
Pathologist
U.S. Military HIV Research Program
Phone: 301-251-5073
Fax: 301-762-4177
E-mail: sfrankel@hivresearch.org

Antonia Geber, M.D.
DVRPA/OVRR/CBER/FDA
1401 Rockville Pike
HFM-485, Room 370N
Rockville, MD 20852-1448
Phone: 301-827-3070
Fax: 301-827-3532
E-mail: geber@cber.fda.gov

Karen L. Goldenthal, M.D.
HFM-475; Suite 370 North
DVRPA/OVRR/CBER
1401 Rockville Pike
Rockville, MD 20852
Phone: 301-827-3070
Fax: 301-827-3075
Email: goldenthan@cber.fda.gov

Hana Golding, Ph.D.
Chief, Laboratory of Retrovirus Research
Division of Viral Products
CBER, FDA, HFM-454
1401 Rockville Pike
Rockville, MD 20852-1448
Phone: 301-827-0784
Fax: 301-496-1810
E-mail: goldingh@cber.fda.gov

Phillip L. Gomez III, Ph.D.
Director, Vaccine Production
Vaccine Research Center, NIH
Bldg. 40, Room 5502
40 Convent Drive
Bethesda, MD 20892-3005
Phone: 301-594-8485
Fax: 301-480-2788
E-mail: pgomez@nih.gov

Lance Gordon, Ph.D.
VAXGEN, Inc.
1000 Marina Boulevard
Suite 200
Brisbane, CA 94005
Phone: 650-624-1000
Fax: 650-624-1003
E-Mail: lgordon@vaxgen.com

Barney Graham, M.D., Ph.D.
Vaccine Research Center, NIH
Bldg. 40, Rm 2502
40 Convent Drive, MSC 3017
Bethesda, MD 20892-3017
Phone: 301 594-8468
Fax: 301- 480-2771
E-mail: bgraham@nih.gov

Sanjay Gurunathan, M.D.
Director, Clinical Development
Aventis Pasteur
Swiftwater, PA 18370
Phone: 570 839 6185
Fax: 570 839 0934
E-mail:
sanjay.gurunathan@aventis.com

Marc Gurwith, M.D., JD
VAXGEN, Inc.
1000 Marina Boulevard
Suite 200
Brisbane, CA 94005
Phone: 650-624-1000
Fax: 650-624-2322
E-mail: mgurwidth@vaxgen.com

Laraine Henchal
HFM-478, Suite 370 North
DVRPA/OVRR/CBER
1401 Rockville Pike
Rockville, MD 20852
Phone: 301-827-3070
Fax: 301-827-3532
E-mail: henchal@cber.fda.gov

Don Hildebrand
CEO
GeoVax Inc.
Suite #1
Yerkes Research center
954 Gatewood NE
Atlanta GA, 30329
Phone: 404-727-0779
Fax: 404-727-7768
E-mail: dghilde@aol.com

Vanessa Hirsch
Phone: 301-496-0559 x136
E-mail: vhirsch@niaid.nih.gov

Arifa S. Khan, Ph.D.
Chief, Molecular Retrovirology Section
Division of Viral Products, OVRR, CBER, FDA
Bldg. 29B, Rm 4NN10, HFM-454
1401 Rockville Pike
Rockville, MD 20852
Phone: 301-827-0791
Fax: 301-496-1810
E-mail: khan@cber.fda.gov

Dr. Michel Klein
Aventis Pasteur
2, Avenue Pont Pasteur
F-69367 Lyon cedex 07
Phone: 33 4 37 37 3664
Fax: 33 4 37 37 3976
Assistant: Sylvie Gimenez

Dennis Klinman, M.D., Ph.D.
Section Chief, DVP, OVRR
Bldg. 29A, Rm. 3D10 HRM 454
CBER/FDA
1401 Rockville Pike
Bethesda, MD 20892
Office: 301 827 1707
Fax: 301 496 1810
E-mail: klinman@cber.fda.gov

Peter Kwong, Ph.D.
Research Scientist
Vaccine Research Center
40 Convent Drive
Bethesda, MD 20892
Phone: 301-496-1852
E-mail: pkwong@nih.gov

Peter Lachenbruch
Division Director
DHHS/FDA/CBER/OBE/DB
Building WOC1, Room 200S
1401 Rockville Pike
Rockville, MD 20852-1448
Phone: 301-827-6055
Fax: 301-827-3529
E-mail: lachenbruch@cber.fda.gov

Michael Lenardo
Phone: 301-435-3385
E-mail: ml8e@nih.gov

Norman L. Letvin, M.D.
Associate Professor. of Medicine
Beth Israel Deaconess Medical Center
Harvard Medical
41 Avenue of Louis Pasteur, RE-113
Boston, MA 02215
Phone: 617-667-2766
Fax: 617-667-8210
Email:
nletvin@caregroup.harvard.edu
Assistant: Nicole Siciliano
E-mail:
nsicilia@caregroup.harvard.edu

