



MEMORANDUM

Date: January 25, 2011

To: Daryll Miller, M.A. HFM-478

From: Rajesh K. Gupta, Ph.D., HFM-680

Through: William McCormick, Ph.D., HFM-680

cc: Robin Levis, Ph.D., HFM-451
Helen Gemignani, HFM-478

Subject: STN 125296: Duramed Research, Inc.(Teva Women's Health, Inc.) – Review of Drug Substance and Drug Product Analytical Procedures for Adenovirus Type 4 and Type 7 Vaccines, Live, Oral

Reviews of the analytical procedures and the associated validation protocols and reports were performed by the staff of Division of Product quality (Reviewers from DPQ: Rajesh K. Gupta, Alfred Del-Grosso, James L. Kenney, Manju Joshi, Muhammad Shahabuddin, Ramakrishna Velicheti).

Submissions Reviewed

Original Submission 125296/0 sections 3.2.S.4, and 3.2.P.5
125296/0.2 (amendment received on January 30, 2009)
125296/0.3 (amendment received on February 03, 2009)
125296/0.4 (amendment received on February 09, 2009)
125296/0.5 (amendment received on February 12, 2009)
125296/0.7 (amendment received on March 30, 2009)
125296/0.8 (amendment received on April 6, 2009)
125296/0.10 (amendment received on April 17, 2009)
125296/0.12 (amendment received on May 01, 2009)
125296/0.13 (amendment received on May 08, 2009)
125296/0.14 (amendment received on May 26, 2009)
125296/0.16 (amendment received on June 01, 2009)
125296/0.30 (amendment received on September 14, 2010)
125296/0.31 (amendment received on December 09, 2010)
125296/0.33 (amendment received on January 13, 2011)
125296/0.34 (amendment received on January 18, 2011)

Methods Reviewed:

Production Control Cells/Viral Harvests

- Sterility
- Mycoplasma

Drug Substance

- Water (Karl Fisher)
- Identification (SAS)

Drug Product

- Test for Disintegration
- General Safety
- Identification (PCR and SAS)
- Infectivity (Infectivity and Content Uniformity)
- Microbial Limits
- Residual Solvents (Acetone and Ethanol)
- Water (Karl Fisher)

Recommended Action

The data submitted to support the analytical methods used for testing of Drug Substance and Drug Product of Adenovirus Type 4 and Type 7 Vaccines, Live, Oral, were reviewed and a number of issues with regard to these methods were communicated to the sponsor as information requests. Based on the review of original submission and amendments listed above providing information and data to the information requests, I recommend approval of this application.

I. Production Control Cells and Bulk Virus

1. Sterility Test (section 4.2 in 3.2.S.2. Manufacture)

Final Adenovirus Product (Drug Substance and Drug Product) is not claimed sterile. Microbial Limits test is performed on the DP. Sterility test is performed on the bulk virus during an earlier step in the manufacturing process. Sterility test is performed by direct inoculation following the USP/EP/JP Harmonized version.

The test is suitable for this manufacturing stage for a product which is not claimed sterile.

2. Mycoplasma Test (section 4.2 in 3.2.S.2. Manufacture)

Test for Mycoplasma is performed on the bulk harvest, following FDA's Points to Consider, 1993 document, which is acceptable. However, this test is not performed on production control cell fluids as required by 21CFR 610.30. The following comments were communicated to the sponsor:

CBER's Comments

Section 3.2.S.2. Manufacture, Subsection 4.1 "Bulk Virus Production Controls", it seems the spent media from Production control cells is not tested for Mycoplasma. Mycoplasma testing of control cell fluids is required by 21CFR 610.30. Please comment.

Duramed's Response from amendment 125296/0.7

Mycoplasma testing was not performed on the control WI-38 cells used in the Phase 3 adenovirus vaccine production and we had not planned to perform a mycoplasma test on control cells used for future commercial bulk virus production. This vaccine is in the final form of an oral tablet and is not intended to be sterile. Mycoplasma testing is being performed using the Points to Consider Mycoplasma assay on virus bulk harvest material. This involves a culture in broth and agar and incubation with Vero cells to detect non-cultivable Mycoplasma. The 2006 Note for Guidance on Cell Substrates for viral vaccines indicates that both these parts of the assay should be performed. Furthermore, all the components used to produce the bulk virus are tested for mycoplasma prior to use including the fetal bovine serum, media containing 10% or 2% serum, working virus seeds and the WI-38 cells. Since testing is being performed directly on the bulk virus harvest, we think the requirement for Mycoplasma testing on supernatants from control cells is not scientifically required.

