

WINTER MEETING

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1 back exactly at five of ten.

2 (A short recess was taken.)

3 DR. OSTROFF: Our next presentation is by
4 another old friend, Dr. Charles Hoke, who is now the
5 Chief Scientist, Anteon Medical Advisor, Medical
6 Systems Program at U.S. Army Medical Research and
7 Materiel Command.

8 COL Hoke has the opportunity to brief us
9 on the status of a topic that has been of longstanding
10 interest and concern to the Board, which is the
11 restoration of the adenovirus vaccine. I had asked
12 for us to receive an update on where things stand and
13 it's particularly pertinent based on what has
14 transpired over the last several months with some
15 additional fatalities, and again, the Board is really
16 extremely concerned about the loss of this vaccine and
17 efforts to make sure that we can restore it as rapidly
18 as possible, so we look forward to your presentation.

19 COL HOKE: Thank you, Dr. Ostroff and
20 members of the Board, it's a pleasure to be here.

21 COL Riddle has asked me not to spend too
22 much time on telling you what you already know, so
23 I'll go through the first slides fairly quickly.

24 But just to tell you what I wanted to
25 cover, I wanted to give just a little historical

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1 review, talk about your recommendations and some of
2 the IOM, give you a little update on the
3 epidemiological situation with adenovirus in basic
4 training and then tell you what's gone on with the
5 capability restoration.

6 As you know, acute respiratory disease in
7 recruits was actually a significant problem of
8 longstanding, but in the '50s and '60s work identified
9 adenoviruses as an important player. An NIH/DoD
10 effort established a vaccine, the vaccine was
11 manufactured for the DoD by Wyeth. It was used in
12 recruits from the '70s onward. After many warnings,
13 Wyeth halted manufacturing in 1996.

14 The AFEB has weighed in on this issue 17
15 times, according to your website. When one searches
16 on adenovirus vaccine, this is --

17 VOICE: This will be 18.

18 (Laughter.)

19 COL HOKE: This will be 18.

20 The theme in the next slide -- I can
21 hardly read this because I just cut and pasted it, but
22 you can see it says the single greatest priority is to
23 re-establish a stable supply of adenovirus vaccine and
24 that every reasonable effort be made to assure
25 availability of oral vaccine and the impact of

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1 adenovirus on our military recruits is such that a
2 vaccine needs to be established or replaced.

3 And the next slide, the Institute of
4 Medicine was asked to look at military vaccines and
5 published a book Protecting our Forces, which was in
6 the read-aheads for the meeting. In the middle of
7 their deliberations, they realized that adenovirus
8 vaccine was falling off the tracks and they sent a
9 letter to the Commanding General of the Medical
10 Research & Materiel Command that said that the
11 Committee recommended a much greater sense of urgency
12 be placed on reacquiring an effective adenovirus
13 vaccine; that a significantly larger and long-term
14 commitment be made to restore and maintain the ongoing
15 availability of adenovirus vaccine; and that the DoD
16 not only evaluate the causes underlying this serious
17 procurement system failure, but also make a clear
18 commitment to the changes necessary to prevent similar
19 breakdowns in the future. These are really pointed
20 recommendations.

21 The current epidemiological situation was
22 provided to me by people at the Naval Health Research
23 Center and the Air Force Institute of Occupational
24 Health and the Armed Forces Institute of Pathology.

25 This data from the NHRC website, from

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1 Commander Kevin Russell, shows -- it looks a little
2 chaotic, but what it really shows is continuous
3 isolations of adenoviruses, almost all adeno 4, at
4 levels substantially above those observed during the
5 period of time during which adenovirus vaccine was
6 used.

7 This graph, which shows the febrile
8 respiratory illness rates and adenovirus morbidity
9 among symptomatic trainees at eight military training
10 centers, shows a gradual increase in the monthly
11 numbers of adenovirus cases in the green bars and the
12 blue lines show a gradual increasing number of
13 adenovirus isolations over that period of time as
14 well.

15 The next slide shows the overall isolation
16 proportions of adenovirus from specimens from recruits
17 with respiratory disease, and obviously the adenovirus
18 part of the pie is the great preponderance. And you
19 might ask yourself well what might this have looked
20 like during a similar period when the vaccine was
21 available. And what it would have looked like would
22 have been a much smaller number overall and virtually
23 no adenovirus isolations, or very, very few when the
24 vaccine was being used. So this tells you what a
25 dramatic part of the overall respiratory illness

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1 burden is caused by adenoviruses.