MaryAnne Luzar
NIAID
6700 Rockledge Drive
Rockville, MD 20892
Phone: 301-435-3737
E-mail: mluzar@niaid.nih.gov

John R. Mascola, M.D.
Deputy Director, VRC
Vaccine Research Center, NIH
Bldg. 40, Room 5512
40 Convent Drive
Bethesda, MD 20892-3005
Phone: 301-594-8487
Fax: 301-480-2788
E-mail: jmascola@nih.gov

Timothy D. Mastro, MD
Chief, HIV Vaccine Section
Division of HIV/AIDS Prevention
CDC
1600 Clifton Road, Mailstop E-45
Atlanta, GA 30333
Phone: 404-639-2982
Fax: 404-639-6127
E-mail: tdm3@cdc.gov

Bonnie Mathieson
E-mail: mathiesb@od.nih.gov

John G. McNeil MD MPH
Deputy Director
Division of Retrovirology
Walter Reed Army Institute of Research
Suite 250; One Taft Court
Rockville, MD 20850
Phone: 301-251-5035
Fax: 301-294-1898
E-mail: jmcneil@hivresearch.org

Loris Mcvittie
FDA
E-mail: MCVITTIE@CBER.FDA.GOV

Karen Midthun, M.D.
Director, OVRR
1401 Rockville Pike
Bldg 29B, Room 1H16, HFM 400
Rockville, MD 20852
Phone: 301-827-0655
Fax: 301-827-0448
Email: km305w@nih.gov

Abe Mittelman
Associate Director
Vaccine Research Center
40 Convent Drive
Bethesda, MD 20892
Phone: 301-594-8493
E-mail: amittelm@nih.gov

F. Zoe Moodie, Ph.D.
Statistical Center for HIV/AIDS Research & Prevention (SCHARP)
Fred Hutchison Cancer Research Center
1100 Fairview Ave. N., MW-500

PO Box 19024
Seattle, WA 98109-1024
Phone: 206-667-7077
Fax: 206-667-4812
E-mail: zoe@scharp.org

Bernie Moss
Laboratory of Viral Diseases
National Institute of Allergy and Infectious Diseases
National Institutes of Health
Building 4, Room 229
4 Center Drive, MSC 0445
Bethesda MD 20892-0445
Phone: 301-496-9869
Fax: 301-480-1147
E-mail: bmoss@nih.gov

Jeffrey Murray
E-mail: murrayj@cder.fda.gov

Gary Nabel, MD, Ph.D.
Director
Vaccine Research Center
National Institutes of Health
40 Convent Drive, Room 4502
Rockville, MD 20892-3005
Phone: 301-496-1852
Fax: 301-480-0274
E-mail: gnabel@nih.gov

Keith Peden
DHHS/FDA/CBER/OVRR/DVP
HFM-454
Bldg. N29A, Room 3D08
1401 Rockville Pike
Rockville, MD 20852-1448
Phone: 301-827-1708
Fax: 301-827-1810

E-mail: peden@cber.fda.gov

Vladimir Popovic, M.D.
VAXGEN, Inc.
1000 Marina Boulevard
Suite 200
Brisbane, CA 94005
Phone: 650-624-1000
Fax: 650-624-1003
E-mail: vpopovic@vaxgen.com

Mike Pensiero
NIAID/DAIDS
6700-B Rockledge Drive
Rockville, MD 20892
Phone: 301-435-3749
E-Mail: mpensiero@niaid.nih.gov

Douglas Pratt, M.D., M.P.H.
Medical Officer
Office of Vaccines and Research and Review
Division of Vaccines and Related Products Applications, HFM-475
Food and Drug Administration
1401 Rockville Pike
Rockville, MD 208542-1448
Phone: 301-827-3070
Fax: 301-827-3532
E-mail: PRATTD@CBER.FDA.GOV

Rino Rappuoli, Ph.D.
Catherine Mallia
The Office of Rino Rappuoli
IRIS, Chiron S.p.A.
Via Fiorentina, 1
53100 Siena - ITALY
Phone: +39-0577-243414
Fax: +39-0577-243564
EFax: +39-0577-278508
E-Mail: Rino_Rappuoli@chiron.it
Assistant: Catherine Malia
Email: catherine_mallia@chiron.it

Wasima Rida
DHHS/FDA/CBER/OBE/DB
HFM-217
Bldg. WOC1, Room 200S
1401 Rockville Pike
Rockville, MD 20852-1448
Phone: 301-827-3034
E-mail: rida@cber.fda.gov

