

MEETING OF

ARMED FORCES EPIDEMIOLOGICAL BOARD

Dalrymple Conference Room (1425)

The U.S. Army Medical Research Institute

Infectious Diseases

1425 Porter Street

Fort Detrick

Frederick, Maryland 21701

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TRANSCRIPT OF PROCEEDINGS

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1 interested particularly to hear about the two
2 topics that I understand are next on the agenda
3 and I'm interested about the presentations, the
4 two issues that's there's a lot of attention, not
5 just in the media, but concern among a lot of
6 people. So we need to hear about that and I
7 look forward to the presentations. Thank you
8 again.

9 PRESIDENT OSTROFF: Although at
10 times we tend to be a little bit critical I need
11 to say for all of us that we really do
12 appreciate the fine work that's done by Health
13 Affairs and by the services and we congratulate
14 all of you for the things that you do for us.

15 Let me turn the podium over to
16 Dr. Hoke for those on the board who weren't here
17 at the last meeting you know we had an updated
18 presentation from Dr. Hoke on the status of the
19 adenovirus vaccine reacquisition. And,
20 suffice it to say we left Dr. Hoke a little bit
21 bruised and wounded, but he looks like he's

1 healed pretty well.

2 And,, so we're very much looking
3 forward to another presentation. Thank you for
4 coming.

5 DR. HOKE: Thank you very much.
6 Believe it or not it's a pleasure to be back and
7 I think that we heard really a very good
8 presentation from Colonel Berte in the last hour
9 that was at 50,000 foot level of the chem/bio
10 medical systems and this presentation is going
11 to be very much more down in the weeds for you
12 and in part -- the motive is to address the
13 issue that the devil is in the details, so I
14 wanted to share with you some of the details so
15 that you can see where we are in this project.

16 The things I'm going to address
17 are going to be your letter first and specific
18 actions that we've taken to address the items
19 mentioned in the letter. The schedule at this
20 time, some of the milestones we've achieved
21 since the February meeting.

1 I wanted to share with you some
2 details of the critical trial of the old vaccine
3 that was done fairly recently so that you can
4 see what that vaccine looked like in people
5 recently. And, then talk to you about what I
6 see of the acquisition plan risks at this point
7 and then summarize.

8 In your letter you expressed
9 concerns over the time line, the contact we've
10 had with the FDA, requirements, lack of single
11 and double individuals responsible that DoD
12 could not address the underlying causes of the
13 procurement failure and that the DoD must
14 provide the impetus for adenovirus vaccines.

15 These were concerns. They didn't
16 require specific action at that time. The
17 things you specifically recommended are here on
18 a high level point of contact with
19 responsibility to the realm of the media to
20 sustain your action with the FDA counterparts so
21 that time frames for vaccine acquisition could

1 be established. I'm sure that various obstacles
2 can be overcome. And, that this individual will
3 be required to work with whomever necessary at
4 DoD to create a formal requirements document for
5 adenovirus vaccine. And, the board would
6 appreciate an opportunity to review such a
7 document as its next meeting.

8 With respect to the first
9 recommendation, is going to be deputy for
10 acquisition, but Mr. Howell did the briefing
11 Colonel Rousch in ASD health affairs has been
12 identified to provide oversight and has been in
13 daily contact to check on progress. We have a
14 product manager and deputy -- manager identified
15 in USAMRMC and have formed an integrated product
16 team of our first meeting. We have drafted an
17 ITT charter and this supplements ongoing working
18 integrated product team meetings that were
19 already happening between the contractor and the
20 rare scientists that are working in support.

21 With respect to the state

1 interaction with the FDA the contractor had had
2 a meeting with the FDA on the 5th of March, 2003
3 to discuss plans for the production facility and
4 perhaps I hadn't made that as clear as I should
5 have, but in addition to that the contractor had
6 requested a meeting that took place on the 10th
7 of May, two days ago in which they participated
8 with the FDA to discuss the specifics of the IAV
9 package that was proposed for submission.

10 My next civil slides summarize the
11 recommendations that the FDA made in that
12 meeting on Monday. And, I should say at the
13 outset, and perhaps you would rather say in
14 conclusion, that this was a little bit of an
15 unusual meeting in that the FDA came to the
16 meeting with 30 or 40 specific recommendations
17 for us all constructive and helpful designed to
18 smooth the road ahead in terms of regulatory
19 bumps.

20 They wanted an update from
21 epidemiology, very reasonable. In terms of the

1 general strategy they did appear to accept the
2 notion that the vaccine was a replacement
3 vaccine. They agreed that the 4 & 7 products,
4 which are going to be separate tablets, they
5 agreed that they could be filed under a single
6 I&B and presumably a single licensure
7 application. This is a huge administrative
8 help.

9 They reminded us that any clinical
10 trial that they might do that we should talk to
11 them first and that will come up later as to why
12 they reminded us of that fact. But that's very
13 good advice.

14 They were curious as to how the
15 DoD intended to use the vaccine, because the
16 intended use of the vaccine, the indication for
17 it that's in the package insert then becomes the
18 target of the clinical trials and the
19 recommendation for clinical trials and so it's
20 updating -- it would be initial thinking on that
21 usage might fall into the purview of this board

1 and I'll say more about that later.

2 They did not feel that as the data
3 had been presented support the argument that
4 neutralizing antibody is a surrogate for
5 protection. In the olden days when the vaccine
6 was developed the tests were not validated as
7 they are today and different tests may have been
8 used and the concept here is if they're going to
9 license the vaccine for protection they're going
10 to ask us to show that it protects.

