Adenovirus Vaccine Restoration

Presentation to
Armed Forces Epidemiological Board
May 12, 2004
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Chief Scientist, Anteon Corporation
Outline

• AFEB Letter from February Meeting
  – Specific actions taken to address points in letter.
• Schedule
• Milestones achieved since February Meeting
• Summary of 1997 clinical trial of previous vaccine done at WRAIR
• Acquisition Plan Risks
• Summary
Summary of AFEB concerns from February 2004 Meeting

4. Concern over the timeline, minimal contact with FDA, requirements, and lack of single high level responsible individual to assure timely re-acquisition.

5. Concern that DOD had not addressed the underlying causes of procurement system failure and make necessary changes.

6. DOD must provide the impetus for adenovirus vaccine.
Summary of AFEB recommendations from February Meeting

7. Recommendation:
   a. Appoint a high-level, single point of contact for this vaccine.
   b. Charge individual with responsibility to develop immediate and sustained interaction with FDA counterparts so that specific time-frames for vaccine acquisition can be established and to assure that barriers and obstacles can be overcome.
   c. Empower this individual to work with whomever else is necessary within the DOD to create a formal requirements document for adenovirus vaccine. The board would appreciate the opportunity to review such a document at its next meeting.
Actions taken to address AFEB recommendations from February Meeting

7. Recommendation:

a. Appoint a high-level, single point of contact for this vaccine.

- ASD(HA) briefed by CG, MRMC and Deputy for Acquisition
- ASD(HA) identified officer to provide oversight
- Product Manager and Deputy Product Manager identified
  - Formed Integrated Product Team and held first meeting
  - Drafted IPT charter
b. Charge individual with responsibility to develop immediate and sustained interaction with FDA counterparts so that specific time-frames for vaccine acquisition can be established and to assure that barriers and obstacles can be overcome.

- **Barr had met with FDA on 5 March 2003 to discuss plans for production facility**
- **Product Manager and Deputy Product Manager participated in pre-IND meeting (10 May 2004) with FDA, requested by Barr, to discuss adenovirus vaccine reacquisition effort. Numerous areas were discussed and clarified. (see below)**
Meeting was requested by Barr and chaired by their Director of Regulatory Affairs.

FDA officials offered numerous suggestions regarding safety, manufacturing, immunogenicity, clinical trial design, and licensure considerations.

Names of attendees will be provided immediately.

FDA will provide minutes within 30 days.

The following slides detail the suggestions/requests that were made.
Regarding epidemiology, FDA

Regarding general strategy, FDA

- accepted notion that this vaccine is a replacement of a similar, previously licensed vaccine.
- agreed that adenovirus 4 and 7 vaccines could be filed under a single IND and, presumably, license application.
- requested advance consultation on any study that will contribute to the licensure data package. Felt that study with old vaccine was not sufficient bridging study to allow them to approve vaccine on basis of safety and immunogenicity alone.
- wanted to know how DOD intends to use the vaccine (so information to support intended use could be sought for the label)
- did not feel that adequate data had been presented to support the argument that neutralizing antibody was a surrogate for protection.
  - Methods for neutralizing antibody testing varied and were not validated
  - Single available study was not convincing that a general principal had been established.
Regarding vaccine, FDA

- stated that later transition to MRC-5 cells would require a new IND.
  - (PM requested collaboration from CBMS on obtaining MRC-5 cells)
- requested chromosomal spread to assure diploid nature of WI-38 cells.
- suggested type specific PCR to demonstrate lack of cross infection of vaccines.
- requested tracking pedigree of cells to assure no possibility of exposure to serum that might contain agent of BSE
Regarding Safety, FDA

- Requested old data on use of vaccine in women by military, particularly in any women who might have received vaccine while pregnant. (and what was the outcome?)
- Implied that military should seek any old data that might shed light on safety of vaccine.
- May request reproductive toxicity testing, but later in process. (Requested Barr’s thoughts on reproductive toxicity).
- Will want post marketing surveillance data, particularly from female recipients.
- Requested current safety data on 1500 subjects
- Wanted to know how vaccine would be used in female trainees (e.g. after testing for pregnancy, if such testing is done before basic training).
Regarding Clinical Development Plan/Protocol, FDA:

- Asked for statistical basis for size of initial protocol with safety determination as a primary endpoint.
- Asked that spouses of subjects not be pregnant.
- Asked that female subjects not become pregnant for 3 months.
- Asked that subjects with history of GI surgery for the past year be excluded.
- Requested both throat and stool swabs in shedding studies.
- Requested 6 month verbal (by telephone) follow up of subjects to detect new medical conditions.
- Suggested that we add cancer to list of conditions to ask about.
- Requested a stopping rule for the study.
- Suggested that we consider excluding former military.
- Requested a study that demonstrated efficacy, with a reasonable number of subjects (maybe 300 per arm) and a relatively easily identified case definition (hospitalization due to adenovirus infection).
- Adjust protocol to allow second dose if vomiting occurs within 2 hrs of dose.
Regarding Endpoint Assay, FDA