2 Next slide -- I think I'll skip this and
3 the next one and go on to the next one.

4 The Air Force provided data here that
5 shows the number of specimens submitted from patients
6 with respiratory illness. You can see that in the
7 years covered, the number went up dramatically after
8 1999 to 3000 and the percentage of specimens that were
9 positive for adenovirus went up as well as the total
10 number that were positive. So this is really a
11 remarkable increase in the number of adenovirus
12 isolations in the population sampled.

13 Now there have been eight fatal adenovirus
14 infections in recruits. This goes back a long time,
15 this isn't eight recent ones. And these are the
16 citations for them. The first citation is of three
17 cases due to adeno 7 from 1972, so that's long ago.

18 Then from Commander Ryan, two cases were
19 reported in the MMWR in 2000.

20 And cases that are currently under
21 investigation are three cases that were reported to me
22 by CDR Russell and MAJ Pearse at the AFIP. These are
23 from September, November and December of 2003, so just
24 a couple of months ago, associated with adenovirus
25 either PCR positive or culture positivity in cases B and

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1 C. So that there is rather clear evidence that these
2 recruits died with and probably of adenovirus
3 associated disease and the serotypes that are in the
4 two vaccines.

5 So in summary then, of the epidemiological
6 situation, the rates of febrile respiratory illness on
7 basic training posts continue to be above levels
8 observed when adenovirus vaccine was available.
9 Isolates are made in large numbers year round but more
10 especially associated with times during which recruit
11 camps are fullest. Occasional fatalities have
12 occurred with three recently at the end of 2003 and
13 isolates have been obtained from recruits in all
14 services.

15 The return of adenovirus disease to
16 recruit camps following withdrawal of licensed
17 adenovirus vaccine is a profound epidemiological
18 demonstration. Really, it's that a vaccine is
19 effective, but I think also that a vaccine is needed.

20 Now I want to tell you now about the
21 vaccine restoration effort and I want to take just a
22 moment to talk to you about the military, both DoD and
23 Army, acquisition system. Now medical scientists'
24 eyes usually glaze over right about now when we start
25 talking about acquisitions, but I want to just tell

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1 you some features of the system that I think are
2 applicable to vaccines as well as tanks and guns.

3 The concept is fairly simple. You start
4 with a requirement for an item with a capital R, and
5 then you start off on a program and you give someone
6 the responsibility to make decisions at certain points
7 and these points are called milestones. And the guy
8 who makes those decisions, the person who makes those
9 decisions, is called the milestone decision authority.

10 It's usually a general who is given the acquisition
11 responsibility for this capability. These are all
12 sort of abstract words that are in this regulation.

13 So these milestones are A, B and C. and
14 what's the process? Well, the process is pretty
15 logical, you start with a requirement and then you
16 refine the concept, develop the technology, put the
17 system together and demonstrate it, then produce it
18 and deploy it. So it's very common sense. Now there
19 are some documents that you need as you go along and
20 they're called initial capability documents or
21 capability development document and a capability
22 production document. These are the way that DoD tells
23 you that you're starting off in the right direction
24 and you're still going in the right direction.

25 Now adenovirus vaccine comes to us as a

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1 rather advanced technology. The basic work has been
2 done, so we're talking about what's called a
3 technology insertion. We need to start kind of at the
4 phase before you start producing it. We don't need to
5 invent it again, it needs to be produced and licensed
6 and fielded.

7 And so if you're starting right here, you
8 might expect that we would need a capabilities
9 production document to formalize this process and to
10 establish for subsequent people that we're actually
11 working on something that the DoD told us to do. You
12 know, we're frequently asked a question who told you
13 to do that.

14 So at this point, we don't actually have
15 the formal document. The system is in a state of re-
16 examination and the process for getting these
17 documents is being formalized, but we don't have such
18 a thing for adenovirus vaccine at this point.

19 Nevertheless, we've moved ahead with
20 Defense Health programming funding and we have
21 developed a schedule. And in the acquisition lingo
22 the three parameters are cost, performance and
23 schedule. Of course, everybody wants things free,
24 perfect and now. Those are the optimal parameters,
25 but cost, performance and schedule. And so I'm going

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1 to tell you a little bit at least about the schedule
2 and performance.

3 The schedule is shown on this scan chart
4 and this has been worked out with the selected
5 manufacturer and the product manager at USONDA, the
6 Medical Materiel Development Activity, and it calls
7 for activities having to do with building the plant
8 and establishing the tableting capability, then
9 producing material for a phase one clinical trial,
10 phase one clinical trial being conducted and then
11 materials for phase two and materials -- and
12 conducting the phase two, materials for phase three
13 and conducting phase three, and eventually the
14 regulatory efforts associated with filing a product
15 license application and licensure by the FDA,
16 converging on completed facility and production
17 capability so that the vaccine can be fielded.

