UNITED STATES OF AMERICA{PRIVATE }

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ARMED FORCES EPIDEMIOLOGICAL BOARD

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MEETING

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TUESDAY,

FEBRUARY 19, 2002

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SAN DIEGO, CALIFORNIA

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The Board met at the Island Club, North Island Naval Air Station, San Diego, California, at 7:24 a.m., Dr. Stephen Ostroff, presiding.

1 DR. OSTROFF: Thank you. The preventive medicine
2 update -- that is, I think we're going to modify the schedule a
3 little bit. Dr. Winkenwerder has to leave fairly soon, and what
4 we'll do is we'll move on to the adenovirus presentation and make
5 sure we get that in before he has to leave.
6 We have Mr. Bill Howell who is deputy director for
7 acquisition and advanced development who accepted our invitation
8 to give us an update about an issue that's been of great concern
9 to the board for a long time. Thank you for coming.
10 MR. HOWELL: Not a problem. Thank you. In fact,
11 I've been able to leverage a couple other meetings, one of which
12 is at 1:00 this afternoon in the north side of San Diego, so I
13 appreciate moving me forward as well.
14 Okay. I don't want to talk too much about
15 background. Most everybody here probably is familiar with
16 adenovirus and how we got in the dilemma that we're in, but just
17 to make sure we're on the same playing field, Wyeth was the
18 original manufacturer of the tablets that we use, both for set 4
19 and 7 adenovirus, two separate oral tablets which they use for
20 the vaccine.
21 In time, as the FDA does, they go through and they
22 look at your projection methodologies and such and in many cases
23 will force you to do an upgrade to your facility to be able to
24 maintain to whatever GMP standards that are there.
25 They came through -- this particular vaccine is a

1 fairly old vaccine -- they came through the manufacturer back in
2 the '90s, said, "You have to upgrade." Wyeth was not making a
3 profit to speak of on this particular vaccine, so they came to
4 the service and said, "Okay, I need y'all to fund this upgrade,"
5 and in fact then we got stuck with a bill that none of us had
6 anticipated, and in the end the dollars -- I don't want to get
7 into the political game -- the earlier administration did not
8 support it, and so the actual vaccine -- Wyeth discontinued it
9 and went away.

10 We used up the last of the vaccine in '99, and as
11 we saw quickly thereafter, the outbreaks followed.

12 That got the attention of the administration, and
13 since then we have some dollars. We had 14 million originally in
14 '99; we've had another seven million offset to that.

15 We spent a great deal of time -- I have to tell
16 you -- there was an effort about three years ago to get Wyeth to
17 pass that particular technology on to Greer down in North
18 Carolina, and we worked for about three quarters of a year trying
19 to make that pass. It failed.

20 In so doing, Wyeth became very hesitant to get
21 back in the game at all. They say, "We spent about a million
22 dollars of our time and effort trying to pass over to Greer for
23 DOD," and at that point in time they said, "We've done our best
24 offer, and we're just out of the business. Goodbye." And so it
25 took us awhile.

1 If we were going to actually go to the quickest
2 and most efficacious way to get a vaccine, going out and getting
3 a new manufacturer and starting from scratch wasn't the way to
4 get there 'cause it would have cost a heck of a lot more in time
5 and money.
6 So we went back and we basically, you know, cooled
7 our heels and went over to Wyeth and sucked eggs and tried to
8 plead to them to come back in, and in fact, after about three
9 quarters of the year, working actually with the president of
10 their vaccine division, we finally got them to come back and say,
11 "Okay, we will work with whoever you contract to. So, once you
12 have a contract and you're firm, you're going to somebody, we
13 will come back, we will sit down with them, we'll give them our
14 production methodologies, we'll give them all the formulary and
15 the rest so that they can make it, but until that time period
16 we're going to sit on the sidelines and watch."
17 At this point -- at the same time we were doing
18 this, we also had Wrair doing some work to try and help out to
19 reduce the risk for whoever the new manufacturer would be and
20 trying to pre-do some workup that would assist them in their
21 process of getting FDA approval, and you can see the list of
22 things there; I'm not going to go through all of them
23 individually.
24 The bottom line is what we tried to do is -- by
25 getting this effort in Wrair, we wanted to try and show whoever

