

**Adenoviral Standard Working Group
November 8, 2000 Meeting/Teleconference Minutes**

Attendee/Participant List attached. 27 Institutions including FDA and WBF participated.

ACTION ITEMS FOR FOLLOW-UP:

- [1] FDA to establish MOU for WBF role and administration of proposals.
- [2] FDA to write and publish FR notice requesting bid proposals. Deadline for receipt of proposals by FDA will be 30 days after FR notice is published. Publication is anticipated in late December 2000.
- [3] Working Group to submit a list of other types of characterization desired for standard to FDA for discussion at next meeting.
- [4] FDA and Working Group to determine common procedures to use for determination of particle concentration and infectious titer. Suggestions included use of a published method from an academic group.
- [5] FDA and coordinators to determine best time for next meeting. Meeting to take place before the end of 2000 or in early January 2001 in Washington, D.C.

Meeting Minutes:

1-Goal of Group. FDA reiterated the charge of the Working Group. The primary goal is to develop an Adenovirus Type 5 Wild Type (Ad5 WT)-based adenovirus standard that is produced under well-documented conditions and is well-characterized by the end of 2001. The particle number and infectious titer will be assigned to the standard on the basis of analyses conducted by participating laboratories. The goal is not to endorse any specific method of cell culture, viral culture, purification, formulation, or analytical method. A secondary goal of the working group is to develop a characterized replication-defective adenovirus standard. The group will take up the second goal, once the first is underway. For each standard the Working Group endorsed the idea of a Virus Bank being made as a source material for production of future lots of the standards.

2-Representation. FDA will advise the Working Group if additional representation is needed. The current Working Group membership list is attached along with contact information for each member. The Working Group consists of 33 institutions including regulatory, academic, pharmaceutical, testing, contract manufacturer, and supplier institutions and has US, Canadian, and European representation.

3-Role of Williamsburg BioProcessing Foundation. FDA will arrange a Memorandum of Understanding with WBF to outline each party's role. WBF will then be able to act as a clearinghouse for information related to the Adenoviral Standard Working Group's activities. WBF will also assist in coordinating Working Group activities such as arranging meetings and teleconferences.

4-How Selection of Group(s) Will Be Made for Standard-Related Activities. The Adenoviral Standard Working Group will determine the list of component activities that will be open for “bid proposals” in creating and characterizing each standard. The Working Group will establish criteria upon which selection can be made. Volunteer institutions will submit their proposals for performing an activity (or activities) to the FDA. Proposals will be requested to include information on their facility, experience, and capacity or capabilities pertinent to the activity. FDA will arrange for a Federal Register notice to announce [1] the request for bid proposals for activities, [2] the criteria for each bid proposal, and [3] the deadline for bid proposals. FDA will evaluate the proposals and make recommendations to the Working Group. The Adenoviral Standard Working Group will then make the final selection. Joe Senesac of Introgen volunteered to work with FDA and create a template form that can be used for proposals in order to standardize them.

5-Activities and Criteria. The following activities will be placed in the first FR announcement along with the associated criteria. Bid proposals are to be submitted to the FDA. Because the Working Group consists of representatives from many institutions across industry and academia, all information in bid proposals should be able to be made public. It is unclear whether funding will be available to support the activities; thus the activities are listed below as "donations".

- (a) ***Donation of characterized cell bank vials to be used in production of the Ad5 WT Standard Virus Bank and purified lots.*** Cell vials should be part of a Master or a Working Cell Bank that has been tested according to the Points to Consider Guidance and current FDA regulation. The cell line should support Ad5 WT virus production. A minimum of 20 one-mL vials is requested. The donation should be available by March 15, 2001. The bid should indicate the number of vials to be donated, the cell line, the cell concentration and volume per vial, a copy of the Certificate of Analysis detailing the characterization of the cell bank, and information regarding thaw and propagation of the cells upon thaw. If vials are to be donated from a Working Cell Bank, then a copy of the Certificate of Analysis for the Master Cell Bank from which the WCB was derived should also be included, along with information regarding the relationship between the WCB and the MCB such as passage number. Additionally a commitment to provide bank re-certification information is requested.
- (b) ***Donation of source Adenovirus Type 5 Wild Type virus material for production of the Virus Bank.*** The material will be used to create a virus bank that is intended to support the production of at least 10 lots of purified Ad5 WT standard. The bid should include the material’s history and information regarding characterization of the material to be donated, particularly with regard to freedom from adventitious agents. The bid should include the amount and form of the material (purified or lysate, volume per container, number of containers). The donation should be available by March 15, 2001.
- (c) ***Donation of production of Ad5 WT Virus Bank.*** The production of the Ad5 WT Virus Bank should occur in a well-documented manner. Production under complete CGMP is not a requirement. The virus bank should be in lysate form and of a size that it can support production of 10 lots of purified standard (lot size is described under donation of production of Ad5 WT purified, formulated bulk). A certificate of analysis should be provided as part of the donation detailing the characterization of the viral bank, including testing, test methods and specifications. The bid for this activity should include information on the bidder’s experience with production of adenovirus and virus banks, and describe the production

facilities and capacity. The bid should include a description of the proposed method of production (cell and viral culture) and proposed vial configuration. The bid may also include information regarding any additional characterization that would be performed. The bidder must be able to complete this activity by the end of May 2001.