18 Now another concept of the acquisition
19 system, is that the entire life cycle needs to be
20 managed, not just, you know, getting the clinical
21 trial done or even building the facility, which is
22 expensive, but maintaining this commodity over time.
23 That is, someone has got to build into the budgets of
24 the various people in the DoD that would take care of
25 these things the money to do these various parts of

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1 this acquisition.

2 Now we are here today and this is where we
3 hope to field this vaccine in 2009. So that's the
4 schedule.

5 There are some uncertainties in this
6 schedule related to what the FDA is going to ask for,
7 and meetings with the FDA have not taken place yet but
8 will soon. The boundaries are that they could accept
9 this vaccine as one that's very similar to the old
10 one, a little bit of immunogenicity comparability and
11 they might say that's enough. Or they might ask for
12 more safety studies, several thousand volunteers, or
13 they might ask for those kinds of studies in addition
14 to efficacy studies on training posts. Those will all
15 extend the time line considerably and so the FDA is
16 kind of a wildcard here.

17 Now in terms of performance, in terms of
18 getting the job done, a manufacturer was selected,
19 Barr. Much has been done to transfer everything that
20 was known from Wyeth, but we're finding that
21 everything that was known at Wyeth still may not quite
22 have been enough. Lots of progress has been made by
23 the manufacturer and lots of progress has been made at
24 WRAIR.

25 The production facility -- this is just a

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1 simple picture but it's actually quite a nice -- and
2 it's actually quite a nice facility -- has been
3 completed. This facility was built from the ground up
4 for this vaccine. It has all gone very well and
5 actually the representative from the company is here
6 if you have any specific questions about the -- Dr.
7 Tole -- about the production facility itself.

8 The tableting equipment has been installed
9 and Barr is actually very experienced at tableting.
10 They make a billion pills a year I'm told and when I
11 visited with the Wyeth people long ago, the tableting
12 -- I was told that the tableting part of this vaccine
13 was where the real art lay. So we're hopeful that
14 we'll get this right the first time. This is the
15 bottling line.

16 Now one of the things that has to happen
17 in the contract is that the contractor needs to
18 provide a quarterly report. I took the report and
19 wanted to summarize it for you, the report that we
20 received just a month and a half ago, and these issues
21 here are mentioned in the report. There's some
22 technical detail, but I wanted to provide some of that
23 detail for you so that you can get a feeling for some
24 of the irreducibility of the technical aspects of
25 producing a vaccine.

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1 Bulk virus production. You know, you need
2 to make enough virus to put in these pills and you
3 need to grow it. They've demonstrated that it grows
4 sufficiently well in the WI-38 cells that are the type
5 of cells that were used by Wyeth. The production of
6 the master virus banks was finished in September and
7 the GMP lots for vaccine production were initiated in
8 September. Both have been completed.

9 The initial lyophilization is being
10 conducted at WRAIR, Walter Reed Army Institute of
11 Research. Processes were developed last summer.
12 Pilot runs without virus and then with non-GMP virus
13 have been completed and with GMP virus lyophilization
14 has now been completed as well. You can see that
15 these things are happening practically right now. So
16 we're really in a very active phase on this vaccine.

17 Assays have been developed at Barr for a
18 number of important measures of the quality of the
19 tablets. Sera that are needed to demonstrate lack of
20 adventitious agents in the virus production have been
21 produced. More are needed, however, and virus
22 inactivation on equipment has been demonstrated.

23 The tableting facility I showed you a
24 picture of has been completed and all the basic work
25 there has been done. Five trial batches have been

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1 produced with pilot lyophilized material and material
2 is being brought in from WRAIR for GMP production of
3 tablets.

4 This is a picture of a mock tablet. You
5 can see it's got an outer coating and an inner table
6 that has to be suspended in this outer tablet. And
7 this inner tablet is what contains the virus.

8 This is a schematic of the tablet. It's
9 got a polymer outer coating, an inner virus core and
10 an outer core of inert material so that the recruits
11 will take this, it will be protected as it goes
12 through the stomach and then it will infect the
13 intestinal tract.

14 As I mentioned before, the regulatory
15 strategy is to first strive in every possible way to
16 make this vaccine the same as the Wyeth vaccine,
17 except that it is being manufactured in a modern
18 facility with modern equipment. And then to show in
19 every possible way that the vaccine is similar or the
20 same as the Wyeth vaccine was. So all the
21 specifications are being designed with this approach
22 in mind.