11 Now, we're going to specifics of
12 the vaccine those were some comments on general
13 strategy. On the vaccine itself the interest we
14 had in transition for MRC 5 cells later was
15 acceptable, but it would be part of the YND. We
16 can't go back and do this now because too much
17 effort has been invested in the WI38 cells. But
18 we have spoken with Colonel Berte, I guess an
19 e-mail counts as spoken, we have communicated
20 with Colonel Berte on taking advantage of some
21 MRC 5 cell experience that CDMS has and we might

1 get some acceleration there, but that's a
2 downstream issue. The request is specific tests
3 on the WI38 cells to demonstrate -- nature.
4 They suggested a specific TCR test to be sure
5 that there's no cross contaminations in the
6 vaccines and they advised some tracking pedigree
7 of cells to be sure that there was no
8 possibility of exposure to BSE.

9 On safety data they wanted us to
10 bring together any old safety data that might
11 exist from DoD experience. We're really at this
12 point not entirely sure if we used the vaccine
13 in women, although there is one report that
14 suggests that it may have been given to some
15 recruits; some trainees, and because of the way
16 the immunization records were kept at the time
17 and particularly the way adverse events may have
18 been reported the information is very diffuse.
19 It may only be in people's shot records, for
20 example.

21 So this will take some doing and

1 they will certainly want post-marketing
2 surveillance data on females once the vaccine is
3 licensed. This comment on safety, I said
4 current, but I really meant they will want
5 safety data on at least fifteen hundred
6 recipients of the vaccine during clinical trials
7 and they want to know how the vaccine will be
8 used with respect to the young women trainees
9 later. Those are all safety issues.

10 They made a number of comments
11 regarding the clinical development plan. The
12 statistical basis for the initial trial. They
13 commented that we said the trial would show
14 safety, but then there wasn't any discussion of
15 the study size based on an analysis of what
16 safety we wanted to show. It sounds like a
17 picky point, but what they're saying is, "why
18 don't you do this, so that when we're reviewing
19 the results we won't have a question. We want
20 it taken care of now."

21 Issues about -- some issues that

1 we may take exception to assuring that spouses
2 of basic trainees are not pregnant is a very,
3 very difficult and not practical thing to do at
4 all. We may have to have further discussion
5 with them about that. Concern over pregnancy
6 issue again and how will we take care of that.
7 That's subjects of the history of GI surgery be
8 excluded. That's a helpful suggestion so that
9 we don't have complications that arise that
10 might be attributable to the vaccine that's
11 orally administered. And, a number of other
12 issues, stopping (inaudible) of the study. A
13 number of other technical issues.

14 The most important one is that
15 they did request a study that demonstrated
16 efficacy and suggested that this didn't have to
17 be a massive study, a figure of maybe three
18 hundred per arm was mentioned with a relatively
19 easily identified case definition,
20 hospitalizations due to adenovirus infection and
21 upper respiratory symptoms or something like

1 that in a procedural controlled trial is what
2 they were looking for.

3 They were trying to tell us they
4 wanted it, but it wasn't going to be too bad.
5 The inpoint assays they suggested that we use a
6 PRNT50 instead of the TCID 50 assay for antibody
7 testing. This seems like an incredibly --
8 virological point. But the idea is that in a
9 virologic assay a fact reduction -- in a fact
10 reduction assay you're actually showing
11 inhibition of viral replication and viral
12 particles. In a TCID assay you're showing that
13 no single virus particle remain uninhibited and
14 so by nature the PRNT 50 assay is more sensitive
15 to antibody.

16 Again this is a hint, hint,
17 they're saying use this kind of assay instead of
18 that kind and they of course wanted permission
19 about the assays I mentioned by this case
20 definition.

21 So just to pause for a second and

1 say then in response or in association with your
2 recommendations that we have these discussions
3 with the FDA, that meeting has taken place and
4 as you can see it was filled with
5 recommendations, all of which will be very
6 helpful in smoothing the way forward, which I
7 think was the intent of the recommendation.

8 Now, the board recommended that
9 the individual be empowered to work with people
10 within the DoD to create a formal requirements
11 document for adenovirus vaccine. And, would
12 appreciate the opportunity to review such a
13 document.

14 Immediately following the last
15 meeting the Deputy Director Physician Mr. Howell
16 did request requirements documents from the
17 (inaudible). Our liaison down there, the MRC...
18 liaison Dr. Nelson is working with them. And,
19 the priority to the moment has been to generate
20 a place called an initial capabilities document.
21 This is for all infectious disease products and

1 the specific capability production document for
2 the adenovirus vaccine will be done after that,
3 so I don't have that to show to you. I guess it
4 would be made an open issue.

5 MEMBER: They acknowledged that
6 they were doing it. It's not a case that we
7 have to convince them any more, they're
8 convinced.

9 MR. HOKE: Right. Now, there was
10 another recommendation that he made on the
11 diagnostic testing and approved antiviral
12 treatments, and I must say I confess that this
13 is to be dealt with not as great detail as our
14 concentration on the vaccine. We've looked on
15 the FDA website and found that there are a
16 number of assays for adenovirus infection that
17 might be useful. In addition the folks at WRAIR
18 have been developing assays that will be
19 intended for the clinical trials of the vaccine.
20 These might be useful.

21 The drug picture is considerably

1 more murky. There is one drug, Cidofovir that
2 Dr. Huggins here at USAMRIID mentioned to me and
3 I found one paper and I'm sure there are others
4 where it was promising a (inaudible) model, but
5 this is obviously a long way from use and
6 approved for our trainees.

7 So we really don't have a strategy
8 for implementation for this recommendation yet.
9 We really don't have any wherewithal to do
10 anything, but I think we really -- I know we
11 certainly owe you a plan for how we would
12 approach this recommendation in the future.