CBER's Review of Duramed's Response

DPQ consulted the Division of Viral Products for Duramed's explanation in not performing the test for Mycoplasma on Production control cells. Dr. Robin Levis in an email dated May 29, 2009, explained that the scientific rationale put forth by the sponsor for not conducting mycoplasma testing on the control cell fluid is acceptable and can be approved under 21 CFR Part 610, Subpart B- General provisions, 610.9 Equivalent methods and processes. Dr Levis further confirmed that testing done on the cell bank and on the growth media, in addition to the testing done on the harvested supernatants prior to clarification support this. DPQ concurs with Dr. Levis's decision.

II Drug Substance

1. Water (Residual Moisture) By Karl Fisher

Documents Reviewed

- MTH-729 for the determination of water content in Lyophilized Intermediate preparations.
- MTH-732 Finished Product Test Method for Adenovirus Tables, updated in amendment 125296/0.5.
- MTH-58 General Test Method, Water Determination by Karl Fischer Reagent, Method 1c (Coulometric Titration).
- ARD_RPT-4014 Analytical Method Validation Report, Formulated Adenovirus Type 4 and Type 7.

Water content (moisture) is determined on lyophilized intermediates (Drug Substance) and on finished product tablets (Drug Product). The method used is a coulometric Karl Fischer titration using non-pyridine reagent. Samples are extracted into the Karl Fischer cell reagent, after grinding to a fine powder in the case of the Adenovirus tablets, then introduced into the Karl Fischer cell and analyzed. Testing is performed under contract by Barr Laboratories Inc. These procedures are consistent with Method 1c described in USP <921> *Water Determination* and were sufficiently detailed.

CBER's Comments

MTH-729 for the Lyophilized Intermediate Raw Material and MTH-732 for the Finished Product, Adenovirus tablets, Type 4 and Type 7.

- a. Please indicate the number of sample extractions performed and the number of titrations performed on each extract along with the procedure in which these are averaged to report the analytical result for the test material. A minimum of two sample extractions and two titrations from each extract is suggested.
- b. Please submit information establishing the qualification of the described procedures for the determination of water content of the raw material and finished product. Although the general test procedure is described in USP <941>, the suitability of this procedure for this specific non-compendial test article needs to be established. At a minimum, data supporting accuracy and repeatability at the specification level should be submitted.

Duramed's Response from amendment 125296/0.7

- a. Current Barr SOPs and test methods are based on 1 sample preparation and 1 determination for analytical procedures. The function of the test instrument is monitored by running standard preparation throughout the run. Based on analyzing solid dosage forms with an automated Karl Fischer Titrator, it has been our experience that one extraction and one titration provide accurate quantitation of moisture content. Current Barr SOPs and test methods for this procedure are based on one sample extraction and one titration for each analysis. As an additional control, the system is monitored using control standards throughout the analysis.
- b. To address any concerns, we will execute a method validation protocol to provide data supporting accuracy and repeatability at the specification level for MTH-729 and MTH-732. This data will be summarized in an internally approved report prior to April 20th, 2009.

Subsequently, a method verification study, ARD_ RPT-4014 was submitted (125296/0.13).

CBER's Review of Duramed's Response

- a. In the information amendment submitted on March 30th, 2009 (125296/0.7) it was indicated that routine product testing utilizes one replicate from one sample preparation. This approach is not sufficient to ensure compliance with the specifications. In a tele-conference on January 6, 2011, the sponsor was contacted to modify the procedure to perform duplicate sample preparations and replicate titrations and to submit a revised procedure that incorporates this change. In an amendment submitted on January 13, 2011 (125296/0.33), the sponsor has committed to modify the procedure, as requested. This is acceptable.
- b. Method verifications were limited to the Drug Product finished tablet formulation as lyophilized intermediate preparations were not available at the time of the study. The sponsor has indicated that the evaluation of the Karl Fischer procedure on Drug Product samples containing excipients as well as the lyophilized intermediates represented a worst case scenario and that an additional validation study of the API is not necessary. This approach is found acceptable.

The method is suitable for intended use.