1 the prospective manufacturer was going to be that we were in the
2 long haul with them, and in fact we were willing to take on some
3 of the effort to try and reduce their risk in getting this
4 vaccine used and approved.
5 As I noted before, we got another seven million
6 dollars this last year. The reason we needed that is because the
7 actual first proposals that came in when we finally got to the
8 contracting stage were over the 14 million dollars. We had to
9 get to about 18 million dollars to get somebody in.
10 And we did award back on September 1 to Barr
11 Laboratories. Now, those who are not familiar, Barr is a generic
12 drug manufacturer.
13 We had about three different bidders. All of them
14 were combinations of different people.
15 Barr has a great deal of knowledge in the
16 tableting process and the production process which, of course,
17 that's what this is, and that was one of the problems we had with
18 the Wyeth process to start off was the tableting methodology they
19 had was almost a World War II vintage tableting system.
20 And that's why -- one of the reasons why Barr
21 Laboratories and Best Value Contract was looked at as a valued
22 partner in this.
23 Also, they have combined themselves with VaxGen.
24 VaxGen actually has an offshoot -- is an offshoot of Wyeth and
25 has hired some of the people who were involved in the actual

1 production of the product, so it has been somewhat insidious in
2 the sense they moved over from one manufacturer to another, but
3 that is certainly something that we can leverage, and we're all
4 in favor of.
5 So our strategy, then, was obviously to pursue the
6 quickest means of getting back into remanufacturing with any
7 reasonable cost. That sounds like motherhood and apple pie.
8 But in so doing, we wanted to maintain our
9 relationship with the FDA. We had talked with the FDA certainly
10 up front as to what was the best methodology for us to get there
11 and would they accept the old one with an -- old vaccine with an
12 upgrade if we did bridging studies and things of that nature that
13 would try and expedite it, and they've been pretty good, the FDA,
14 so far.
15 We wanted to make sure the contract was with an
16 established manufacturer.
17 When we first did an RFI two years ago out on the
18 street -- and how we ended up with Greer three years before is
19 nobody else wanted to touch it. It just didn't have a profit
20 motive in it. There's just so little manufacturing involved in
21 this and so little use of the product outside of the services, it
22 was not worthwhile.
23 So we tried to get the contract in a manner that
24 we could get to someone who was fairly established -- obviously,
25 keep Wyeth in the process as best we could, and the other two I

1 already talked about.

2 So where are we at the moment right now? Barr is
3 in the process of doing -- or in the process of getting whatever
4 their agreement they need with Wyeth to be able to gain the
5 information to be able to build their production plant.

6 Now, two pieces in that. One, many of you may
7 know that the adenovirus is actually a very good carrier for
8 other particular means.

9 So they don't want to give it away free. There
10 is -- in the sense they will do it free -- rephrase -- but they
11 do have proprietary rights -- Wyeth does -- and they have to make
12 sure from a legal standpoint they've got those agreements in
13 place before they can pass it. But they're doing that at no
14 cost.

15 They're in the process right now -- American Home
16 Products owns Wyeth now in the new conglomerate of vaccine
17 manufacturers, so Wyeth has already forwarded that legal packet
18 up to American Home Products, and so we're working now with
19 American Home Products -- and hopefully get that packet out and
20 get the disclosure -- the information there all done.

21 In the meantime, we're working -- Wrair is working
22 also to continue that support for the next three, four years.

23 The important piece out of that is not only the
24 expertise that Wrair has in the science behind it but also when
25 we get into clinical trials -- many of you know that we'll be

1 doing the clinical trials, actually, with military people.

2 And so to have a military institute to help Barr
3 get in and do their clinical trials, I think, is pretty
4 essential.

5 Here sort of shows you the schedule as it was laid
6 out as to how long it will take.

7 Barr does not have to build a whole new facility
8 for this. It's just an offshoot that they're -- basically a
9 little wing that they're going to build to be able to do this.

10 That was one of the things that stopped us with
11 Greer. Greer wanted to build a whole manufacturing plant for it,
12 so we would have taken on a lot of the infrastructure costs that
13 we will not have to take on in this particular contract and why
14 the cost is less.

