

Minutes of the Adenovirus Reference Material Working Group August 9, 2001 Teleconference

<i>Teleconference Meeting:</i>	Adenovirus Reference Material Working Group
<i>Date:</i>	August 9, 2001
<i>Topic:</i>	Discuss and award RFP 12.0 for Long Term Stability Characterization of the Ad Ref Mat

Participants:

Steven Bauer (CBER/FDA)
Mark Bowe (GTI/Novartis)
Charles Buck (ATCC)
Andrew Byrnes (CBER/FDA)
Keith Carson (Williamsburg BioProcessing Foundation)
Larry Couture (City of Hope Nat. Med. Ctr.)
Mark D'Andrea (Selective Genetics)
Jonna Ellsworth (Canji)
Beth Hutchins (Canji)
Jesse Keegan (Genzyme)
Alex Kotov (UAB)
Steve Ramsone (GenVec) - for Bryan Butman
Paul Shabram (Canji)
Stephanie Simek (CBER/FDA)

Absentee comments and votes provided in advance from:

Geoff Sharpe (Cobra Therapeutics)
Victoria Sluzky (Onyx)

Minutes:

[1] Introductions and Background

Introductions were made, followed by a short summary of the RFP 12.0 for Long Term Stability and the requirements called for by the Working Group (WG). Three proposals were submitted for the Long Term Stability study, one from the University of Alabama at Birmingham, one from Transgene, and one from Canji.

Since representation was not available from Introgen or Invitrogen during the teleconference, the WG did not have an update on the status of the 293 Testing Phase Cell Bank (Invitrogen) or on the production of the purified Adenovirus Reference Material (Introgen). Beth Hutchins did report that virus bank vials had been transferred to Introgen and that her understanding was that the cell culture phase of production was in progress.

[**POST TELECON NOTE:** Invitrogen indicated that the 293 Testing Cell Bank would be vialled shortly. They are anticipating 50 vials at 1×10^7 cells/vial (1 mL). They will be transferring the vials to ATCC ASAP. Mycoplasma and viability tests were scheduled. They were reminded to also include sterility assessment, per the WG's original request.]

[2] FDA Review and Discussion

FDA representatives reminded the WG that they would discuss the proposals submitted but would abstain from voting to make the award.

Dr. Simek presented the FDA review of all 3 proposals submitted for RFP 12. The proposal from the University of Alabama included assessment of vials at both -80°C and -20°C , use of the three requested analytical methods, OD260/SDS, Infectious Titer, and an AE-HPLC assay, as well as container integrity testing. The proposal raised a question as to UAB's readiness for performing the HPLC assay. Additionally, FDA wanted clarification on the container integrity testing; did that mean sterility or something else? The UAB proposal did not specify when UAB would be ready to begin the T=0 testing and how often they would submit reports to the WG.

Dr. Alex Kotov of UAB addressed the points raised. He assured the group the new HPLC system would be installed next week, and available in time to start T=0 testing. Dr. Kotov also confirmed that container integrity would be assessed via sterility testing and resistance to CO_2 . He stated that UAB would be able to initiate T=0 testing within 2 weeks of receipt of the Ad Ref Mat vials. This is well within the WG's stated timeframe for T=0 testing.

Dr. Simek then presented the FDA review of the proposal from Transgene. Transgene proposed 4 methods of analysis plus sterility assessment but only at 1 temperature, -70°C . Transgene's proposal indicated that they did not feel -20°C data was essential and would use up reference material vials unnecessarily. Dr. Simek said they were not entirely clear that Transgene intended to use the Working Group SOP for infectious titer assessment. The Transgene proposal refers to a "TCID50 assay". However Transgene did include a method additional to that required by the WG, Determination of Aggregation by Photon Correlation Spectroscopy. This is notable. Not clear from the Transgene proposal was the number of replicates proposed per time point and test. It was thought that multiple replicates were intended by Transgene as the chart indicated more than 1 vial required for some tests, e.g., sterility and OD 260 nm/SDS.

Dr. Simek then presented the FDA review of the Canji proposal. She commented that this proposal was the most comprehensive of the three including both temperatures and several additional analytical methods beyond those requested by the WG. For FDA the biggest concern was not the proposed methodology but the number of vial that would be used if this proposal was selected.