23 This table lists a number of important
24 specifications -- type of cells, the seed virus, the
25 growth media, the dye that's used in the tablet, that

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1 pink color, potency and route of administration. And
2 you can see that across the board, except for the case
3 of where antibiotics are not being used in the growth
4 medium -- this is actually an improvement -- and the
5 dye that is being used for the pink color is being
6 changed. These are felt to be minimal changes but the
7 major parameters of the virus, the type of cells, the
8 seeds, the dose and the administration, they will all
9 be identical to what was done before.

10 Now the first clinical trial has been
11 planned and that will begin following meetings with
12 the FDA, so in the next month or two I think. It'll
13 be a very small trial, 30 volunteers will receive both
14 adeno 4 and 7 or a placebo, mainly looking at safety,
15 but also immunogenicity as well.

16 There are some specific issues having to
17 do with the filing of the IND. Typically in the past,
18 the DoD would file the IND with the Surgeon General of
19 the Army as the sponsor. In this case, we felt that
20 it would save time if Barr would file the IND itself,
21 so that cross-referencing of a master file wouldn't be
22 necessary. They would move smartly from IND through
23 the clinical development plan to the product license
24 application, all in their hands. So that's what we
25 decided to ask them to do. Pre-IND letters have been

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1 written but the meeting has not been scheduled and the
2 FDA will specifically be -- their opinions will be
3 solicited on the manufacturing and on the proposed
4 clinical trial plan.

5 DoD, for its part, did request Barr to
6 file the IND and there are some contracting issues
7 relating to the fact that there's a first phase of the
8 contract and a second phase of the contract and that
9 was I think advisable, so in case things hadn't been
10 working out with the manufacturer, the DoD could
11 pursue another option down the road.

12 Now there are a number of personnel that
13 are involved with this and I won't recount their
14 names. You all provide a very important role as
15 advisor to ASD Health Affairs. We have requirements
16 generators who really haven't weighed in on this yet,
17 but milestone decision authority would be MAJ GEN
18 Martinez-Lopez. That's in accord with AR 70-1. And I
19 didn't mention that earlier but for those of you who
20 are interested in whether or not, you know, vaccines
21 should fall under the usual acquisition rules of the
22 DoD, you might look at Army Regulation 70-1 -- you can
23 get it on the internet -- and read through that and
24 see if you don't think that applies to vaccines. The
25 answer is it does. There's every intention for

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1 vaccines to fall under that regulation. And specific
2 jobs are laid out for people.

3 Anyway, the Deputy for Acquisitions is Mr.
4 Howell and it's Mr. Howell who asked me to come and
5 give this presentation. The pharmaceutical systems
6 project manager is Dr. Lightner. LTC Moser is
7 actually the product manager for adenovirus vaccine
8 and COL Wellington Sun at WRAIR has provided input on
9 the clinical plan and test development. And Dr. Tole
10 and Dr. Listz at Barr and Vacsgen have really in fact
11 done all the work in terms of getting the facility
12 ready and will continue to lead this effort from the
13 company's side.

14 A lot more functions will have to be
15 fulfilled as we move into the clinical development
16 phase to make sure that the clinical trials are done
17 right and up to snuff according to all the good
18 clinical practices rules and all the other data
19 management and all the other things that have to be
20 done to actually do a clinical trial. The rules and
21 regulations are changing almost by the day. And to
22 really get to a top quality trial, you have to have a
23 lot of people helping you get it right.

24 So I'd just like to conclude then. We
25 talked, remember, about the initial -- all the initial

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1 history and the recommendations of the Board, the
2 epidemiologic situation and all the work that has gone
3 in so far to restoring this vaccine capability. It's
4 on schedule I think to complete the first clinical
5 trial by the fall of this year. I think there's some
6 risks in the plan, it's not perfect. The FDA
7 acceptance of the clinical development plan is
8 unknown, whether they're going to give us the short
9 option or the long option. I think the lack of formal
10 requirements documents from the DoD may in times of
11 budget crunches or needs for budget to go do something
12 else may hurt us. DoD contracting always takes time
13 and as acquisition staff and other staff turn over,
14 that disrupts the continuity of this program.

15 On the plus side, the relationship with
16 the company has been superb. Everyone that's been
17 involved has been most enthusiastic, lots of good
18 faith on both sides. Many problems have been dealt
19 with successfully and we are hopeful that the
20 replacement vaccine should be available by 2009.