13 Now, the last time it was the
14 schedule that really attracted attention and so
15 unlike Colonel Berte, I'm showing you the
16 schedule that I showed you before.

17 So here's the one -- of course it
18 was the 2009 issue down here and we went back
19 and looked at this very hard and we tried to
20 identify areas that we could squeeze it, better
21 more manage the time more tightly and we -- this

1 is now our working chart and it calls for
2 licensure in 2007, which is what you have been
3 told in the previous briefing and I think we can
4 do that. We can do that if things work out and
5 it's likely to be complicated, but we took out
6 some intermediate trials I think if you really
7 went back and compared -- so we're really going
8 to be planning two sets of trials, an initial
9 trial and a very much larger trial, but still
10 honestly hasn't been designed, because we just
11 got our guidance from the FDA on Monday.

12 By a trial that will look at
13 efficacy inner basic training folks and then
14 also the 1500 safety data will probably come
15 from that environment as well.

16 Now, the next several slides I
17 have are really just our -- just to show a
18 little more detail for each of the major areas
19 that are in that first gant chart. It's
20 probably just to remind you that actually we
21 have done an awful lot at the time of the last

1 presentation. And, honestly I dare say more
2 than we've ever done on anything before. You
3 know, you actually have, through the contractor
4 have built a production facility for the
5 (inaudible) part and, you know, that was all
6 planned here and the equipment's been installed
7 and validated and so that's, you know, we had to
8 have a facility, so that was good news.

9 To work on hylic and GNP (sic)
10 tablet production is all planned and those steps
11 are taking place now. The regulatory issues,
12 all the steps in terms of draft IND has been
13 written. The company is planning to file the
14 IND on the 1st of June. That's just a few days
15 away and they are having to adjust that filing
16 based on what was told to us in the pre IND
17 meeting here on May 10th, day before yesterday.
18 So you know all these things we're trying to
19 work them all together.

20 The clinical trial work in Phase
21 1. The clinical trial with all this information

1 shows the preparation of the protocol. The
2 protocol was approved by the HSR (inaudible)
3 implementation in March. There's going to have
4 to be some changes to it now based on what the
5 FDA told us. And, that may take -- that'll take
6 some time to make the changes and then they'll
7 have to do whatever needs to be done with that.
8 But the team has already gone down to Ft. Sam to
9 meet with the commander down there and begin I
10 think to identify the population for that study
11 which will be the 91 Whiskey group of soldiers.
12 And, they're down there today, in fact,
13 collecting blood from cohorts to learn about the
14 prevalence of antibody adenovirus in that group
15 as the trial goes forward.

16 Then the planning all the way
17 through the final study report that's shown
18 here, these are the details. The tablet in
19 production then becomes the next big issue for
20 the Phase 2 pre-clinical trial and that is
21 outlined here along with the planning for the

1 Phase 3 pre-clinical trial, which I said earlier
2 hasn't actually been done yet. But it's part of
3 the process.

4 Then finally the regulatory
5 affairs package and submission for the license
6 agreement out here in Post 7. That plan has
7 already been done.

8 So that's the overall plan again,
9 this is the same slide as you saw before and we
10 think that we're reasonably confident that this
11 has been planned in a level of detail that will
12 allow us to actually do this by 2007.

13 Now, I just wanted to mention a
14 few milestones that I've actually already
15 mentioned about them except to tell you that we
16 did get a quarterly report from the contractor
17 and I'm going to go over that with you in a
18 minute.

19 I've been meaning to tell you
20 about the Phase 1 and 2 clinical trial. And,
21 the contracting issues are important and because

1 we worked through USAMRA, the U.S. Army Medical
2 Research Acquisition Activity, and they are
3 included in our integrated product team so that
4 we can make sure the contracting issues are
5 smoothed out to the extent possible.

6 Of course, the government has its
7 rules and regulations and has to follow the law.
8 And, the company has its perspective on things
9 and we don't always agree, but we can try to
10 work them out through our contracting officers.

11 Now, the contractor's quarterly
12 report is where we find out just what progress
13 is being made. These are the issues that are
14 dealt with and these are the same issues that I
15 presented to you before, but this quarterly
16 report, the bulk virus production, the
17 formulation and -- assay development tablets,
18 trials, DoD issues from the company's point of
19 view and financial issues.

20 Now, the both virus production
21 issues which the (inaudible) virus were tested

1 and passed all of these tests. You know, the
2 passing of the test means the substance wasn't
3 there. Or that the materials were identified
4 correctly, so that's good news and good
5 progress. The ADV-7 GMP lots for vaccine
6 production have been done and have been saved.
7 The type of lot that was made in October was
8 titer and the titer was sufficient metal for
9 vaccine production and the infiltration step you
10 often lose a lot of virus when you filter it.
11 Very little was lost at this time.

12 And, that has been sent for
13 storage for later transferring to the facility
14 down in Virginia. A whole bunch of tests were
15 done on the adenovirus and the results were
16 satisfactory. For the ADV-7 similar work was
17 done, although in this case they needed to make
18 a replacement batch which was done and shipped
19 to WRAIR in January with titer for ...zation,
20 and it passed all its tests as well. So that's
21 GMPADV- 4 and 7. The next step is the

1 formulation and authorization and for the ADV-4,
2 the run was done in 8000 doses which was
3 (inaudible) produced and stored at WRAIR and
4 that will be shipped to the Virginia facility,
5 and similarly in February (audience noise).

6 Assay development is being done
7 largely at WRAIR. ECR tests where the
8 validation is ongoing. They tested a number of
9 specimens from the facility and it indicates
10 that the screening program is adequate to
11 proceed. Assays for clinical trials are under
12 development at WRAIR as well.