- Suggested use of PRNT50 (instead of TCID50) type of assay for antibody testing for immunogenicity endpoint.
- Requested information relating old and new assays.
- Suggested manageable case definition for efficacy studies (e.g. febrile, acute respiratory infection with adenovirus present in throat culture.)
c. Empower this individual to work with whomever else is necessary within the DOD to create a formal requirements document for adenovirus vaccine. The board would appreciate the opportunity to review such a document at its next meeting.

• **MRMC Deputy for Acquisition requested appropriate requirements documents from AMEDD Center and School. Current status is that MRMC Liaison to AMEDD Center and School is working with staff there to generate general Initial Capabilities Document by 1 June. Subsequently, adenovirus vaccine specific Capability Production Document will be generated.**
8. Recommendation:
   a. Make assays available for diagnosis of recruits in training camp medical facilities.
   b. Develop and adapt antiviral treatment algorithms for individuals with severe adenovirus illness.
   • **FDA website consulted on availability of FDA approved adenovirus diagnostic tests. Several assays are available.**
   • **Dr. John Huggins at USAMRIID was consulted regarding anti-adenovirus drugs. Cidofovir has been evaluated, and may have some promise. (see: Kaneko H, et al. The cotton rat model for adenovirus ocular infection: antiviral activity of cidofovir., Antiviral Res. 2004 Jan;61(1):63-6.)**
   • **No strategy for implementation of this recommendation has been adopted.**
   • **Neither funding nor staff within the laboratory is currently available to address this recommendation.**
   • **A plan will be prepared for presentation in the near future.**
Schedule
Schedule for Adenovirus Vaccine Restoration Presented at Feb 2004 AFEB meeting.

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**Vaccine Ready to Field 2009**

**TODAY 2004**
Revised (5/2004) Schedule for Adenovirus Vaccine Restoration

Subsequent slides expand plans for major components
Schedule for Facility Construction and Equipment Installation and Qualification

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Legend:
- ✔: Activity scheduled
- (): Activity not scheduled
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**Notes:**
- D: Day
- M: Month
- F: Follow-up Visit
- R: Repeat Treatment
- W: Washout Period

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**Legend:**
- Blue squares represent active treatment periods.
- Grey squares indicate follow-up visits.
- Purple squares denote washout periods.

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**Legend 2:**
- Blue line: Treatment A
- Green line: Treatment B
- Yellow line: Control Group
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Schedule for Regulatory Affairs
Overall Schedule for Adenovirus Vaccine Restoration

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Milestones

- Received March 31st 2004 quarterly report from contractor
- Clinical trial (Phase I/II) protocol submitted (March 2004)
  - Completed HSRRB review and obtained approval for implementation. (date)
  - Study team from WRAIR visited Ft. Sam Houston to organize trial.
  - Study team from WRAIR visited Ft. Leonard Wood to identify study site for recruits.
  - Arranged smaller scale seroprevalence survey of prospective study population.
- Contracting issues
  - Modification put in place. Awaiting confirmation.
  - Option 2 exercised.
  - IND responsibility transferred by MRMC to Barr.
  - Identified minor contract changes that are needed.
Summary of Contractor’s Quarterly Report (Through 31 March 2004)

A. Bulk virus production at Q-One
B. Formulation and Lyophilization at WRAIR
C. Assay Development
D. Tablet Production
E. Clinical Trials
F. DOD issues
G. Financial issues
A. Bulk Virus Production

Master Virus Banks extensively tested and passed all required tests

- Sterility
- Mycoplasma
- Titer
- HBV
- HCV
- HIV-1
- HIV-2
- HTLV-1
- HTLV-2
- HHV-6
- HHV-7
- HHV-8
- HCMV
- SV40
- PERT
- In vivo
- Supmavirus
- Mycobacteria
- AAV
- Identity
- Bovine
- Porcine
- Number of vials (447 type 4 and 465 type 7)
ADV-4 GMP Lots for Vaccine Production