21 So I wasn't keeping track of the time, but
22 that's all I have to say.

23 DR. OSTROFF: Let me start out by thanking
24 you for your willingness to give this update.

25 For those on the Board who haven't been on

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1 the Board for that long, the last time that we had a
2 significant update on the adenovirus vaccine I believe
3 was in San Diego possibly two years ago. I think it
4 was done by Mr. Howell. And I guess I would start my
5 comments, I recently heard a presentation on the SARS
6 outbreak in Toronto by Alison McGeer, who was a
7 participant in that outbreak, and she used a quote
8 that always sticks with me, which is that if you think
9 prevention is expensive, try diseases.

10 And it looks like that's a deficiency that
11 the Department of Defense has made in this situation;
12 when we had the update from Mr. Howell two years ago,
13 he set out time lines as well and assured us at that
14 time that there would be a product available in 2007
15 and that by this time there would be phase two trials,
16 et cetera. And now what we're hearing is that somehow
17 the production table has slipped backwards to 2009.
18 Even though I appreciate everything that was being
19 said, I am missing the sense of urgency and Dr.
20 Winkenwerder sat at that meeting and swore to us that
21 he would do everything that was in his power to try to
22 speed it up for 2007. And I'm trying to figure out
23 where things aren't going right and what we on the
24 Board can do to try to convey in our strongest
25 possible terms that we are really, really concerned

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1 about what we are hearing. I don't know if other
2 members of the Board share this concern, but you know,
3 you're not hearing anybody that is suggesting that
4 this isn't an urgently needed vaccine -- it is. And I
5 guess I would like to be clear where are we now on
6 this? Is it money?

7 COL HOKE: Well, I didn't hear Mr.
8 Howell's presentation. My surmise would be that the
9 actual -- to use some project management terminology -
10 - the actual work breakdown structure and time lines,
11 gantt charts had not been made at that time.

12 You know, the devil is in the details to
13 some extent. When people really sit down and look at
14 the things that need to be done and really look at the
15 time lines, they do take sometimes longer than one
16 thinks. There's some substantial risks that are being
17 taken here to accelerate the process. For example,
18 all the construction has been completed on the
19 assumption that the vaccine is going to work, just the
20 way it did before.

21 It appears to me that the manufacturer has
22 worked very, very hard and very conscientiously to get
23 that building up. I had a lot of slides that showed
24 the construction going and so forth, but it's actually
25 pretty remarkable to build the whole facility in this

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1 period of time.

2 Undoubtedly there are days and weeks that
3 can be squeezed out of the schedule to shorten the
4 time line and, to some extent, some of the trial plans
5 do -- we were trying to shoot for the middle because
6 we really don't know what FDA is going to ask for in
7 terms of the amount of studies that are required. But
8 you can see that the bulk of the time is used up in
9 clinical trials.

10 So, you know, the Institute of Medicine
11 recently completed the study on giving full measures
12 to counter-measures, which was not at all
13 complimentary to the DoD process, and I felt during
14 some of those meetings that, you know, they might have
15 looked -- focused a little more on the specific time
16 lines to see where, in the judgment of the
17 pharmaceutical people, development people, time could
18 be squeezed out of those lines.

19 One presentation we heard suggested that
20 going from, you know, from beginning work to
21 completion of a vaccine took 14 years. So, you know,
22 the fact that this is happening in -- well, nine years
23 is better than 14.

24 I don't know how you can squeeze time out
25 of a process when you've got to get up to about

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1 several thousand people safely receiving a vaccine and
2 you've got to do it carefully. Protection of human
3 subjects is the most important focus of the IRBs. But
4 I do imagine that, you know, you could write the
5 clinical protocol in a way that allowed you to go from
6 10 to 100 to 1000 volunteers perhaps a little more
7 efficiently rather than starting a new protocol at
8 each phase.

9 DR. OSTROFF: With all due respect -- and
10 I'll open it up to other Board members -- I mean if
11 you're saying you don't know what FDA is going to
12 require out of you, why doesn't somebody sit down with
13 them later this week and ask them so that you know?
14 You know, that's -- again, I'm just missing -- I'm
15 trying to figure out like who's responsible for this
16 and who is the single individual that we can sort of
17 get to to say this is really, really essential and we
18 need to be assured that everything possible is being
19 done to truncate this process to the degree possible.

20 I appreciate that it takes 14 years to
21 produce some other vaccines, but let's not lose track
22 of the fact that this is a pre-existing vaccine. This
23 isn't something being created from scratch. And so
24 again, I'm missing some essential urgency here. And
25 maybe others would like to comment on this. Greg.

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1 DR. GRAY: This is Greg Gray.