2. Identification (SAS)

Documents Reviewed

Doc ID: MTH-729 Raw Material Test Method Formulated Adenovirus Type 4 and Type 7, Lyophilized and Formulated Adenovirus Type 4 and Type 7, Lyophilized Intermediate

Barr Laboratories, Inc Validation Protocol (Doc ARD_PRT-1277): “Using the SAS Adeno Test to Identify Adenovirus Tablets, Type 4 and 7, Placebo for Adenovirus Tablets, Type 4 and 7 and Stabilized Adenovirus Type 4 and 7, Lyophilized”

Barr Laboratories, Inc Validation report (Doc ARD_RPT-1760): “Validation of the SAS Adeno ID Test for Adenovirus Tablets, Type 4 and 7, Placebo for Adenovirus Tablets, Type 4 and 7 and Stabilized Adenovirus Type 4 and 7, Lyophilized”

The SAS Adeno Test is a commercial, FDA approved clinical test for in-vitro diagnosis of Adenovirus and Adenovirus antigens, manufactured by SA Scientific, San Antonio, TX. It is a qualitative test that uses a pair of adenovirus specific monoclonal antibodies, which create a reaction with a colored particle conjugate antibody in the presence of Adenovirus and Adenovirus antigens to produce a colored line. This test is currently approved for clinical use with eye swabs, nasal and pharyngeal secretions, fecal samples, and cell culture supernatant. It has been suitable for establishing identity of Adenovirus in the Adenovirus Tablets and Stabilized Adenovirus raw material. However, this test does not distinguish between live and dead virus or between the different types of Adenovirus. This aspect is not important as an Infectivity assay is performed on the Drug Product.

This test is suitable for the intended use.

III. Drug Product

1. Test for Disintegration

The test is performed as per the USP to ensure that the tablets do not disintegrate in simulated stomach fluid for at least 60 minutes and get disintegrated in the simulated intestinal fluid within 45 minutes. In amendment 125296/0.14, the sponsor provided qualification protocol (Doc ID ARD_PRT-3333, version 1.0) and qualification report (Doc ID ARD_RPT-4063, version 1.0) for the Disintegration Test.

CBER's Comments (Question 7 in the March 12, 2009 information request)

The USP Disintegration Test is performed on the finished product. Please justify choice of the USP Disintegration Test rather than the USP Dissolution Test for the finished product. Please provide actual results in minutes for the disintegration test for simulated gastric fluid TS and simulated intestinal fluid TS disintegrations.

Duramed's Response in amendment 125296/0.7

Disintegration was the test being performed by Wyeth when the product was manufactured by them. We agreed that this was the proper choice because of the nature of the material and the product complies with USP<701> Disintegration.

Since human adenovirus may be inactivated by passage through the stomach, it is critical that the Adenovirus tablets do not disintegrate in the stomach and that the tablets disintegrate after passing into the small intestine. The virus is then released from the tablet and results in an asymptomatic infection and subsequent replication leading to a protective immune response. Therefore the Disintegration Test specification of the enteric coated tablet is 1 hour in Simulated Gastric Fluid and less than 45 minutes in Simulated Intestinal Fluid.

CBER's Review of Duramed's Response

In subsequent discussion with sponsor with regard to comments on lot release protocol, the sponsor agreed to provide actual results in minutes for the disintegration test for simulated gastric fluid TS and simulated intestinal fluid TS disintegrations. The test is suitable for the intended purpose.

2. General Safety

Protocols and samples preparation instructions were submitted in amendment 125296/0.3

General Safety test is performed as per 21 CFR 610.11 using 2 guinea pigs and 2 mice.

3. Identification (PCR and SAS)

Documents Reviewed:

MTH-732 : Finished Product Test Method Adenovirus Tablets, Type 4 and Type 7 .

Focus Diagnostics Doc. # CTAVAL.119.009: “Adenovirus 4- and Adenovirus 7- Specific Real Time Quantitative PCR”

Focus Diagnostics SOP Doc. # TSOP.119.050: “Adenovirus 4- and Adenovirus 7- Specific Real Time Quantitative PCR”

BioReliance Doc. No. KVPO1084.R02: Transfer and Qualification Report for Quantitative Polymerase Chain Reaction (QPCR) Assays for the Identification of Adenovirus 4 and 7 in Biological Samples
TSOP.119.050, SOP

BioReliance Doc. No TS107844.R01: Detection of Adenovirus Types 4 and 7 in sponsor’s samples by Quantitative Polymerase Chain Reaction- Technical Specification for Assay Performance.

