Adenoviral Standard Working Group
June 06 2002 Meeting/Teleconference Minutes

ACTION ITEMS FOR FOLLOW-UP:

[1] Product information sheet to be written for ATCC so that ARM can be released to the public (as soon as possible).
[2] Manuscript volunteers to be established for publications.
[3] Release of remaining 3 lots of Ad Ref Mat to be determined.
[4] Data and assigned particle concentration and infectious titer to be posted to the WBF website.

PRE-MEETING ACTIVITIES:

[1] Impurity Subgroup Teleconference – See Telecon Minutes April 11 2002 for discussion on how the impurity observed during the characterization phase will be further investigated. Group concluded that impurity did not interfere with particle concentration determinations.

[2] May 06 2002 Subgroup Tentative Assignment of Particle Concentration and Infectious Titer. Another subgroup, consisting of Keith Carson, Beth Hutchins, Estuardo Aguilar-Cordova, Stephanie Simek, Andrew Byrnes, Steven Bauer, Paul Shabram, and Barry Sugarman held a teleconference with Jan Callahan, the statistician, to discuss the conclusions and actions from the March 25, 2002 ARMWG meeting, the statistical re-analysis of the data (see attached report), and application of these analyses to the particle concentration and infectious titer data. The minutes for this telecon are attached. The FDA recommended that the conclusions from the report should be put to the ARMWG for a vote after the statistician's report is circulated.

[3] Vote by Email on Assignment of Particle Concentration and Infectious Titer. Based on the discussions of the subgroup, the ARMWG was asked to vote Yes-Agree or No-Disagree on two proposals:

- It is proposed that the label claim for the particle concentration of the Adenovirus Reference Material be assigned as 5.825×10^{11} particles per mL, based on the FDA's recommendation.
- It is proposed that the label claim for the infectious titer of the Adenovirus Reference Material be based on the Maximum likelihood method of analysis and be assigned as 7.37×10^{10} Infectious Units per mL, based on the FDA's recommendation. The Maximum Likelihood method of analysis examines all raw data and has the least bias. Information on this method is contained in the Statistician's Report.

The results of the vote are contained in the attachment, Results of ARMWG vote & June-6 meeting info/agenda.

JUNE 06, 2002 MEETING MINUTES:

1-FDA Recommendations for Using the Adenovirus Reference Material. FDA reviewed their recommendations for how the ARM should be used by sponsors and laboratories. These recommendations are contained in the attachment, FDA perspectives PhRMA slides on application ARM, and consist of:

- The sponsor should use the ARM to validate an internal reference used at the sponsor's laboratory
- The internal reference material should demonstrate some degree of parallelism with the ARM in the method, but the degree of variance to the assay will determine how closely the results should be
- If the results are parallel but the numbers are different, the FDA is amenable to a scaling factor being incorporated into the sponsor method.

There was considerable discussion about these points. Jan Callahan reviewed the information in Table 1 on sample size and Table 2 on CV and detectable differences and how to apply this information.

2-Assignment of Particle Concentration. Based on the vote and email discussion prior to the meeting, the main issue with assignment of particle concentration is agreement on the number of significant figures. After limited discussion the ARMWG voted on limiting the particle concentration assignment to 2 significant figures, and assigning the particle concentration as 5.8×10^{11} particles per mL. The group agreed with Yes – 25, No – 0, Abstentions – 3. **The ARM is officially assigned the particle concentration of 5.8×10^{11} particles per mL.**

3-Assignment of Infectious Titer.

[1] *Determine number of significant figures for infectious titer assignment.* Based on the vote and email discussion prior to this meeting, the group discussed whether one or two significant figures were reasonable for infectious titer. Based on the ARMWG SOP and on the behavior of infectious titer assays generally, the group voted on accepting a single significant figure for the infectious titer, *i.e*., 7 or 8×10^{10}, infectious units per mL. **The group agreed with Yes – 24, No – 1, Abstentions – 3, on use of a single significant figure for reporting infectious titer.**

[2] *Application of statistical methods and reporting the variance*. Discussion focused next on alternate proposals for how to apply analysis to the raw data to establish the assigned infectious titer. A proposal from Paul Shabram agreed with use of the Maximum Likelihood method but also wanted to incorporate the use of pooled estimates. This proposal included the establishment of a subgroup to further analyze the data to make the assignment. The proposal is attached. Nancy Sajjadi agreed with the pooled estimates proposal and provided some examples of how this approach could work. FDA and other members of the ARMWG disagreed with the proposal and felt that the original statistical analyses were valid. FDA members felt that the assignment could be made by the ARMWG at the meeting. Estuardo Aguilar-Cordova reminded the group that the infectious titer assignment was so that sponsors would report infectious titers relative to the reference material. The focus should not be on assigning a "true" titer. Discussion following was vigorous with a number of suggestions put forward. One issue with pooling raised by Jan Callahan was that there is no way to test if the data are really "pool-able" and valid, so there is no way to determine if there are outliers that

should be excluded from the analysis. The group did agree that obtaining a true infectious titer was beyond the scope of the ARMWG goals. The ARMWG voted on a proposal put forth by Nancy Sajjadi and Paul Shabram to use the pooled estimate method to assign the infectious titer. The group did not agree to application of the pooled estimates method with the of Yes – 12, No-13, Abstentions – 4.

[3] *Action and vote on assignment of infectious titer*. Discussion focused back on the recommendation from the statistician's report of using the Maximum Likelihood method. **The group voted as to whether to apply the Maximum Likelihood analysis method to determine the assigned infectious titer, and agreed to this, Yes – 17, No – 3, Abstentions – 5.** Because the analysis of the data included a correction for the virus diffusion, the group agreed that the units should incorporate a name to indicate this. The ARMWG agreed to use of "NAS infectious units". This left the group with the assignment as either 7×10^{10} or 8×10^{10} NAS infectious units per mL to the ARM. Based on the data and report 7×10^{10} was preferred. **The group voted and agreed to assign the infectious titer to sub-lot 001503 as 7×10^{10} NAS infectious units per mL, with Yes – 23, No – 0, Abstentions – 0.**

4-Release of the ARM. The Adenovirus Reference Material will be able to be released to the public by ATCC as soon as the product information sheet is written for distribution along with the ARM. Only lot 001503 will be released at this time. FDA and ARMWG will consider what data to use to release the other 3 sub-lots in the future. Volunteers were solicited for writing the product information sheet. This list included Simek, Byrnes, Carson, Buck, Hutchins, and Vellekamp, among others.

5-Update on Long-term Stability of the ARM. Barry Sugarman provided a summary of the -80ºC stability at the 9-month time point, added as a result of the ARMWG discussions on March 25, 2002. Particle concentration data suggests that the material remains stable and the slight decrease in particle concentration seen at 6 months was a "blip". The table containing the 9-month time point data is attached.

6-Update on analysis of highly chromogenic material noted in some ARMWG vials. Not discussed due to lack of time. Additional report from the subgroup will follow the meeting. Impurity seems not to be a major concern.

Attachments:

- Telecon Minutes April 11 2002, Impurity Subgroup
- Statistician's Report, May 2002, Janice Callahan, Callahan Associates, Inc.
- May06 2002 Telecon Mtg Minutes
- Results of ARMWG vote & June-6 meeting info/agenda
- FDA PhRMA slides on ARM
- Table 1 Sample Size and Table 2 CV
- CV impact
- Shabram proposal
- Long Term Stability 9 month update spreadsheet

Submitted by Beth Hutchins, November-04-2002