2 One way I'd measure the morbidity is some
3 of the data that NHRC collected some time ago, where
4 they saw in some months 1100 unnecessary clinical
5 encounters, many of whom had been hospitalized. Maybe
6 that's something that we could use as leverage in
7 addition to these recent tragic deaths.

8 But it seems to me that there are several
9 things that we could do as a Board. One, we could
10 encourage the Army and the DoD to draft this
11 requirement document that might give prolonged funding
12 line to this such that this would never happen again.

13 That is, to lose a very effective vaccine. I don't
14 know how we effect such a document, but it seems to me
15 it's in the interest of the soldiers and sailors that
16 come on in the future.

17 A second thing is we could write a letter
18 to the FDA emphasizing our view on this and when
19 Charlie and Mr. Howell or whomever meet with the FDA,
20 they might have that as a document that would express
21 our most strong urgency.

22 And finally, there's been a whole bunch of
23 leaps forward in the solid organ and bone marrow
24 transplant patient population who suffered rather
25 egregiously from adenoviruses and then now there is

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1 real time PCR monitoring and somewhat pretty
2 successful treatments with Sudafovir (ph.)

3 So that might be something to consider in
4 some of the recruit camps. There's actually rapid
5 testing now as well. Is there any role for aggressive
6 anti-viral therapy when one of these kids comes down
7 with multi-system failure due to adenovirus?

8 DR. GARDNER: Pierce Gardner.

9 Of course, the IOM has certainly come in
10 very strongly on this as well, so we have a lot of
11 people saying what to do. I agree with your thought,
12 there doesn't seem to be any argument or lack of
13 committee support, but there is a problem in staying
14 on schedule.

15 I have a question and another comment.
16 Would you refresh us briefly regarding the shelf life
17 of this product and how it's stored. Why it's not as
18 virus in a tablet, I'm wondering how -- is this
19 something that's tricky?

20 COL HOKE: I really don't know the answer.

21 COL GRABENSTEIN: The shelf life was about
22 two years and it was stored in the refrigerator in
23 olden days.

24 DR. GARDNER: Normal refrigerator type.

25 COL GRABENSTEIN: Correct.

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1 DR. GARDNER: My comment actually follows
2 a little bit what Greg said. One of the major
3 bugaboos that the live virus vaccines have encountered
4 in the last few years is what I think is an excessive
5 reaction to the transmissibility of an attenuated
6 virus to other populations. The early example is the
7 varicella vaccine which was developed in Japan to give
8 to kids with leukemia and lymphomas because they might
9 get the real virus and by the time we licensed it in
10 the United States, the people for whom it was
11 originally indicated were on the contra-indicated list
12 and they had to do further studies to show that it was
13 safe.

14 We've just been through it this past year
15 I think with the influenza, the live influenza virus
16 where concerns about secondary transmission, which are
17 minimal and have failed to show any real problems,
18 have paralyzed the programs and had layoffs in
19 hospitals and I think have very much inhibited its
20 use.

21 So my advice is as you look at this new
22 thing, I think you really have to look harder perhaps
23 than in earlier studies to make sure you look at
24 transmissibility and issues of possible consequence.
25 I hope that this won't end up paralyzing this virus as

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1 it seems to have some others.

2 COL HOKE: It will be a problem. I didn't
3 show you the data, but the team at WRAIR took some of
4 the last tablets of the old vaccine and did a small
5 clinical trial and looked at immunogenicity as well as
6 shedding and, as had been shown many years ago, 100
7 percent of volunteers shed the virus in their stool,
8 the adenovirus from the vaccine, and none have it in
9 their throat.

10 So that it is possible that issues of
11 transmissibility will have to be addressed, especially
12 when you realize that this is not an attenuated virus
13 in the vaccine.

14 So you raise excellent points that may
15 actually extend the studies that are needed.

16 DR. OSTROFF: Dennis and then I think
17 there was a comment over here.

18 DR. SHANAHAN: I agree with the comments
19 made by Greg. One thing that strikes me, having grown
20 up in the military acquisition process is that I'm
21 somewhat alarmed by the lack of formal requirements
22 documents and I'd like to emphasize that. To me,
23 that's just basically a procedural effort and one that
24 we can distinctly influence, particularly through DoD.

25 In my experience, programs without

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1 requirements documents are hanging out and they can
2 run into substantial problems down the road, given
3 changes in administrations, changes in emphasis in
4 terms of what the military is doing.

5 So I think that that's a relatively simple
6 effort that we might be able to influence. Now
7 there's going to be a lot of politics involved, but I
8 think that that could be something that we could
9 really come out strongly in favor of, because this
10 program can get derailed on that basis alone.