Several general comments were made: [1] None of the three proposals included or specified the sterility method to be performed (USP? PTC? direct inoculation? filtration?). [2] Is testing at -20°C really necessary as an inclusion in the Long Term Stability assessment? Would this better address issues as part of the Short Term Stability assessment? [3] Would a group performing

AE-HPLC be subject to license from Canji and how would this be impacted if Canji were selected and then LT stability support, including the AE HPLC assay, had to be transferred to another group? And finally, [4] Is there a total container number the WG is comfortable targeting as a maximum to be devoted to the Long Term Stability study?

FDA indicated their relative ranking of the three proposals, with highest rank to Canji, second rank to Transgene, and third rank to the UAB proposal. The WG then discussed the issues raised.

Sterility. Canji had proposed 10 vials per timepoint for sterility testing. Dr. Simek commented that this is the number of containers commonly done for EU product testing, but she did not feel product testing requirements should apply. Other WG members agreed that the number could probably be lowered without compromising the intent of the assessment. No one felt that performing sterility on only 1 container was adequate. A suggestion was made that sterility testing be performed on only 5 containers per timepoint.

Total Number of Containers for the Long Term Stability Study. The WG agreed it was comfortable with a total of 150-160 containers being dedicated for the Long Term Stability study. Additionally the WG felt it was possible to modify the submitted proposals to reach that target without compromising the study.

Inclusion of -20°C Monitoring. The inclusion of this temperature was part of the RFP 12.0 posted by the WG. Two reasons were given as to why this was valuable. One is that it could provide early warning to failure of the reference material at ultra-low freezer temperatures (-70 and -80°C). The other reason is that some users might ask the appropriateness of storing the Reference Material at the higher freezer temperature (-20°C). It was clear from the discussion that even if -20°C monitoring is included that the number of time points for -20°C could be reduced as compared to that for ultra-low freezer storage. One comment was that the material is not being frozen at -20°C but at $-70/-80^{\circ}\text{C}$ and will be stored at the ultra-low temperature for at least a few days or weeks prior to being moved to -20°C storage for the stability study. Through discussion of the Short Term Stability RFP, the WG determined that if -20°C monitoring is necessary for a period of months or years, the only place for that is as part of the Long Term Stability study. Also through discussion the WG determined that the CoFA and other information supplied with the Reference Material should clearly specify that the Reference Material was designed for storage at ultra-low temperature and that it would be the receiving institution's responsibility to provide data supporting storage at -20°C or other temperatures. It was commented by 2 different WG members that even most academic institutions have $-70/-80^{\circ}\text{C}$ storage access.

Each WG member was individually polled about the need for stability monitoring at -20°C . Although several individuals felt conflicted about the need, in the end the WG consensus was that -20°C data would be useful. With that the WG also agreed that 3 time points were all that were necessary with the suggested time points being 6 months, 12 months, and 24 months. T=0 data would not be necessary for -20°C .

The final issue discussed was the impact of the Canji patent on AE-HPLC. Canji participants commented that it was not clear how their corporate parent intended to assert its intellectual property rights and that they could not address this issue directly. However the Canji WG participants felt that if Canji were awarded the Long Term Stability study, initiating the Canji AE-HPLC SOP, and that if for some reason Canji were no longer able to perform this commitment, that it seemed likely that the institution selected to continue the Long Term Stability study would be given dispensation to complete the study without adverse consequences.

The comments from two Working Group members who had sent them in, but were unable to participate were communicated. The issues raised had been resolved during the discussion.

With that, a motion was made by Mark D'Andrea to award the Long Term Stability study to Canji, using a modified proposal that incorporated the decision on replicate numbers and -20C monitoring. Keith Carson seconded the motion. The Working Group passed the motion by a vote of: Yes – 12, No – 0, Abstain – 4 (3 of which are FDA).

Keith Carson would take responsibility for notifying the three institutions officially regarding the Working Group's decision. Beth Hutchins indicated that Canji would revise their proposal to incorporate the WG's recommendations. The revised Canji proposal will be presented to the WG at the September 5 meeting for any final comments. Canji plans to begin T=0 testing in mid-September, after the September 5 WG meeting.

Keith Carson commented that he believes that all bids for RFPs 8 through 13 are now posted on the website. He asks that if anyone believes something that should be posted is not, to please let him know ASAP.

Submitted by Beth Hutchins, Aug-9-2001