13 The technical things like an
14 antiserum you need to show you got the virus you
15 think you've got and not other things. It
16 requires that the company use the old serum from
17 (inaudible), but that new serum be developed as
18 well. That's being done and the methods for
19 inactivation for virus in the production area
20 are being evaluated.

21 The tablet production facility

1 further downstream has made progress. The pilot
2 batch of tablets has been produced. No loss in
3 titer and the (inaudible) contents were above
4 expected values. The tablets failed the
5 disintegration test. These kinds of things
6 happen. They're part of the development
7 process. They need to be dealt with and those
8 issues are being dealt with.

9 There was a small problem in the
10 tablet equipment that has been corrected in two
11 pilot batches or have been made and are being
12 evaluated. (audience noise) has had a problem
13 with the solvent content that was too high and
14 too rapid disintegration of tablets so that
15 protocol is being modified and the FDA performed
16 a GMP inspection of the facility in April for
17 other products, but their quality systems were
18 included in the inspection and they passed.

19 On the clinical trials I told you
20 about the CID meeting and the two trials that
21 are proposed, one trial will be done at Fort

1 Leonard Wood and an additional thing I might
2 mention that at Fort Sam and the larger study,
3 the MES... Study will be done at Fort Leonard
4 Wood though we may seek other sites for that.

5 It's not entirely clear or we
6 haven't decided or the company hasn't decided
7 who exactly will do these trials, but that will
8 happen soon.

9 Now, the company, and this is a
10 report to us again as noted, and the AFEB and
11 ASD (inaudible) interest. There was a scope
12 change that they proposed based on additional
13 items and that has taken some time, but I think
14 that has moved along well now.

15 The contract had an option in it
16 for the Phase 2 and 3 trials that was going to
17 be several years from now, but that option was
18 exercised in order to reduce the amount of time
19 that the company would have to spend getting
20 those things done. We've had an issue related
21 to billing procedures that is currently being

1 resolved through negotiations.

2 So the point of the last ten
3 minutes is that the company, the contract
4 company that is working on this vaccine has
5 filed a report and for the last quarter and that
6 the details, I warned you this was going to be
7 down in the leafs, this is down in the leafs of
8 the vaccine development and effort are
9 proceeding and proceeding fairably. There are
10 bumps in the road, but when you get down to the
11 real world those kinds of things always happen.

12 So I want to spend just a little
13 bit of time to tell you about a clinical trial
14 that was done on the old vaccine in 1997. This
15 was done at WRAIR when it was realized that the
16 vaccine was not being manufactured any more and
17 the folks down there had the view that well it
18 might be useful to do one last clinical
19 observation with this vaccine. The hope being
20 that it would serve as kind of a bridging study
21 on to the new vaccine. Even though those

1 tablets were expiring there wasn't going to be
2 an opportunity to do a contemporaneous
3 comparison.

4 So this trial was done and called
5 the characterization of the serologic and
6 biologic responses of healthy adult volunteers
7 and it was done by Colonel Kuschner and Colonel
8 Sonn (sic) provided these data. The vaccines
9 were the approved 4 and 7 vaccines and the
10 purpose was to provide a bench mark for
11 comparison of a replacement vaccine. It was
12 done at WRAIR with healthy adults and
13 neutralize the antibody was evaluated along with
14 symptoms.

15 40 people enrolled, 5 were
16 excluded in the enrolling period due to the
17 development of antibody and 1 lost at follow-up,
18 so 35 were actually analyzed and they broke down
19 like this. None of them had antibody in both 4
20 and 7, 8 had antibodies to neither; 5 had 4 only
21 and 22 had 7 only so there was kind of a mixture

1 of past experiences.

2 The seroconversions which is
3 defined as going from a a sero neutralization
4 titer of less than 2 to more than 2 was 90% and
5 for the adeno 4 and for the adeno 7 it was 100%
6 according to these definitions.

7 And, this was the distribution of
8 titers of the ratio of titer. Well, since this
9 was the seronegatives to start with they were
10 essentially all divided by 2, that's why there's
11 less than, the sign is here. But there were
12 relatively low titer range actually in this
13 trial.

14 And, they looked at shedding and
15 feces and adeno 4 and adeno 7 were shed by all
16 of the recipients of the vaccine, though none
17 had that virus in the throat cultures. And,
18 this was for a fairly long period of time and in
19 some cases the shedding hadn't stopped by May
20 28th. So that is an issue.

21 The symptoms that were reported,

1 and this is an uncontrolled study, were a
2 distribution of things but there were a few
3 upper respiratory symptoms in 12 of the 35
4 recipients.

5 So now remember at the beginning I
6 told you that the FDA made a comment that they
7 wanted to know about things ahead of time. I
8 told you that later I'd explain why they said
9 that. Well, what they said was right out off
10 the bat in the beginning of our discussion they
11 said, "well, did you talk to us about that
12 study?" And, there was an admission that they
13 had not been talked to. And, they said, "well,
14 you know, we think that the study is probably
15 too small to really anchor your program and in
16 the future you should talk to us in advance."

17 So it was -- this was done several
18 years ago and, you know, it was a licensed
19 product and at the time I would have to say that
20 this what seems obvious in retrospect issue
21 wasn't so obvious. It was not obvious at the

1 time and it's a lesson for the future.

2 But it partly led to the wish by
3 the FDA that instead of using this as a
4 comparison with which to license the vaccine met
5 actual clinical trials demonstrating efficacy
6 with the titer.