15 But you can see all the way
16 through -- unfortunately, we will have to do clinical trials
17 because as a new manufacturing process -- we will have to get, of
18 course, the facility through FDA. That just takes time. They
19 have to build it, so we're looking at an 18 -- really, an 18-
20 month-to-24-month window to get the manufacturing piece built and
21 through the FDA to get GMP standards to be able to go into the
22 clinical lots -- clinical trials that will follow thereafter.

23 But our plan today would have an O-7 adenovirus
24 production that we could then start to put back into the
25 troops -- into the trainees.

1 So you can see the bottom end -- the
2 responsibility -- Barr is obviously the overall contractor that
3 we're working at, and they will do the final tablet production.
4 VaxGen is actually going to make the virus
5 itself -- excuse me, Bioreliance is actually going to grow the
6 virus -- that's another affiliation they have -- pass to VaxGen
7 who will then put it into a lifelyzed (ph) form who will pass it
8 to Barr who will then actually put it into its final form.
9 So, unfortunately, it's sort of a convoluted way
10 in which we've got to go about it, but sort of the only way that
11 we saw -- and a reasonable one -- rational manner to get there.
12 I think that's it. Oh -- excuse me.
13 Funding -- this is the good news. If I would have
14 sat here 18 months ago, I would have told you I didn't have any
15 money, and then through time we got about 18 million dollars or
16 20 million dollars to get it started, and this is the money that
17 came down in PDM recently and the last bill that came across.
18 So we have a fully funded program, and if you look
19 at the 10 million in FY07, better than half of that is actually
20 making product -- actually into field.
21 DR. OSTROFF: Thank you very much.
22 MR. HOWELL: Sure.
23 DR. OSTROFF: I continue to be amazed at what a
24 tragedy this entire story is.
25 I appreciate when you say you're making a diligent

1 effort to be able to obtain the vaccine at a reasonable
2 production cost.
3 I guess my question to you was what might
4 potentially be an unreasonable production cost to truncate this
5 schedule somewhat? I mean, here's a situation where you
6 basically had the perfect product. It worked great.
7 And now you're stuck with a situation where you're
8 coming up with a new product that's going to take five years to
9 produce.
10 Many of us have difficulty understanding why it
11 takes so long.
12 MR. HOWELL: By and far, the largest piece of that
13 is -- even though it may be the same product, it has some
14 new -- it will have some nuances because of the way the FDA is
15 rated, but largely it's -- the fact that we've gone to a new
16 manufacturer and you've got a new production piece.
17 The old production line's gone -- actually, Wyeth
18 took it and is making something else there, so we don't have a
19 production plant that we can go back to.
20 So you've got at least a 24-month window bringing
21 that particular piece up.
22 Then the time limit to do clinical trials -- even
23 though it's the same product again -- the time period -- or very
24 close to the same product -- the time period to get through three
25 phases of clinical trials will unfortunately eat up a good two

1 and a half years.

2 And then you look at the time period in between

3 with the FDA discussions and the rest, we get to five years

4 pretty quick.

5 DR. WINKENWERDER: Let me just add my voice here.

6 This is one of the most disappointing facts and stories that

7 I've learned upon coming into my position, and I was extremely

8 disappointed to hear about this, really -- and I don't want to

9 cast aspersions on anybody who had responsibility in the past,

10 but to be blunt this is a major screw-up, and, you know, I am

11 committed to trying to accelerate this.

12 So what I've heard is not acceptable, as far as

13 I'm concerned.

14 MR. HOWELL: Sir, we can certainly go back and

15 talk to Barr and see what means --

16 DR. WINKENWERDER: Well, we will, and I'll

17 be -- and Ms. Embrey will be meeting with whoever we need to meet

18 with to accelerate this because we've got to make it -- we've got

19 to make things move more quickly than this -- and, you know, I

20 understand how the FDA works, but the FDA on the other hand is

21 going to make, you know, the process work with a small pox

22 vaccine in, you know, one fourth of the time. So if it can be

23 done there, it can be done here.

24 MR. HOWELL: Certainly -- I would agree with you.

25 As a minimum, we should anticipate that we'll get into a fast-

1 track sort of situation with them.