BioReliance Doc. No. KPBT6534.R02: Detection of Adenovirus Types 4 and 7 in sponsor’s samples by Quantitative Polymerase Chain Reaction.

BioReliance Doc. No. KPBT6533.R00: Extraction of Genomic DNA using the QIAGEN QIAamp® BLOOD KIT.

BioReliance Doc. No. KPBT4525.R06: Detection of internal control nucleic acid by real time polymerase chain reaction.

BioReliance Doc. No. BR107844GMP_C.R00: Detection of Adenovirus types 4 or 7 in the Sponsors material by Quantitative Polymerase Chain Reaction (QPCR).

BioReliance Doc. No. BR107844GMP_B.R00: Detection of Cowpea mosaic virus (CPMV) internal control nucleic by Quantitative Polymerase Chain Reaction (QPCR).

BioReliance Doc. No. BR107844GMP_A.R00: Extraction of Genomic DNA using the QIAGEN QIAamp® BLOOD KIT.

Identification on Drug Product is performed by PCR and SAS methods. For SAS method, please see section II.2. The PCR method for identification was submitted in an amendment 125296/0.4.

In addition to SAS method, identity of each serotype of Adenovirus in the vaccine is evaluated by amplification and detection of adenovirus 4-specific DNA and/or amplification and detection of adenovirus 7-specific DNA in real time PCR reactions, each incorporating quantitative standard curves. Both real-time PCR reactions target serotype-specific sequence of the adenovirus hexone gene. The adenovirus 4-specific PCR reaction

amplifies and detects a 296 bp sequence, while the adenovirus 7-specific reaction amplifies and detects a 334 bp sequence.

In amendment 0.30, response to CR letter, the sponsor changed the vendor performing PCR identity method from Focus Labs to BioReliance Labs. The basic principle and primers and probes are the same with differences in methodology.

Based on this observation, an information request was sent to the sponsor to confirm that no changes have been made to other tests, compared to the original submission. In an amendment 125296/0.31, the sponsor did not mention changes in any other tests and presented proposed changes to Bioburden assay and fPERT test, which will be implemented in future as corrective action from the FDA-483 or submitted as CBE-30. In an amendment 125296/0.34 a qualification report for the bioburden test has been submitted (Document No. KVPO1101Report.R00, Report for verification of bioburden determination using membrane filtration (European Pharmacopoeia (EP) 2.6.12))

Both the SAS and PCR methods are suitable for intended purpose.

4. Content Uniformity

Content uniformity of the tablets is evaluated by an Infectivity Assay that titrates the live viral particles on A549 detector cells. Viral titration is performed in 96-well microtitration plates following a procedure that is typical for virus titrations. A method utilizing presence of phenol red was also evaluated as a content uniformity test.

CBER's Comments (Question 5 in March 12 request)

Analytical Method Validation Report Adenovirus Tablets, Type 4 Type 7, Content Uniformity Test, Doc ID ARD_RPT-1849, version 3.0, Page 73 of Section 3.2.P.5. "Control of Drug Product".

Purpose of this content uniformity test based on reading absorbance of phenol red present in tablets is not clear. Specifications of Content Uniformity Test for Drug Product are based on the Infectivity Assay. Please clarify if the content uniformity test is performed by the Infectivity Assay or reading absorbance of phenol red. If the content uniformity is evaluated by reading absorbance of phenol red, how the data are translated into infectivity?

Duramed's Response included in amendment 125296/0.10

It was not the intent of Barr to use Phenol Red in place of the content uniformity test. Phenol Red is a component of the formulated virus and was used as a surrogate during development to assess the efficacy of the

mixing process. All subsequent trial batches and clinical batches were tested for content uniformity using single tablet titer determinations. The tests for blend and inner core content uniformity remain in the test method in the event that further validation is desired in the future. Final product release method MTH-732 will be updated to clarify this.

CBER's Review of Duramed's Response

Sponsor's response is acceptable.

5. Infectivity Test (TCID₅₀ Assay)

Infectivity test is performed as a potency test by viral titration in 96-well microtitration plates following a procedure that is typical for virus titrations.