7 So I wanted to switch then from
8 that set of slides and also talk to you a little
9 bit about what I see as risks in this program.
10 The main factor is I think is pretty far down
11 the road, the contractor, in identifying a
12 production facility for the virus material.
13 Remember the facility in Virginia is for
14 tableting.

15 My opinion this is not a perfect
16 arrangement yet. Optimally there would have
17 been a building right next to the tableting
18 facility. That is not the plan. And, it turns
19 out it's fairly difficult to find companies
20 willing to make infectious material in small
21 amounts for you as this company, as a company

1 would have to do as a subcontractor.

2 The contractor believes that this
3 problem will be solved, but I would say until it
4 is solved it's still an open issue.

5 The clinical trial program, the
6 addition of the efficacy study may increase time
7 line and costs, but I'm not a hundred percent
8 sure of the time line. The costs -- the
9 technical issue here is that the contract with
10 the company calls for safety in immunogenicity
11 studies, not efficacy studies. So there's a
12 fine point there that will need to be negotiated
13 and there may be additional costs in the study
14 for that in the development program.

15 We have a time crunch to get the
16 changes made to the protocol. The protocol is
17 now scheduled for implementation in September.
18 If we miss that September window, because of the
19 winter holidays we'll be pushed until after
20 December for starting that trial. And, so
21 there's a large incentive to get everything done

1 by September, but there's also the regulatory
2 review of the changes that have to be done, so
3 it's going to be tough. So that's an issue that
4 may cost us a few months.

5 We then identified the clinical
6 teams for the later study, so that's an open
7 issue. The serological testing, validation of
8 the test has not been completed yet and so again
9 that's an issue that we have not resolved. The
10 site for testing a large number of testings
11 needs to be identified as well.

12 And, also I didn't talk too much
13 about this, although I alluded to it, the issue
14 of female trainees. The issue of reproductive
15 toxicity studies has really not been resolved.
16 The FDA is looking for our thoughts, I think
17 it's as much theirs as to how we can address
18 this issue in a responsible way.

19 So those are risks that are open
20 issues in the trial and development process, but
21 I felt that I needed to share with you. We have

1 additional acquisition steps that we want to do
2 to tighten this program up. I think what
3 Dr. Berte showed you was a pretty tight idea of
4 how vaccine acquisition should be run and I
5 think we're doing a good job. We talked about
6 the capability production document, the charter
7 for the product manager is in the works. We've
8 done the integrated product team in meetings and
9 the charter is in the works for that. We need
10 to -- now that we've got FDA guidance to
11 complete the test plan. We have never dealt
12 with milestone review on this product; partly
13 because it's being funded by a different way
14 than many other products. But this is something
15 that we need to do so that the milestone
16 decision authority, who would be the commander
17 of MRNC, you know, would have the formality of
18 this briefing done, not that the briefing itself
19 is just proforma so that we've looked at all the
20 issues and assure him that -- or inform him of
21 what the issues are. That's an important

1 acquisition step. And, we need to look into the
2 future on budget authority.

3 So I know you're all wondering
4 what you might do to help and I'm sure you have
5 ideas completely beyond what I can think of, but
6 I thought of some of these.

7 Since you all are functioning as
8 kind of an over arching IPT, innovative product
9 team. You're also kind of senior advisors to
10 the DoD, but you know by asking me to come here,
11 you know, sort of checking on the process and I
12 think that's valuable for you to do that. For
13 one thing, you know, it gives me a hammer, if
14 you will, to go back and say, "no, we absolutely
15 need that quarterly report. We absolutely need
16 this information because the IPT has asked for
17 it," or asked for an update. So that is useful.

18 The use of the vaccine, remember I
19 alluded to this, the FDA asked us about that
20 and, you know, we have a notion, the company has
21 a notion, and there were policies before, but

1 the board may wish at some time as licensure
2 approaches to give some thought to what the
3 policy would be so that to make sure that we
4 have a vaccine that will do that when we finally
5 get there.

6 And, also this issue came up and I
7 first was very nervous about it, but I felt kind
8 of duty bound to bring the idea up and I'm glad
9 I felt that, because someone asked a question
10 very similar to this before. You know, would
11 anybody recommend that we should have a
12 treatment IMV at some later time. Once, you
13 know, the studies have been completed and
14 relating licensure, something like that, I would
15 say it certainly should follow a time where
16 convincing evidence of safety and immunogenicity
17 and probably efficacy have been produced. We
18 don't want to rush into something when we
19 haven't got it yet. But that's an item that may
20 be discussed in the future.

21 I mention this 21CFR B12 because

1 that kind of talks about the specifics of the
2 ...IND. I'm not suggesting that we should, but
3 I'm just saying that somebody might think of
4 that.

5 So, the effort is advancing
6 towards its goal. We're working to kind of mold
7 this into the DoD and Army acquisition model.
8 The contractor is making progress. The FDA has
9 provided detail guidance. Many problems remain
10 to be solved, but we don't see any
11 unsurmountable obstacles. We do have a company
12 person here also to show this...

13 So, now this is the vision. I'd
14 have to say that I've been involved in a lot of
15 product development efforts in the last twenty-
16 five years and this really isn't (inaudible)
17 this is a lot better than most of the things
18 that we're doing. I'm not sure that it's
19 betterness is what was being referred to, but we
20 are taking this seriously and we are moving
21 ahead. We've never actually built a facility

1 before. So this is way out -- we've never
2 actually been involved with a product where the
3 DoD has really and truly taken full
4 responsibility for. So it's not -- it's
5 business that's actually in many respects better
6 than usual. And so that's all I have to say.