2 DR. WINKENWERDER: Right.

3 MR. HOWELL: And we would -- I'll be honest with

4 you, sir. The thing that's been driving this timeline to a

5 certain degree has always been dollars as well. I mean, we

6 haven't even gotten to the table till we got to the dollars.

7 DR. WINKENWERDER: It's very simple to me. If you

8 believe that this is something that we should do, then we should

9 do it and do it well.

10 If we don't, then we shouldn't do it, and we

11 shouldn't complain.

12 But I think the decision has been made that we do

13 believe this is important, and we do believe that it prevents

14 morbidity and mortality.

15 MR. HOWELL: Yes, sir.

16 DR. WINKENWERDER: And we need to do it, so we

17 need to get it done.

18 DR. OSTROFF: Here -- and then Greg.

19 DR. PATRICK: Kevin Patrick. Among my other

20 roles, I direct a student health center that services 32,000

21 students -- college students. It's hard for me to imagine that

22 there's not another market here --

23 DR. WINKENWERDER: Yes, sir.

24 DR. PATRICK: -- for this vaccine or drug, and I

25 just wonder if there's an opportunity --

1 MR. HOWELL: That area has been approached. In
2 fact, that was one of the things we tried to stretch with Wyeth,
3 and it was also part of the demographics certainly that Greer was
4 looking at -- is could they sell in another location.
5 Historically, no, there's been no market there.
6 Does that mean that with a good marketing program you could bring
7 a market there? It's certainly possible.
8 DR. PATRICK: Well, I think with a good marketing
9 program, in fact, they could, and our recent experience with the
10 pneumococcal vaccine, for example, amongst college students and
11 directed to consumer marketing and approaching parents has
12 generated a tremendous interest.
13 So I think, if there's an opportunity to pull in a
14 marketing expert on this and work with the population of folks
15 that serve these 15 million people who are college students, it
16 might help accelerate this process.
17 MR. HOWELL: Very good. Yeah.
18 DR. OSTROFF: Dr. Gray being an expert on this
19 particular issue -- and I know you're doing some studies, looking
20 at viral illness and a new college population in Iowa -- maybe
21 you want to comment.
22 DR. GRAY: Well, thanks. Yeah, in addition to the
23 estimated 1,200 to 1,400 unnecessary medical encounters that
24 we're seeing from this loss in the military, there's strong
25 evidence now that this -- some of these strains have changed.

1 In fact, there is a paper in press, _Emerging_
2 _Infectious Diseases_, that's due to come out either in March or
3 April, led by Dean Erdman (ph) of the CDC and Dr. Ryan and I,
4 showing that new genotypes of adenovirus-7 have been associated
5 with 27 deaths in various U.S. civilian populations since 1996.
6 I strongly endorse the concept that there would be other markets.
7 I think we need to try to figure out ways to partner the
8 military interests with the civilian interests and special
9 populations that might benefit from these vaccines.
10 DR. BERG: Bill Berg. I have two questions. In
11 what appears to be a press release from Barr Laboratories,
12 there's a statement among potential problems, outcome of legal
13 proceedings including Eli Luway's (ph) appeal to the Supreme
14 Court. What's that all about, and how does that impact the
15 adenovirus --
16 MR. HOWELL: To be honest with you, we don't know
17 ourselves what that means. I have not even heard that before.
18 DR. BERG: My second question is --
19 MR. HOWELL: Sorry.
20 DR. BERG: -- in your description you said that we
21 have to go through all of these hoops regardless of the fact that
22 it's an old vaccine, and then you also interweave that with "but
23 we're making some changes in it". Could this be speeded up if we
24 exactly duplicated the old process and then refined it later on?
25 MR. HOWELL: I think that's the whole problem is

