FOOD AND DRUG ADMINISTRATION

CENTER FOR BIOLOGICS EVALUATION AND RESEARCH

MEMORANDUM

Date: February 16, 1998

To: Steve Kozlowski, BLA Committee Chairman, HFM-561

From: Janice Brown, BLA Committee Member, HFM-206

Through: Julia Lukas Gorman, Chief, Branch 1, HFM-206

Subject: Review of Biologics License Application (BLA) from MedImmune, Incorporated for the manufacture of Palivizumab™; Reference Number 97-1359

The subject of this submission is a pilot manufacturing agreement between MedImmune Incorporated and Thomae-Boehringer Ingelheim (Thomae). MedImmune's Gaithersburg Manufacturing and Development Facility (GMDF) manufactures and formulates the active drug substance, MEDI-493, at pilot scale (600-L). The drug product is Lot release testing of the bulk and final vialed product, stability testing, and comparability testing is carried out by the Quality Control Department at MedImmune's Frederick Manufacturing Center (FMC). MedImmune has inspectional history (1994 EIR) and recommend waiving the inspection for this site. Their next scheduled surveillance inspection is September 1999.

MedImmune has also contracted Thomae to manufacture, formulate, fill, lyophilize, label, and package MEDI-493 at scale for market at their Biberach, Germany facility.

My review includes of an evaluation of the following sections submitted in the Chemistry, Manufacturing, and Control section of BLA: Volume 1: Section 3.4.1 - 3.4.6, Volume 3: Sections 4.1 - 4.2.1.2, Volume 6: Section 4.2.2 - 4.2.3.2, Volume 9: 4.2.3.4 - 4.2.3.4.4.1, Volume 12: 4.2.3.4.4 - 4.2.3.6.2, Volume 13: 4.2.3.7.1 tabs 4 and 5, Volume 17: 4.2.4 - 4.2.4.2.2.3, Volume 19: 4.2.4.2.3 - 4.2.4.2.3.3, 4.2.7 - 4.2.7.1, Volume 20: 4.2.8 - 4.2.8.6. 4.3 - 4.3.4.3.1, Volume 21: 4.3.4.3.2, Volume 22: 4.3.5.2.1 - 4.5, Volume 96, Volume 97, and Volume 98.

I have separated my review into two sections, the first section are questions related to the submission that can be addressed in an information request letter and/or during their pre-license inspection and the second section is a narrative of my review. Attached is a review memo to Bob Sausville (lead inspector) describing the areas that should be covered during the pre-license inspection in support of this BLA. After review of the submission, I have the following questions and comments.

1. Please review the process validation for the exchange column. The firm should have supporting data demonstrating the performance of the column over the proposed lifetime of the column. The performance should include the following:

Volume 17, page 60 describe a study evaluating cleaning and sanitization effectiveness of the resin (without associated equipment skids) using a protein-specific assay (see number 5 below). We recommend that cleaning validation use chromatography columns at full manufacturing scale unless a small scale replica of the commercial column is used. Some periodic evaluation of cleaning effectiveness should also be performed until the lifespan of the column is demonstrated. Although endotoxin removal was demonstrated using 0.5 N NaOH, their process does not have endotoxin present in the process stream. Sanitization effectiveness should be demonstrated using bioburden/viruses in the chromatography resin (with a worst case protein load) to ensure that in the event of viral and/or bioburden buildup on the column the sanitization agent would effectively kill/inactivate these contaminants prior to the next purification.

2. Please review the process validation for the column. The firm should have supporting data demonstrating the performance of the column over the proposed lifetime of the column. The performance should include the following:

The actual process parameters (protein load capacity, flow rates, elution profiles) should be used in these evaluations. See my comments regarding cleaning and sanitization in questions 1 and 5.

3. Please review the process validation for the column. The firm should have supporting data demonstrating the performance of the column over the proposed lifetime of the column. The performance should include the following:

The actual process parameters (protein load capacity, flow rates, elution profiles) should be used in these evaluations. See my comments regarding cleaning and sanitization in question 1.

4. Please review the process validation for the column. The firm should have supporting data demonstrating the performance of the column over the proposed lifetime of the column. The performance should include the following:

The actual process parameters (protein load capacity, flow rates, elution profiles) should be used in these evaluations. See my comments regarding cleaning and sanitization in questions 1 and 5.