7 There's some ambiguities in this
8 last slide, but I think I'll just... maybe it's
9 telling you that I think we're on target or that
10 I am the target. But I'll be happy to address
11 any questions that you might have at this time.

12 PRESIDENT OSTROFF: Dr. Hoke,
13 thanks for a very comprehensive presentation.
14 I'm sure all of us around the table appreciate
15 the complexities of this process and what you're
16 undertaking. Before I open it up to the board
17 for questions, because I know that there are a
18 number of individuals around the table who have
19 expertise in some of the trial designs and some
20 of the issues that have been raised and I know
21 that there are representatives here from the

1 company and we very much appreciate them being
2 here for this meeting and I was just wondering
3 if any of the company representatives would like
4 to pose any comments. Dr. Tollis is here. I'll
5 introduce Dr. Tollis. He is one of the
6 principals of the company called Maccgen that is
7 a subcontractor for this project.

8 DR. TOLLIS: Thank you very much
9 for the opportunity to have Charlie present our
10 slides. I think that it's been an interesting
11 development program for many different
12 perspectives. I think the one thing I'd just
13 like to point out is that it was the original
14 vision as a tech transfer project and that is
15 really quite an underestimate of the amount of
16 work that we've done over the past few years and
17 ultimately I think making good progress as has
18 been outlined and as Charlie mentioned we had a
19 very good meeting with the FDA and they seemed
20 to be working with us. And, I'll be happy to
21 answer any of the technical questions about the

1 vaccine.

2 In recruit settings and it strikes
3 me as being inconceivable that no one would have
4 data about its use in female recruits. And, I'm
5 really quite amazed that that has arisen as an
6 issue and I'm just wondering if anybody in the
7 front might want to comment based on their prior
8 experiences, because I know a lot of you have
9 been in the service as preventive medical
10 personnel for a lot of years.

11 DR. TOLLIS: While you're thinking
12 I'll just say that the concern is that we
13 diligently and documentatively have looked for
14 such information.

15 DR. KILPATRICK: Have you got any
16 comment? You've had more experience than any of
17 us probably.

18 CT. RYAN: Well, it's surprising
19 how little data we have on female recruits
20 because in the earliest years of vaccine use
21 women recruits weren't vaccinated in all the

1 services. Navy didn't begin getting vaccinated
2 until '94, so we went from '94 to '98 or so
3 when the vaccine ran out that female recruits
4 were vaccinated. The number who were pregnant
5 is very, very small because all pregnancy tests
6 were done before vaccines are given. The
7 number, I estimated it as something like 40, at
8 the most, all services wide per year between
9 those few short years. And, all of those women
10 became civilians very quickly. They're not
11 followed in military corps what happens.
12 They're all counceled about the fact that they
13 received some vaccines while people didn't know
14 they were pregnant and they're quickly separated
15 so we have surprisingly little amount of data.

16 COLONEL GIBSON: This is Colonel
17 Gibson. Back in '85 - '86 - '87 at Lackland Air
18 Force Base working as (inaudible) in basic
19 military training. And, anecdotally I can tell
20 you that I watched females come through the
21 immunization processing system my flight right

1 after they mixed in with the males. And, at
2 that time they all took their pills, went out to
3 a water trough outside, got to drink some water
4 and moved on. And, I saw them go through that
5 exact same process that the males did at that
6 time.

7 As far as documentation I have no
8 clue at that time the documentation of vaccines
9 were going strictly into the shot record. They
10 probably have log books that show what flights
11 were processed on what day, but as far as having
12 whether the females received that adenovirus
13 document is problematic.

14 Our process within the Air Force
15 is exactly the same and -- talked about females
16 were tested. As soon as they got there on Day
17 Zero those that were ACD positive were
18 separated. We tried to do it in such a way that
19 they did not receive any live virus vaccines.
20 But they left the service immediately.

21 PRESIDENT OSTROFF: Let me open it

1 up to comments and questions and in particular I
2 know Dr. Gray probably has some thoughts as far
3 as the recommendation about assays and the
4 things -- the vaccine is available. I know this
5 was particularly an issue that he wanted to
6 insert a recommendation.

7 DR. GRAY: Wonderful summary,
8 Charlie, thanks so much. I guess my concern is,
9 is we're looking at tremendous morbidity numbers
10 by the Naval Health Research Centers data, 1400
11 and some odds unnecessary medical encounters
12 which translates to a significant proportion of
13 hospitalizations and an importance portion of
14 intensive care units and likely 2 deaths per
15 year. So if we take that out to 2007 that's a
16 whole bunch of variable morbidities that we need
17 to think about. I'm thinking with respect to
18 the treatment question, certainly that's
19 probably not appropriate for the product
20 management team, but our thinking was that we
21 engaged some of the clearest thinkers in

1 infectious disease and the DoD internal medicine
2 to review the bone marrow transplant literature,
3 which does have a number of publications
4 evaluating treatment and compromise patients
5 come up with a rapid diagnostic strategy and a
6 treatment perhaps under IND at these facilities
7 such that you would have a chance at saving some
8 of these lives and severe illnesses.

9 It seems like a logical thing to
10 do with this projected time line and I would
11 encourage you to engage, especially advisors in
12 reviewing that literature.

13 There certainly are some wonderful
14 very easy to use point of care rapid diagnostics
15 that even in our not really complex training
16 centers we could easily use those and say yeah,
17 it's an aveno, he or she is in an intensive care
18 unit. Let's engage the algorithm and offer
19 whatever treatment we can besides that which is
20 simply supportive.

21 DR. HOKE: Your point is well-

1 taken and we can do more in this area and we
2 will do more.

3 MR. KILPATRICK: Charlie, can I
4 just say what prevents us from bringing a team
5 together and being able to look at that and ask
6 Dr. Gray to be a part of it?