1 we can't exactly duplicate the old process, because that's what
2 the FDA said wouldn't come up to standard. There's a tavening
3 (ph) piece and a growth piece within the virus that we have to
4 change from the old process that was there.
5 So we do have to make some manufacturing changes,
6 but the -- I have to tell you, I don't think that's a
7 great -- it's going to take a little time, but from a technical
8 risk, there's very, very little technical risk there. The
9 problem is going to be is that we're going to have to do the
10 trials, but we may not have to do them in the size and the number
11 that you'd have to do an initial piece. We're looking at
12 hopefully a bridging study, for example, in a phase 3 trial that
13 would give us a smaller sampling that would allow us to look at
14 the efficacy against the old one and therefore go forward.
15 So there's some means in which I think we can
16 lower the normal standard time, but at least in talking with the
17 FDA at this point, they're not willing to give up the normal
18 standard pieces.
19 DR. BERG: Thank you.
20 MR. HOWELL: Yeah. Dr. Winkenwerder, before I
21 leave, I think it would be of great usefulness if, in fact, you
22 or Ms. Embrey wanted to get involved in the conversation directly
23 with American Home Products -- would work to break that legal
24 stranglehold we've got at the moment to get them forward.
25 DR. WINKENWERDER: Well, the -- we will and

1 with -- not only for the Barr side but also Wyeth is -- we've got
2 another issue with -- you know, they're the owner of the DRYVAX
3 vaccine.
4 MR. HOWELL: Right.
5 DR. WINKENWERDER: So we've got two wonderful
6 topics to talk about. You know, I want action.
7 MR. HOWELL: Yes, sir.
8 DR. WINKENWERDER: I want results. That's what
9 we're here about. I was just saying to Dr. Ostroff that the
10 irony is that -- and all of our worry -- and there is real worry
11 about using the small pox vaccine and the possible mortality
12 associated with that. Just on the back of the envelope, the
13 numbers that you might calculate for mortality associated with
14 that or morbidity for the military population is no different, no
15 worse, in fact, probably less than the mortality and morbidity
16 that we're incurring because we don't have this vaccine right
17 now. That's just -- you know, it's unacceptable. So we've got
18 to make this thing move. We will be in touch. It's the top
19 priority.
20 MR. HOWELL: Great.
21 DR. OSTROFF: Can I ask one quick question? Do
22 you have any sense as to what the track record is of Barr in
23 bringing products to market within the time frames that they say
24 they're going to bring them to market?
25 MR. HOWELL: I think that's one of the reasons why

1 we selected them, because two other people were nowhere near as
2 experienced. Again, they're a generic drug manufacturer. So
3 they do the back -- they're not necessarily a discoverer, but
4 they are able to bring things to market in a manner that they've
5 been able to crack into the market for those generic drugs.
6 So I feel really pretty secure that they'll be
7 able to get it. In fact, I think the five years -- between me
8 and y'all, I think the five years might be a little bit extreme,
9 because that was based upon prior to knowing could they get into
10 a fast track mode with the FDA and what would the time periods be
11 and the turnaround of the paperwork with the FDA and things of
12 that nature.
13 So there is some potential to do some shrinkage in
14 there, not -- it may be somewhat marginal, but I think that's a
15 relatively decent timeline. Anything earlier than that -- we
16 were originally talking three to four years before that. I think
17 that was pretty optimistic, to say the least.
18 DR. BERG: Bill Berg. The -- Merck recently
19 announced a shortage of MMR vaccine. How often is that -- to
20 what extent is that given to recruits? It used to be standard
21 issue, but cohorts who got a second dose may have reached the
22 point where the military no longer needs to do it. So, in other
23 words, is the shortage of MMR impacting the immunizations we give
24 the recruits or is that a past issue?
25 MR. HOWELL: I'm not sure I'm the guy that should

1 be answering that.

2 DR. OSTROFF: I think what we're going to do

3 is -- was there --

4 COL. STAUNTON: I just wanted to raise one other

5 issue on the international front as to what the status is now of

6 the adenovirus vaccine with two potential outcomes. One is

7 (indiscernible) speeding up the process, which obviously is of

8 extreme importance, and the other is actually the potential for

9 partnering in arrangement, say, with the (indiscernible).

10 MR. HOWELL: Traditionally, unless there was

11 some -- how do I say this diplomatically? Unless there was some

12 technology or some mechanism that you were going to bring to the

13 table that we didn't already have in hand, that would certainly

14 increase our capability and then, therefore, shorten it. I would

15 be all in favor of it.

16 In this particular piece I think we've got it all

17 together. It's just going through the -- you know, going through

18 all the numbers.