11 But I just wanted to make a general
12 comment about interacting with regulatory authorities
13 such as the FDA. I think sometimes there's an
14 assumption that they have the answer when you approach
15 them with your dossier of evidence, that they knew all
16 along what should be in it but didn't tell you. But
17 really the issue is it's up to the applicant to
18 persuade the FDA that they have provided the necessary
19 evidence to license the product.

20 I would just suggest that that should be
21 the way that if the AFEB was going to approach the
22 FDA, they should be doing it in that spirit of
23 assisting the applicant with providing the necessary
24 evidence rather than suggesting to the FDA that they
25 ought to speed things up or whatever.

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1 Would you agree with that?

2 COL HOKE: Absolutely. You know, we never
3 want the FDA to lower its bar just because we're the
4 DoD, because we must have products that are safe and
5 effective, according to the highest standards. And so
6 the onus is really on us to bring to the FDA a package
7 that's convincing and we want them to be skeptical and
8 ask questions and be concerned about safety, but we
9 want them -- and we want them to be reasonable in that
10 attitude as well.

11 So the FDA is really, you know, looking
12 out for the welfare of the ultimate recipients of the
13 vaccine, so we don't want them to lower their bar in
14 any way for us. But to help us make a -- I will say
15 the FDA has been very good from the beginning when we
16 first met with them about this with another contractor
17 that we had. They were willing to bring in their
18 facilities people and help with the blueprints from
19 the very beginning so that we would get it right the
20 first time.

21 DR. OSTROFF: Let me just say that no one
22 is at all suggesting that FDA does anything to lower
23 their standards or requirements. I think that
24 Department of Defense has a recent wonderful example
25 of being able to get FDA to certainly work speedily to

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1 address an urgent concern, and there are ways that FDA
2 can move in their traditional pace and there are ways
3 I'm sure that they can move more expeditiously and
4 make this among their higher priorities. And
5 certainly I think all avenues should be explored to
6 see how you can work collaboratively and cooperatively
7 with them to make sure that there aren't any delays on
8 either side.

9 I'm sure that they are quite willing to --
10 you know, they sense the importance of this as well.

11 Greg.

12 DR. POLAND: I was on the IOM committee
13 that first looked at phase one, and while there were
14 lots of things that went wrong, it's interesting if
15 you look at the very beginning of the genesis of this.

16 What we identified is that there was never a champion
17 for this, there was never a very high level opinion
18 maker who trumpeted this and said we need to do this
19 and I will guide this through the process.

20 So I like Greg's suggestions, I like the
21 idea of trying to re-engage Dr. Winkenwerder and maybe
22 we need to identify a Congressman or a Senator who
23 thinks this is a serious issue and can help drive it.

24 UNIDENTIFIED SPEAKER: What is known about
25 the potential for recruit outbreaks to spill over into

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1 the community, and to what degree if that is a problem
2 or potential problem could add some ammunition to the
3 argument?

4 DR. PATRICK: I'm sure Greg has more
5 database than mine. Having spent the better part of
6 my career in college health, university health, there
7 are other markets for this vaccine and other potential
8 champions that could be brought to bear on this.

9 We certainly saw this in college health
10 settings in San Diego where we would have episodes
11 where we thought what else was this but adenovirus,
12 but again, Greg probably has some more data.

13 DR. POLAND: I was going to mention the
14 Great Lakes episode, but you probably know that better
15 than I do.

16 DR. GRAY: Go ahead.

17 DR. POLAND: I'm aware of one report --
18 and was it CDR Ryan reported it? There was an
19 outbreak at Great Lakes Naval Training Center that did
20 cross into the community. And I can't remember, the
21 child was at least hospitalized, if not a fatal event,
22 I'm not sure.

23 DR. GRAY: There's one well-documented
24 study by the Army and I've forgotten, I apologize to
25 the authors, but basically they showed from boot camp

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1 to a post training camp and I'll just tell you that in
2 this country, contrary to some other countries,
3 particularly Japan, surveillance for adenovirus is
4 very poor. It often depends on whether the clinician
5 orders a test or orders a culture, if that culture
6 makes it to a laboratory that would then send it to
7 the CDC. So it's a very low profile and so the data
8 we have are very poor. But the data that we do have
9 suggests that there are two new variants of 7, one of
10 which has been associated with at least one of the
11 deaths at Great Lakes and it probably is associated
12 with about four out of the five last epidemics in
13 confinement facilities.

14 So where there's a big threat to the
15 civilian population I would say in addition to bone
16 marrow transplant and solid organ populations would be
17 these long term care, chronic care facilities,
18 institutionalized children and adults. That's where
19 we're seeing a lot of these outbreaks.