7 DR. HOKE: What prevents us?

8 MR. KILPATRICK: Yeah, I just
9 don't see at this point why there's no reason
10 why we can't put out from (inaudible) put
11 together a one to two day sort of group that
12 looks specifically at that and Dr. Gray would be
13 a part of it and let the group then come up with
14 what they think the treatment routine or
15 algorithm or what those are.

16 For us to go back and do
17 development and stuff it's probably not going to
18 mean we're timely or anything else, but if we're
19 looking at something that is there, that we're
20 looking at other indications or at least some
21 knowledge base that we can go directly into an

1 IND then it would be...

2 CAPT. RYAN: Actually I have one
3 comment going back to the toxicity, I guess a
4 couple comments on the slides were that this
5 (inaudible) I think that may be an
6 underestimation I think there are going to be
7 required and I think probably looking ahead
8 right now to clean up the strategy of how that
9 is going to be looked at, whether or not it's
10 done at this point in time or a year from now or
11 the next year I think we should have some kind
12 of a time line for things to take place. I think
13 we need to come up with a plan as to how that is
14 going take place...(audience noise)

15 PRESIDENT OSTROFF: I think that's
16 an excellent point. This is a different era
17 than the last time that this product was
18 licensed. So I think it's probably correct to
19 say that we're going to presume that that will
20 be required.

21 The other issue of the serigence

1 of, you know, the VEE (inaudible) antibodies...
2 the BW vaccine this is a situation where this
3 illness is basically causing an epidemic in
4 virtually all of the recruit settings and, you
5 know, the importance of having solid
6 epidemiology data, I mean the bottom line is
7 whether or not the product is actually working.
8 Is the audiency respiratory rates of respiratory
9 infection rates dropped like a rock. And, that
10 certainly was the case when the vaccine was
11 being used and when it was not being used they
12 went up like a rocket and so, yes, it's nice to
13 see all those other markers, you know, showing
14 antibody responses and I know the FDA likes to
15 see all that, but the bottom line is this is
16 pretty easy to tell whether or not the vaccine
17 is doing the things it ought to be doing. I
18 don't know if anybody else has any thoughts
19 about that.

20 MR. MALONE: Joe Malone, DoD GEIS.
21 I have a comment and recommendation. With

1 regard to that 1997 study I'd like to say that I
2 compliment people who did that, who had the
3 foresight to do it. There weren't a lot of
4 resources available at that time and I think
5 they did the very best that they could with what
6 they had available.

7 With regard to the future I think
8 there are several things that we need to
9 consider in addition to possible antiviral in
10 the female reproductive studies that could cause
11 us problems.

12 With regard to the immunogenicity
13 studies, Charlie, if we find ourselves losing
14 time on that and getting into winter respiratory
15 disease season we may have a lot of trouble
16 finding an installation where we're going to be
17 able to -- measuring because of circulation
18 virus.

19 That's a study that I think would
20 have greater chance of succeeding if it was done
21 some time in the summer or outside of the

1 respiratory disease season.

2 With regard to the efficacy that
3 also concerns me that the FDA is now talking
4 about efficacy, because the issue that we have
5 been concerned about is that prior to the
6 vaccines, prior to 1970's antiviral type was
7 predominant in adenovirus 7 emerged when 4 was
8 suppressed with vaccine. And, one of the
9 questions that we have entertained is how would
10 we approach an efficacy study for Type 4 and
11 Type 7 vaccines when we aren't seeing Type 7,
12 but we would expect to see Type 7 when we
13 suppress Type 4. If we had to go into something
14 like a two step efficacy trial that would be a
15 lot of time on your time chart.

16 With regard to the reproductive
17 studies, the productive antibody levels I think
18 Dr. Ostroff relate to the comparability issue
19 and if we're going to have to deal with that,
20 then there may be a way that we could use banked
21 sera somewhere and look who developed disease

1 and who didn't and then also with regard to the
2 BNL issue I think we need to consider whether or
3 not we will have to attempt some sort of a look
4 back on that and get documentation and try to
5 identify exactly what happened. All of these
6 are important at this point in time, because of
7 the amount of time that they would require in
8 the future and the impact that would take on the
9 time line.

10 So I would suggest that in
11 addition to looking at the antiviral question,
12 that we address all of these perhaps in
13 different groups, or maybe in the same group,
14 and look at whether or not something should be
15 done immediately to move ahead on these and also
16 to look at what would be involved if we later
17 down the line what impact these studies would
18 have under time lines.

19 DR. HOKE: The FDA was aware of
20 the issue related to the adeno 4 being the
21 principal virus now and that adeno 7 would come

1 after we used the adeno 4 vaccine which was the
2 observation before and the complication that
3 provides in designing comprehensive clinical
4 trial.

5 They seemed to say though that we
6 really needed to -- we needed to go and do it
7 and see what we found and that if we could show
8 that the adeno 4 vaccine was protective and
9 establish at the same time sort of the
10 immunological correlates, you know, just exactly
11 with today's tests what level of neutralizing
12 antibody was associated with, you know, a zero
13 attack rate, for example. That that argument
14 might be advanced to the adeno 7. In other
15 words, there would be much more substantial data
16 at that time that we knew what level of antibody
17 was protected.

18 It was a little bit, it was left a
19 little bit vague. Dr. (inaudible) did you hear
20 that any differently?

21 DR. : That's quite correct.

1 DR. HOKE: So I had the distinct
2 impression that they weren't going to be asking
3 us to do something that was, you know,
4 practically impossible in a reasonable time
5 frame. That is you wait until adeno 7 emerged
6 and then show that we had efficacy against adeno
7 7.