- Production done with limited quality control data saved a 6-8 months.
- Production of ADV-4 GMP lot from October 2003 had acceptable titer.
- Filtration step lost little virus.
- ADV-4 GMP lot was transferred from Q-One to WRAIR for production of lyophilized, stabilized virus for further processing into tablets for the clinical trial.
- Following tests were completed on ADV 4 virus with satisfactory results:
  - Titer Bulk Harvest (10 exp7.07 TCID50/ml)
  - Titer (Post Filtration) (10 exp 7.05 TCID50/ml)
  - Sterility
  - Mycoplasma
  - PERT
  - Identity
  - In vivo
  - Final Harvest Volume (480 ml)
- Control Cells
  - Hemadsorbing virus
  - In vitro
  - PERT
ADV-7 GMP Lots for Vaccine Production

• Replacement batch shipped to WRAIR in January 2004. Titer was good and sufficient virus was harvested to formulate and lyophilize virus for subsequent GMP production. The testing of the type 7 GMP lot has passed all tests as summarized below.

• Following tests were completed on ADV 7 virus with satisfactory results:
  – Titer Bulk Harvest (10 exp7.34 TCID50/ml)
  – Titer (Post Filtration) (10 exp 6.9 TCID50/ml)
  – Sterility
  – Mycoplasma
  – PERT
  – Identity
  – In vivo
  – Final Harvest Volume (1444 ml)

• Control Cells
  – Hemadsorbing virus
  – In vitro
  – PERT
B. Formulation and Lyophilization at WRAIR

• **GMP ADV-4**
  - Single GMP production run of 2 Lyoguard trays containing 8,000 ADV-4 doses in total was produced and is being stored at WRAIR until shipment to the Barr Virginia facility for GMP Tablet production.

• **GMP ADV-7**
  - GMP ADV-7 lyophilization was successfully performed at WRAIR PBF in February 2004. A single production run of 5 trays containing sufficient virus to make 20,000 tablets was produced and is stored at WRAIR until shipment to Barr.
C. Assay Development

• WRAIR will perform identity test by PCR.
  – Assay validation is ongoing
  – 352 swabs from environmental cleaning
    • Tested at WRAIR
    • Results indicate that current cleaning program successfully removes adenovirus to levels below those obtained by hydrogen peroxide.

• Assays for clinical trials
  – Neutralization test under development at WRAIR.
  – Protocol to obtain human sera for use in neutralization assay approved
C. Assay Development

• Antisera for In Vitro Adventitious Agents
  – Serum required to neutralize virus
  – QS for current GMP lots and 2 additional lots.
  – New antisera program to be initiated in current year.

• Methods for Virus Inactivation
  – Conducted experiment to show that BioQuell vapor phase hydrogen peroxide system could inactivate ADV 4 and 7.
  – BioQuell contracted for decontamination services.
D. Tablet Production Facility

- ADV-4
  - 1st pilot batch of ADV-4 tablets produced.
  - Virus titer did not change.
  - Bioreliance General Safety Test passed.
  - Acetone and ethanol contents were above the expected values.
  - Tablets failed disintegration test.
  - Testing of second pilot lot deferred until disintegration issue solved.

- ADV-7
  - Core tablet equipment malfunction delayed production.
  - Problem corrected.
  - 2 pilot batches of ADV 7 tablets are currently undergoing testing.

- Enteric Coating
  - Process uses ethanol and acetone to dissolve a polymer (CAP) used to coat tablets.
  - In coating pilot lots, found solvent content was too high, and tablets disintegrated too quickly.
  - Coating Protocol being modified.

- FDA GMP inspection April 5-14.
  - Did not include adenovirus tablet facility, but did include Barr Quality Systems.
  - Barr pleased with FDA inspection results.
E. Clinical Trials

• Pre IND meeting 10 May 2004 (see earlier slides.)

• Plan:
  – Two trials proposed:
    • AMEDD C&S 60 volunteers: enlisted soldiers in advanced training (91W)
    • Ft. Leonard Wood: 1500 volunteers (Officers Advanced School)
  • Sites visited.
    – Commanders are very supportive.
    – Resources identified
  • Seroprevalence study will be conducted at Ft. Sam to determine prevalence of antibody in 91W population.
    – Plan approved for implementation at WRAIR.
  • FDA has requested efficacy testing, and this trial will be factored into above plan.
F. DoD Issues

• AFEB and ASD(HA) interest are noted.
• Scope change proposal discussed on April 14 2004. Barr asked for $5.2 M above original contract for items mostly related to insufficient records from Wyeth.
• Option 1. Contract Mod 10 exercised option 1 which covers both Phase II and III Clinical Trials.
• FY03 billing rates. Contractor was unfamiliar with government procedures for billing for overhead, and remedies are being negotiated.
Results of Trial of Original Adenovirus Vaccine Conducted by WRAIR in 1997
Characterization of serologic and virologic responses of healthy, adult volunteers to the licensed, live adenovirus vaccines