CBER's Comments (Question 6 in the March 12 information request)

Summary Report for Validation of a TCID₅₀ Assay used to measure Adenovirus Infectivity, Document No. KVPO0083.R00, Page 40 of Section 3.2.P.5. "Control of Drug Product".

- a. Validation was performed using only one lot of type 7 tablets. It is mentioned in the report that the validation of the method using type 4 tablets would be performed later, if necessary. Please comment on the use of only one lot of type 7 tablets to validate a biological assay for a biological product, live virus vaccine. Also provide information on the plans for validation of this method for type 4 tablets.
- b. Precision of the Infectivity Assays based on virus titration by TCID₅₀ is usually accepted as ± 0.5 log when data are used from a single test. Please justify evaluation of precision of this assay using 0.5 standard deviation of log values.

Results for the intraassay precision specification on page 7 are shown in standard deviation, whereas results on page 18 are discussed with regard to standard error. As discussed above, evaluation of precision of such assay should be evaluated from ± 0.5 log of the average titre determined in multiple tests on a single day (Repeatability), and determined on different days by different analysts (Intermediate Precision). Please re-evaluate data according to this criterion and also evaluate intermediate precision separately for days and analysts.

- c. Section 11.2, Accuracy studies by spiking into matrix do not demonstrate accuracy of the method. Accuracy of such type of methods is relative depending upon the type of cell line used, conditions/passage of the cell line and conditions of the test, such as incubation time. In this case, it should be demonstrated that the method has not changed with regard to cell line, cell passages allowed for titration, and conditions of the test from the original test performed on the product used in the clinical trials or when it was previously licensed by Wyeth. Alternatively, such type of assays can be validated for accuracy if a standard and control preparation with known titer is available. Testing that preparation by the method to be validated and getting results within ± 0.5 log of claimed titer demonstrates accuracy.
- d. Page 30 of the Report discussed the choice of incubation time. The incubation time of the test should be the same as used in the original test performed on the product used in the clinical trials or when it was previously licensed by Wyeth.

Duramed's Response in answer to question 6a in amendment 125296/0.7

- a. The TCID₅₀ Assay validation was performed using Adenovirus type 7 tablets, development batch D5A023021B, which were available at the time the assay was validated. In order to provide additional validation data for 3 batches of type 4 and type 7 tablets, we propose to use titer data from the initial time-points of stability studies. The stability of the tablet titers is remarkably consistent over time periods of up to and including 24 months, so these samples will be appropriate for providing additional validation data. The T=0 content uniformity assays contain repeated assay of the same sample and will be statistically analyzed to provide validation data for intra-assay precision. For each batch, pooling of the titre results from the T=0, T=3 month and T=6 month timepoints will be used to address inter-assay precision. The additional validation data will be incorporated into the validation and issued as a revision to the existing validation report. Addendum to validation report, Doc ID KVPO0083.R01, dated 25 June 2010 was submitted in an amendment 125296/0.33. Additional data presented in the validation report are acceptable.

Duramed's Response in answer to question 6b in amendment 125296/0.8

- b. As noted above, when the precision of the infectivity assay is ± 0.5 log, and a sample is repeated in same assay, the result would be

expected to differ from the first by up to approximately 0.5 of a log in either direction. That is the same as saying that the standard deviation is < 0.5 of a log unit so to clarify, in this case the precision of the assay at $\pm 0.5 \text{ Log}_{10} \text{ TCID}_{50}/\text{ml}$ is the same as a Standard deviation of $< 0.5 \text{ Log}_{10} \text{ TCID}_{50}/\text{ml}$. Trend analysis of all infectivity assays which include a positive control Adenovirus type 4 or Adenovirus type 7 reference standard since November 2005 have shown that the titer precision in this assay is less than or equal to $\pm 0.5 \text{ Log}_{10}$.

The standard error of the mean and the standard deviation of a set of n assays have a ratio of \sqrt{n} . In the case where $n = 1$, as on page 18 of the validation report (Section 18.1) the SD and SE are equal.

Evaluation of precision was evaluated from ± 0.5 log of the average titer determined in multiple tests on a single day (Repeatability) and as determined on different days by different analysts (Intermediate Precision) and is reported in the original validation report dated 17 October 2005 (Document KVPO0083.R00) on page 21. The additional evaluation of intermediate precision for both days and analysts has been performed by our statistician from the original data. For this analysis, we define *inter-day precision* as measured by the standard deviation of assays done on the same material by the same person on different days, and define *inter-operator precision* as measured by the standard deviation of assays done on the same material by different operators on the same day. We would get numerous estimates of each of these statistics, and the best estimate would be their root-mean-square values.