19 Does that mean we wouldn't share our information

20 and our findings and the rest of it? Certainly we can do that.

21 But I'm not quite sure at this point, without seeing what it is

22 you could bring to the table, where's the differential we're

23 looking at at the moment? Unless you already had an adenovirus

24 that was there and a production plant already there, but

25 we -- I'm unaware of -- if there is, I'm unaware of that.

1 COL. STAUNTON: You're quite right. As far as I'm
2 aware, that's -- your information is correct. What I was
3 particularly referring to, the fact that we're -- when we speak
4 of such issues, it seems to me -- and I'm speaking personally
5 here (indiscernible) it seems to me that the importance of the
6 work, the importance of -- the importance of the work that you're
7 following, the programs that you follow don't stop or stay within
8 the United States. They actually have implications which are of
9 extreme importance. I know very well that the information is
10 very readily shared, and we're extremely grateful for that.
11 The aspect of actually pushing the envelope a bit
12 further in terms of using the vaccines with other services, with
13 other forces internationally, I think is worthy of exploration.
14 MR. HOWELL: Certainly. I have to tell you, sir,
15 I'm not smart enough to know what, if any, incident rate there is
16 overseas. Certainly if there is, any way you can crack a CE mark
17 as well as doing the FDA, I'm sure they would be in favor
18 thereof, but I'm not knowledgeable enough of that overseas usage
19 or requirement.
20 COL. STAUNTON: Thank you.
21 CMDR. RYAN: We have a little bit of overseas data
22 from the collaboration we did with the UK in the Royal Navy Basic
23 Training Center. About one third of their respiratory specimens
24 grow adenovirus. That compares to about 60% of the specimens we
25 get from CONUS, but still, a large proportion of their recruit

1 febrile respiratory illness is adenovirus.

2 MR. HOWELL: Great. Bad, but great.

3 CMDR. RYAN: And they're -- it's -- type 4 is what

4 we got in the low number.

5 DR. OSTROFF: Let's take one more. Captain Yund?

6 CAPT. YUND: Captain Yund. I have a partial

7 answer for Dr. Berg's question. I'm the person at UMED who

8 usually gets the frantic calls from Great Lakes when they're

9 having trouble getting a hold of something. I recently got a

10 call about Baryvax (ph) from Great Lakes. I haven't received any

11 calls about MMR. So it may be next week when I get back, but so

12 far I haven't heard anything about Great Lakes having trouble

13 getting MMR.

14 DR. BERG: But Great Lakes is continuing to give

15 it to all recruits?

16 CAPT. YUND: Yes, sir.

17 MR. STUERKE: My name is Stacy Stuerke. I'm with

18 the Merck vaccine division. I just wanted to echo the comments

19 in your question about MMR.

20 We are making military first priority for any new

21 releases that we have. Last week I understood we got over

22 500,000 doses released. The same with varicella. When we got

23 that call I think it was a 600-dose order. We made military top

24 priority. Otherwise it's always first in, first out as far as

25 the orders, but military does have first crack at any new

1 releases.

2 We are still making the vaccine. It's coming.

3 It's just not as fast as what the orders are right now. So we

4 hope we'll get this solved in the short term, but at the same

5 time the military will get first priority.

6 DR. OSTROFF: Thank you very much. I think what

7 we're going to do is take a break.

8 Before we do, let me just thank you for coming to

9 give us this presentation and, in particular, let me thank Dr.

10 Winkenwerder for his support on this particular issue. It's one

11 that we will continue to watch very closely and look forward to

12 hopefully seeing a better timeline in the not too distant future.

13 MR. HOWELL: If I can conclude, I'm taking two

14 taskers home with me. I will certainly get with Ms. Embrey about

15 who at American Home Products -- on that end. We will also sit

16 down with Barr and see if there's any way that they can speed up

17 and what the costing differentials or whatever would be involved

18 in that. We'll shoot that to you as well.

19 DR. OSTROFF: Thank you so much. Let's take a 15-

20 minute break and then we'll come back and get the rest of the

21 updates.

22 (A break was taken.)

23 DR. OSTROFF: Let's go ahead and try to get

24 started, because we really do have to be out of here at about

25 11:30 so that those of us who are heading up to the Marine