20 How you bring that to a Congressman's
21 attention, I don't know.

22 DR. OSTROFF: One last comment and then
23 we're going to have to move on.

24 VOICE: Should we be thinking about some
25 systematic effort to monitor spillover from

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1 communities into selected sites where we know that the
2 outbreaks recur predictably?

3 DR. OSTROFF: Greg.

4 DR. GRAY: Well, I just propose doing
5 studies.

6 DR. OSTROFF: From my perspective, more
7 data is always better than less data but I certainly
8 don't want to give any impression that the impetus to
9 have this vaccine is anybody else's responsibility but
10 the Department of Defense, because it is, from my
11 perspective. This is a niche vaccine, the niche is
12 the recruit setting. We know there are problems
13 there, we know the vaccine has to be used and the
14 responsibility is the Department of Defense's to do
15 everything they can to make sure that the vaccine is
16 available.

17 Dr. Shamoo.

18 COL HOKE: Thank you very much.

19 DR. SHAMOO: Drugs and vaccine development
20 is a continuing effort by DoD, I presume. All the
21 time we have some kind of wanting some vaccine or drug
22 development.

23 Is there in DoD or one of its contractors
24 who continuously looks at expanding the drugs --
25 expediting -- sorry, expediting -- drugs and vaccine

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1 development and should there be one? Because the
2 process is the same, it's only the technology change.

3 The regulatory affair is the same, the FDA is the
4 same. And you could have an expert group who could
5 help any unit in expediting those issues on a
6 continuing basis.

7 DR. OSTROFF: I think your point is a very
8 well taken point. I mean, the Department of Defense
9 has such an illustrious history in this particular
10 arena, whether it's in the vaccine production arena or
11 whether it's the drug arena. And you know, we hate to
12 see any potential loss of that capability. And so --
13 but I think as, you know, certainly Greg can point out
14 or others can point out, there have been a number of
15 recent studies that have looked at current
16 circumstances under which DoD is operating and have
17 come to the conclusion that basically it's just not
18 working and that it needs to be fixed. And you know,
19 that is a message that's coming out loud and clear
20 from every direction.

21 So I think from at least my perspective,
22 the Board needs to do whatever they can to help
23 support efforts to correct the current situation.

24 You're the last comment.

25 DR. MORRIS: I'm the last comment. Glenn

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1 Morris.

2 Along those same lines, I guess this is
3 actually a very interesting list that we were given
4 this morning and there was one point I believe that
5 the Board was receiving a regular sort of update on
6 the status -- overall status of vaccines. And I would
7 like to ask that perhaps we are able to see this on a
8 regular basis with each meeting, with more than what's
9 on here, sort of a pipeline analysis, particularly for
10 the vaccines that are either in early stage
11 development where there are no vaccines, or where
12 there are significant concerns about reactogenicity,
13 to get a feel for where things stand, what the funding
14 levels are, how things are moving, so that at least we
15 can get a look.

16 I mean, this is a disturbing chart --
17 plague is in early development, we've got problems in
18 terms of yellow fever, Japanese encephalitis -- and I
19 think it would be worthwhile to see this on a regular
20 basis at the meetings.

21 DR. OSTROFF: Usually we get that update
22 at the May meeting, which is the meeting where we hear
23 about the status of the biodefense vaccines. So I
24 feel pretty certain that we'll get that at the next
25 meeting.

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1 DR. MORRIS: I was wondering if we perhaps
2 could do it not just at the May meeting.

3 COL HOKE: If I could just say a last
4 word, that there are many people that would advocate
5 one thing or another for the DoD to do, but it seems
6 to me after 25 years of working in the DoD that all
7 the best intentions and recommendations have to be
8 translated into requirements that are approved by the
9 appropriate authority. That was said earlier but
10 without -- but that is a key aspect to establishing
11 and sustaining an acquisition effort for any
12 particular product that might be needed.

13 DR. OSTROFF: Thanks once again. We do
14 appreciate your willingness to come and brief us and I
15 would anticipate certainly hearing more from us.

16 Let's move on to the next presentation.
17 We're a little bit behind schedule and we'll have a
18 second round from COL Grabenstein concerning the
19 question that's before the Board related to multiple
20 vaccinations.

21 COL GRABENSTEIN: Thank you very much.
22 It's always a pleasure to share the podium with Dr.
23 Hoke and thanks for the chance to come back.

24 The question to the Board is at Tab 5 and
25 I'll summarize it after discussing an Institute of

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