To estimate inter-day precision as defined above, the 144 assays carried out for the purposes of estimating precision can be classified and summarized as follows in Table 1 (Table not included in the review memo, Refer to CMC Amendment 8).

These 16 estimates of inter-day precision are all within our criterion of acceptability, and so is their root-mean-square value of 0.210 log units.

To estimate inter-operator precision as defined above, the 144 assays carried out for the purposes of estimating precision can be classified and summarized as follows in Table 2 (Table not included in the review memo, Refer to CMC Amendment 8).

These 24 estimates of inter-operator precision all satisfy our criterion of acceptability, and so does their root-mean-square value, which is 0.225 of a log_{10} unit.

**Duramed's Response in answer to question 6c in amendment
125296/0.7**

- c. The accuracy study was not performed by spiking into the matrix. Accuracy was determined from analysis of the Adenovirus type 4 and Adenovirus type 7 frozen liquid reference standards which had previously established internal reference titers. The data for establishing accuracy was taken from the values produced for the reference standards when assayed repeatedly in the precision assays and compared to the previously established mean titers for the reference standards. It was demonstrated that the titer results obtained were reproducible to within the range of the mean batch titer $\pm 0.5 \text{ Log}_{10} \text{ TCID}_{50}/\text{ml}$ and could therefore be deemed accurate.

The current titration assay was used to perform the titer testing on all process intermediates and finished product used in the Phase 3 clinical trial. There have been no changes to the assay format used since validation of the assay in 2005. The A549 cells used in the assay have been between passage 86 and passage 99 and are from the same batch used in the validation. The assay method is described in BioReliance SOP KPBT0627, which is provided as an attachment in the response to Question 9.A. The method is considered to be accurate as the reference standards are included in each titration test and consistently demonstrate reproducibility within the range of the mean batch titer $\pm 0.5 \text{ Log}_{10} \text{ TCID}_{50}/\text{ml}$.

**Duramed's Response in answer to question 6d in amendment
125296/0.7**

- d. The clinical trial samples were analysed using a 21-day assay, which is the current standard format. Although the incubation time used in the assay was validated for reads at 14 days and 21 days, the 14-day endpoint has not been used for determination of potency results. The read on Day 21 is specified in Section 10.3.1 of the assay SOP (KPBT0627, which is provided as an attachment in the response to Question 9A). Incidentally, Wyeth also used a 21 day read.

CBER's Review of Duramed's Response

Sponsor's responses for a, b, c, and d are acceptable.

6. Microbial Limits

This product is not claimed sterile and is tested for Microbial Limits tests following the USP method.

CBER's Comments (Question 4 in the March 12, 2009 information request)

Summary Report for the Validation of Harmonized Microbial Limits Testing for Adenovirus Tablets, Type 7, Lancaster Laboratories Number: Ns-04944589, Page 111 of Section 3.2.P.5. "Control of Drug Product".

- a. Details of sample preparation are not provided. It is mentioned in the report that the samples were diluted. Since the product being a tablet, please provide details of sample preparation for this study and for testing samples for the Microbial Limits test with details on number of tablets tested. Please also provide the number of lots tested in this study.
- b. The method was qualified for Type 7 tablets only. Please provide an explanation for not validating this procedure for Type 4 tablets.

Duramed's Response from amendment 125296/0.7

- a. The sample tablet is added to a volume of diluent and allowed to disintegrate. The disintegration is aided by physical agitation of the sample. Details of the sample preparation are given in the attached document, Microbial Limits Testing Validation, Analysis 0507. A single lot was used in this study because the tablet formulation contains materials that are currently tested by Barr using standard USP microbial limits test procedures. Adenovirus is not known to attack cells other than eukaryotic cells as was deemed to not have an impact of the spiked organisms.
- b. The type 7 tablet formulation contains a dye and dyes have a potential to inhibit microbial growth when present at low levels. Using the type 7 tablet for the validation represents a worst case scenario in that if we were able to validate in the presence of the dye its absence in the type 4 virus has no detrimental effect on microbiological recovery.