Study conducted by COL Robert Kuschner
Data provided by COL Wellington Sun
Trial of Previously Licensed Wyeth Adenovirus Vaccine

- Investigator: COL Robert Kuschner
- Conducted: 1997
- Vaccines (Both vaccines administered orally to all subjects)
  - Adenovirus 4 FDA Approved Vaccine
  - Adenovirus 7 FDA Approved Vaccine
- Purpose of trial: To provide benchmark for comparison with replacement vaccine
- Location: WRAIR
- Subjects: Healthy adults
- Endpoints:
  - Virus neutralizing antibody
  - Reported symptoms
Results of trial

• Subjects
  – 40 enrolled
    • 4 developed antibody between the time of screening and the time of vaccine administration.
    • 1 lost to followup.
    • 35 analyzed.
      – Antibody status before immunization:
        • Both 4 and 7: 0
        • Neither 4 nor 7: 8
        • 4 only: 5
        • 7 only: 22
      – Total starting without type 4 antibody: 30
      – Total starting without type 7 antibody: 13
Seroconverters following immunization with Wyeth Vaccine

• Adenovirus 4
  – Seronegative (SN*<2): n=30
  – Seroconverters: 27 (90%)

• Adenovirus 7
  – Seronegative (SN(2): n=13
  – Seroconverters: 13 (100%)

*SN=Serum Neutralizing Antibody
Distribution of adenovirus antibody at day 28 following oral immunization

<table>
<thead>
<tr>
<th></th>
<th>Ratio of day 28 titer:day 0 titer (all were &lt;2)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Indeterminate</td>
</tr>
<tr>
<td>A 4</td>
<td>3</td>
</tr>
<tr>
<td>A 7</td>
<td>0</td>
</tr>
</tbody>
</table>
Adenovirus excretion following immunization

<table>
<thead>
<tr>
<th></th>
<th>Fecal Culture Positive</th>
<th>Throat Culture Positive</th>
</tr>
</thead>
<tbody>
<tr>
<td>A 4</td>
<td>30/30</td>
<td>0/30</td>
</tr>
<tr>
<td>A 7</td>
<td>13/13</td>
<td>0/13</td>
</tr>
</tbody>
</table>

Samples were cultured on days 3, 7, 10, 14, 21, 28
Adverse events following immunization with previously licensed Wyeth adenovirus vaccine

<table>
<thead>
<tr>
<th>Symptom</th>
<th>N=35 Subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Feverishness</td>
<td>3</td>
</tr>
<tr>
<td>Nasal Congestion</td>
<td>12</td>
</tr>
<tr>
<td>Sore Throat</td>
<td>6</td>
</tr>
<tr>
<td>Cough</td>
<td>6</td>
</tr>
<tr>
<td>Vomiting</td>
<td>1</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>8</td>
</tr>
</tbody>
</table>

Total of mild, moderate or severe symptoms recorded in volunteer diaries.
Adenovirus Vaccine Reacquisition Program Risks

- Permanent virus production facility has yet to be identified.

- **Clinical trial program**
  - Efficacy study requested by FDA may increase timeline and costs.
  - Initial clinical trial
    - Protocol amendments from FDA will require expedited IRB review to avoid delay onset of first trial.
    - If September start date cannot be met, start will be postponed until January 2005.
  - Clinical teams for later studies not yet identified.

- **Serological testing**
  - Serological endpoint test remains to be validated.
  - Site to perform large number of tests remains to be identified.

- Reproductive toxicity studies may be required.
Additional Acquisition System Steps

• Obtain Capability Production Document
• Complete Product Manager’s Charter
• Complete Integrated Product Team charter
• Complete Test Plan
• Hold Milestone Review (C)
• Present Test Plan to Milestone Decision Authority for Approval
• Assure adequate future budget authority
How can the AFEB help?

• Continue to function as ASD(HA) Overarching Integrated Product Team to track vaccine availability, sustainment, and restoration.

• Consider what policy for use of this vaccine AFEB would recommend.

• Consider recommendations regarding Treatment use of Investigational New Drug once all required studies have been completed. 21 CFR 312.34 requires that the treatment is for a serious disease, that there be no satisfactory alternative, that the drug is under investigation in a controlled clinical trial or all clinical trials have been completed and the sponsor is actively pursuing licensure.
Summary

• Adenovirus vaccine acquisition effort is advancing towards the goal.
• MRMC is molding program into a model acquisition effort.
• Contractor is making progress.
• FDA has provided detailed guidance.
• Many problems remain to be solved, but no unsurmountable obstacle is presently foreseen.
The Adenovirus Vaccine Re-acquisition program is NOT business as usual.
QUESTIONS?