8 PRESIDENT OSTROFF: One more quick
9 question from Dr. LeMasters and then we're going
10 to have to move on to our other issues.

11 DR. LEMASTERS: This question that
12 I have no idea about, but when we talked about
13 female reproduction I also know that the --
14 involving male reproduction and we know about
15 shedding the secal culture, how about semen
16 culture, is there any information out if the
17 virus would be shedding in semen and if so what
18 about the exposures to women, their spouses,
19 etc., and is there a concern about, I don't know
20 what the concern was about the pregnancy, if the
21 spouse was pregnant and they were concerned

1 about exposure was that because of possible
2 shedding in semen or oral or something else,
3 whatever it is, I think we need to at least know
4 why there is a concern and how we can educate
5 and caution our recruits in possibly exposing
6 others. You have to think about human sexuality
7 in its entirety.

8 DR. HOKE: I think that the points
9 are excellent. We have a complicated situation
10 where our intent is to use this in recruits,
11 where I'm under the impression that the policy
12 is there's no sexual activity allowed. And,
13 that seems -- I have never myself been a basic
14 trainee myself and I do think that the trainees
15 are released at some point, they're not
16 incarcerated, so we're going to have to look at
17 exactly how the vaccine would be used and
18 address those issues in terms of what risks one
19 might imagine.

20 PRESIDENT OSTROFF: Thanks very
21 much. What I'd like to say is we really do

1 appreciate your work and hopefully in the not to
2 distant future the recruits will thank you and
3 their families will thank you.

4 Let me turn it over to
5 Dr. Winkenwerder before we move on to the other
6 issues.

7 DR. WINKENWERDER: Thanks, Steve.
8 I appreciate the presentation we just heard. I
9 also appreciate the AFED's concern about the
10 adenovirus vaccine program. From my vantage
11 point your involvement and your concern is
12 helpful. It's very helpful. The schedule and
13 timing that was laid out in the past you had, as
14 members of the board, the same reaction I did
15 and in that that that was not acceptable. And,
16 in a meeting a couple of months ago we had in my
17 office I made that clear to General Martinis and
18 Dr. Hoke and others.

19 It appears we've made some
20 progress, some real progress, most particularly
21 in the last two or three months. I know there's

1 been work that's been going on but we seem to
2 have more of a clear game plan now.

3 I did have a couple of questions
4 just before I leave I want to make sure I
5 understand. The leadership is clear within MRNC
6 in terms to product manager. I didn't hear you
7 identify who that person is.

8 DR. HOKE: Yes, sir, it is clear
9 that Mr. Howell is the focal point and
10 Dr. Lightner works for Camden, any ambiguity
11 that there is directly been due to the ambiguity
12 of my employment status as contractor versus...

13 MR. : We're in the process of
14 making contractors government employees so that
15 is controversial, but there is clear
16 accountability there.

17 DR. WINKENWERDER: Okay. And, also
18 are we clear about who has accountability for
19 your ICD and CPD documents.

20 DR. HOKE: Yes, they have been
21 requested from individuals by name.

1 DR. WINKENWERDER: Okay. And
2 then, let me finally add my voice to I think
3 what I've heard in terms of prudence of rapidly
4 pulling together eighteen people to look at the
5 matter of rapid diagnostics and rapid diagnostic
6 and treatment algorithm as something that's in
7 here a measure that we ought to do. I will be
8 glad to ask one of my staff to task this issue
9 to be sure that it's clear it needs to be done
10 to General (inaudible) and General Martinez, and
11 others, but I think we're in agreement that that
12 needs to be done and quickly.

13 I also would agree that getting
14 pregnancy toxicity studies done or a plan for
15 that seems to make a lot of sense.

16 The last couple of issues I'd just
17 say is being able to use this potentially as an
18 INB product I would ask AFVP to think about that
19 and give us some thought and recommendation
20 about that as well as the other questions that
21 were teed up for you. Go ahead from my vantage

1 point and do those, address those questions that
2 you've been asked to address.

3 And, then finally for you and
4 Mr. Howell I would ask you to identify now any
5 -- even if it definitely don't come to pass,
6 funding issues or shortfalls or gaps or
7 whatever. Because our budget process is a long
8 drawn out kind of thing and we need to identify
9 those issues now and not have to deal with them
10 in a short crunch time when it becomes harder to
11 move the money.

12 So with that I'm going to say that
13 I'd like to see that we make every effort to
14 meet this schedule or beat it and frankly get
15 something available sooner in terms of approach
16 as it relates to diagnostic and antiviral
17 treatment regiment. Because I've had concerns
18 about the morbidity and mortality associated
19 with the adenovirus.

20 If there's ever any (inaudible) on
21 this, if people look back on it they're going to

1 have to ask why did all of this happen and we
2 only can look at ourselves. We are collectively
3 responsible, so let's keep it moving, let's get
4 the job done. Thank you.

5 PRESIDENT OSTROFF: Thank you,
6 Dr. Winkenwerder, for those comments and for
7 your leadership on this issue. I know that you
8 were also very interested in the other topic.
9 This presentation will not be quite as long. I
10 will say that we've had some fairly extensive
11 discussions about these recommendations
12 yesterday in the afternoon and there were some
13 modifications made, so I'll turn it over to
14 Colonel Phillips.

15 COLONEL PHILLIPS: In response to
16 growing concerns about the safety of use of
17 mefloquine from the media and congress and
18 service members Dr. Winkenwerder asked that an
19 AFEB commission, a sub-panel to look at
20 developing study formats for looking at adverse
21 effects of Mefloquine and that subcommittee met