Harriet L. Robinson, Ph.D.
Asa Griggs Candler Professor
Chief, Division of Microbiology and Immunology
Yerkes Primate Research Center of Emory University
954 Gatewood Road, NE
Atlanta, GA 30329
Phone: 404-727-7217 or 727-7377
Fax: 404-727-7768
E-mail: hrobins@rmy.emory.edu

Mario Roederer
Director, Immunology & Flow Cytometry Core
Vaccine Research Center
40 Convent Drive
Bethesda, MD 20892
Phone: 301-594-8491
E-mail: marior@mail.nih.gov

Jerald C. Sadoff
Executive Director
Vaccine Integration
Merck & Co., Inc.
P.O. Box 4, Attn: VNC-151
West Point, PA 19486
Phone: 484-344-2615
Fax: 484-344-7679
E-mail: Jerald_sadoff@merck.com

Anne Scanley
NIAID/NIH
Building 31, Room 7A52
Bethesda, MD 20892
Phone: 301-435-8494
E-mail: ascanley@niaid.nih.gov

Bob Seder
NIAID
Building 10, Room 11C217
Bethesda, MD 20892
Phone: 301-402-4816
E-mail: rseder@nih.gov

Steve Self, Ph.D.
Fred Hutchinson Cancer Research Center
1100 Fairview Avenue North
MP-1168
PO Box 19024
Seattle WA 98109-1024
Assistant: Carrie Kalinak
SCHARP/Administrative Assistant
Phone: 206-667-5172
Fax: 206-667-6888

Stuart Z. Shapiro MD, Ph.D.
Medical Officer, Pre-clinical Research & Development Branch
Vaccine & Prevention Research Program
Division of AIDS, NIAID, NIH
Room 4108, MSC 7628
6700-B Rockledge Drive
Bethesda, MD 20892-7628
Phone: (301) 402-0122
Fax: (301) 402-3684
Email: sshapiro@niaid.nih.gov

George M. Shaw, M.D., Ph.D.
Investigator, Howard Hughes Medical Institute
Director, Division of Hematology/Oncology
University of Alabama at Birmingham
Room 205 WTI
1530 3rd Avenue South
Birmingham, AL 35294-3300
Phone: 205-934-9591
Fax: 205-934-9573
Email: gshaw@uab.edu
Assistant: Bonnie Zarzaur
E-mail: bonniez@uab.edu

Bill Snow
AIDS Vaccine Advocacy Coalition
40 Alta Road
Berkeley, CA 94708
Phone: 510-524-5257
Fax: 510-524-5723
Email: WmSnow@aol.com

Donald Stablein, Ph.D.
President/Statistician
The EMMES Corporation
410 N Washington St #700
Rockville, MD 20850
Phone: 301-251-1161
Fax: 301-251-1355
E-mail: dstablein@emmes.com

Judy Stein
NEI
9000 Rockville Pike
Bethesda, MD 20892
Phone: 301-496-5248
E-mail: jstein@nih.gov

Edward Tramont, M.D.
Division of AIDS
National Institute of Allergy and Infectious Diseases
6700-B Rockledge Drive
Room 414r
Rockville, MD 20892
Phone: 301-496-0545
E-mail: **et89f@nih.gov**

Sten H. Vermund, MD, Ph.D.
Professor, Department of Epidemiology and International Health and the
John J. Sparkman Center for International Public Health Education
Director, Division of Geographic Medicine
The University of Alabama at Birmingham
Birmingham, AL 35294-2170
Phone: (205) 975-7700
Fax: (205) 934-5600
E-mail: sten@uab.edu
Assistant: Adrienne Ellis (ale@uab.edu)
Phone: 205-975-7700

Jerry Weir
DHHS/FDA/CBER/OVRR/DVP
HFM-457
Bldg. N29A, Room 3B05
1401 Rockville Pike
Rockville, MD 20852-1448
Phone: 301-827-2935
Fax: 301-496-1810
E-mail: weirj@cber.fda.gov

Carol Weiss
Division of Viral Products
FDA/CBER, HFM-466
Bldg. 29, Room 532
1401 Rockville Pike
Rockville, MD 20852-1448
E-mail: weiss@cber.fda.gov

Nathan Winslow
VAXGEN, Inc.
1000 Marina Boulevard
Suite 200
Brisbane, CA 94005
Phone: 650-624-1000
Fax: 650-624-1003
E-mail: nwinslow@vaxgen.com

Richard Wyatt
Structural Virology Section
Vaccine Research Center
Building 40, Room 3502
40 Convent Drive
Bethesda, MD 20892
Phone: 301-594-8690
E-mail: richw@nih.gov

Kathy Zoon
DHHS/FDA/CBER/OD
HFM-1
Bldg. N29B, Room 5NN02
1401 Rockville Pike
Rockville, MD 20852-1448
Phone: 301-827-0548
Fax: 301-827-0440
E-mail: zoon@cber.fda.gov