- (d) ***Donation of production of purified, formulated bulk Ad5 WT Standard.*** The production and release of the Ad5 WT Virus Standard bulk should take place under CGMP. The purified formulated bulk should be of a size that it can support vialing of 4500 to 5000 containers each filled with 0.5 mL at approximately 2 to 5×10^{11} particle/mL. A certificate of analysis should be provided as part of the donation that includes a description of lot release testing, test methods and release specifications. The proposed formulation should be part of the bid. The proposed formulation should not be PBS-based nor should it contain protein. The bid for this activity should include information on the bidder's experience with production of purified adenovirus and describe the production facilities and capacity. The bid should include a description of the proposed cell and viral culture, harvest, and purification method. The bid should include a detailed proposal for formulation with supporting data indicating the formulation's ability to provide stability for storage of adenovirus at $\leq -55^{\circ}\text{C}$. The supporting information should also indicate the formulation's compatibility with characterization methods (biological and physical). The bidder must be able to complete this activity by the August 15, 2001.
- (e) ***Donation of vialing of standard and freezing and preparation for storage.*** The vialing and preparation of the vials for frozen storage should take place under CGMP. Vialing will consist of a 0.5 mL fill into 4500 to 5000 containers. The storage condition for the vials will be $\leq -55^{\circ}\text{C}$. The bid for this activity should include a description of the bidder's experience with vialing biologicals under CGMP and describe the facilities and capacity. The bid should include a description of the proposed container/closure system and supply supporting data as to its appropriateness. The bidder must be able to perform this activity in late August 2001.

The Adenoviral Standard Working Group will complete development of criteria for bids on the following activities at their next meeting:

Proposal for Repository/Distribution of Ad5 WT Standard

Proposal for Participation in Characterization of Infectivity and Particle Determination of the Ad5 WT Standard

Proposal for Participation in Other Characterization of the Ad5 WT Standard

Proposal for Participation in On-Going Stability Study of the Ad5 WT Standard

6-Timeline for Adenoviral Standard Working Group Activities. The following timetable was developed but will be revised as activities proceed. Publication dates of FR notices will determine the deadlines for the bid proposals.

<i>Proposed Date</i>	<i>Activity</i>
November 2000	First Meeting of Working Group
December 2000	Second Meeting of Working Group Federal Register Notice Announcing Request for Bids
January 31, 2001	Deadline for bid proposals to be received by FDA
February 2001	FDA reviews bid proposals
March 2001	Working Group awards bids based on FDA recommendations and discussion
March/April/May 2001	Production of Ad5 WT Virus Bank
June/July/August 2001	Production of Purified Ad5 WT Standard Bulk
August 2001	Vialing of Ad5 WT Standard
September – October 2001	Characterization Phase
November 2001	Working Group meets to review characterization data and assign particle and infectious titer numbers
December 2001	Standard made available

7-Notes on Proposals that require additional discussion. The following notes will assist the Working Group with their discussions at the next meeting.

Proposal for Repository/Distribution of Ad5 WT Standard: Repository bid proposal should have capacity for 5000 vials, ability to monitor temperature during storage under CGLP/CGMP conditions, and should be able to perform the service for at least 5 years. Proposals should include information regarding shipment capability and the types of shipment containers that will be used. It is anticipated that requests for the standard could come from around the world. The proposal should also address a proposed cost for the standard and rationale for the cost.

Proposal for Participation in Characterization of Infectivity and Particle Determination of the Ad5 WT Standard

And

Proposal for Participation in Other Characterization of the Ad5 WT Standard: Characterization for particle concentration and infectious titer will take place using a procedure that is provided. The Working Group and FDA have yet to determine the procedures to be used. However each testing group proposing to participate may propose to perform additional procedures to assist in establishing particle concentration and infectious titer. The details of those procedures should be provided. The testing group proposing to participate should also provide some data supporting the suitability of the procedures. Other characterization is also desired but the Working Group will formulate a list and submit that to FDA for further discussion. For example, this might include analyses relating to purity. A minimum of 3 testing groups is desired for the

characterization phase. The Working Group agreed that the FDA would examine the data first and make recommendations to the Working Group for the discussion and agreement regarding assignment of particle concentration and infectious titer. The Working Group will issue a Certificate of Analysis for the standard.

Proposal for Participation in On-Going Stability Study of the Ad5 WT Standard: The Working Group desires to have groups propose to take part in on-going stability monitoring of the standard. However the characteristics to monitor were not established during the meeting.

Submitted by Beth Hutchins, November-21-2000