CBER's Review of Duramed's Response

Sponsor's response is acceptable and the test is suitable for intended purpose.

In an amendment 125296/0.34 a qualification report for the bioburden test has been submitted (Document No. KVPO1101Report.R00, Report for

verification of bioburden determination using membrane filtration (European Pharmacopoeia (EP) 2.6.12)). The European Pharmacopoeia method for bioburden and the verification report are suitable for the Microbial Limit or Bioburden test.

7. Residual Solvents (Acetone and Ethanol)

Documents Reviewed

- MTH-732, Finished Product Test Method for Adenovirus Tablets
- ARD_RPT-1824 Analytical Method Validation Report

Ethanol and acetone are residual impurity components in the enteric coating formulation of the Adenovirus tablets. ICH Q3C Impurities: Residual Solvents, classifies acetone and ethanol as Class 3 “low toxic potential”. Quantitation in the finished product tablets (Drug Product) is by headspace gas chromatography with detection by flame ionization. Specification limits are 1.5% for ethanol and 1.0% for acetone.

CBER’s Comments (Question 3 in the March 12, 2009 information request)

- a. Please indicate the number of sample extractions performed and the number of replicate chromatograms obtained from each extract along with the procedure in which these are averaged to report the analytical result for the test material. A minimum of two sample extractions and two chromatograms from each extracted sample preparation is suggested.
- b. Please submit information establishing the qualification of the described procedures for the determination of ethanol and acetone in the finished product. Although the procedure described in MTH-732 Section 8 is generally consistent with the USP <467> General Chapter on Organic Volatile Impurities, Method IV, the suitability of this procedure for this specific non-compendial test article needs to be established. At a minimum, data supporting accuracy and repeatability at the specification levels should be submitted.

Duramed’s Response in amendment 125296/0.7

- a. The residual solvent test procedure was fully validated (as filed in 3.2.P.5.3). The validation included linearity, accuracy, and precision studies. The validation demonstrated that the test procedure can generate accurate and reproducible results.

Therefore, per Barr procedure, a single sample preparation and injection are made for each sample.

- b. The residual solvent test procedure was fully validated and was submitted in ARD-RPT-1824 (as filed in 3.2.P.5.3). The validation included specificity (section 4), linearity (section 5), accuracy (section 6), and precision (section 8) studies. The validation data demonstrated the test procedure is suitable for its intended use.

CBER's Review of Duramed's Response

- a. Routine product testing with one replicate from one sample preparation is not sufficient to ensure compliance with the specifications. This approach is not sufficient to ensure compliance with the specifications. In a tele-conference on January 6, 2011, the sponsor was contacted to modify the procedure to perform duplicate sample preparations and replicate titrations and to submit a revised procedure that incorporates this change. In an amendment submitted on January 13, 2011 (125296/0.33), the sponsor has committed to modify the procedure, as requested. This is acceptable.
- b. Sponsor's response is acceptable.

8. Water (Karl Fisher)

Residual moisture (water) in the drug product is determined by the same method used for Drug Substance (Section II.1).

IV. Specifications for Content Uniformity

CBER's Comments (Question 8 in the March 12, 2009 information request)

Specifications for Content Uniformity for individual tablet should be same as specification for the assay. Please comment.

Duramed's response in amendment 125296/0.7

The specification for the average of 10 dosage units tested during the Content uniformity test is the same as the assay, the difference is in what the acceptable variation of the batch will be. Content uniformity is a test of tablet to tablet potency as it varies around the mean, the mean being the target assay value. Before it was revised to its current wording, the USP specification for traditional small molecule pharmaceuticals out of 10 dosage units not more than one tablet was less than 85%. This was in recognition by both the USP and the FDA that within any batch it was unreasonable to expect 100% of the dosage units would have 100% of the specified dose. The reason is first no blending process can be

100% effective and that the precision of the assay procedure must be accounted for. In the case of the Adenovirus titer assay, the precision of the assay is $\pm 0.5 \text{Log}$ which represents the most dominant variable in the process. Additionally the effects of the assay precision are compounded at the lower concentration of virus used for the single tablet content uniformity test than for the 20 dosage unit composite sample used for the assay. In addition, the assay is performed in triplicate and the reported value is the average of these three results whereas content uniformity is by definition a test on 10 individual dosage units.

CBER's Review of Durmed's Response

Sponsor's response is acceptable.