5. Volume 17, page 60 describe a study evaluating cleaning effectiveness of the various chromatography resins using a protein-specific assay. Please clarify whether this assay can detect that may potentially build up on the column(s). Additionally, please verify that this assay has been validated.

6. Volume 12, page 110 describes the evaluation of the hold at of the harvest (conditioned medium). Typically, validation studies in support of a hold period include three manufacturing lots to ensure results are reproducible over several manufacturing batches. During the prelicense inspection, please review two other manufacturing batches held for at

7. Volume 12, page 109-110 and Volume 17, page 31-32 describe the harvest operation using the Millipore plate-and-frame microfiltration system. Please review the cleaning validation, sanitization effectiveness, and bacteriostatic performance of the cleaning and storage solutions.

8. Please review the PLC system validation for the following: (the PLC controls the

and SIP; medium or harvest tank (PLC controls both temperature and agitation speeds);

and chromatography controller that is equipped with a programmable logic controller (PLC) and UNICORN software (the during a chromatography operation). The operational cycle in the PLC validation package should be compared with the operational parameters presently used in manufacturing.

9. Please review sterilization validation for one of the following: bioreactor, largest and smallest portable and fixed holding tanks used for the most downstream process.

10. Please review the cleaning validation and routine monitoring for the following: largest and smallest mobile and fixed vessel, chromatography skids.

11. Please review validation of the water system and the most current six months of water monitoring for points of use servicing LMA.

12. Volume 97, page 26 describes the container closure of the formulated bulk drug substance. The submission did not include container closure integrity testing once the formulated bulk is into the however, the stability program included sterility testing. During the pre-license inspection, please determine how the integrity of the bulk fill system is verified once it arrives at

13. Please review the shipping validation studies for the formulated bulk from the MedImmune facility in Gaithersburg, Maryland to and the final dosage form from

14. Please review the HVAC (re)validation and the most current six months of environmental monitoring for Rooms

15. The submission states that buffers are and product streams are before each chromatography step and again into the product collection vessel. Although, no claim of sterility is described for the in-process product, there should be some evaluation of buffer/filter compatibility. Please review the filter extractable and compatibility studies for the used in these operations.

16. Drug Substance Stability Studies Stability protocol outlines the stability conditions used for evaluation of For this study, MEDI-493 drug substance is stored in

316L stainless steel containers as scaled down simulations of the 20-L pressure cans used to store the Phase III material following formulation. During the study, material is stored at and is removed aseptically at the required time points. The temperature was selected to represent the condition for storage of MEDI-493 drug substance prior to fill/finish. MEDI-493 material was formulated in 25 mM histidine, 1.6 mM glycine, 3% mannitol, pH 6.0 at a protein concentration of 54 ± 5 mg/mL. During the pre-license inspection, please review two additional lots stored in stainless steel containers to support the expiry.

17. Volume 97 states that container/closure integrity was validated for the MEDI-493 components using microbial immersion techniques. Please review the container-closure integrity study for the vials with stoppers.

18. Please review the lyophilization validation cycle to include length of time primary and secondary drying is performed and shelf temperature selection (product eutectic point).

19. Volume 97, page 58 describe the visual inspection of the lyophilized vials. The submission describes that each vial is inspected against a white and black background for defects and defective vials are removed. Please clarify if the finished dosage form are visually inspected for particulates.

1. Please review the three media fills using the and Verify that these media fills included a lyophilization simulation and the replacement of nitrogen with compressed air. (Nitrogen is used to transfer the bulk to the filling heads by overpressurizing the bulk stainless steel vessel and also to relieve the vacuum in the lyophilizer.)

2. Please review the most current (re)validation for the in the for the stoppers and the filling machine parts load used to fill MEDI-493.

3. Although the product contact equipment is dedicated to the manufacture of MEDI-493, there should be validated methods for cleaning. Please review cleaning validation for the receiving vessel and the filling needles and pump used to fill MEDI-493.

4. Please review the following for the multiproduct lyophilizer:
   a. Routine monitoring following the manual cleaning procedure at product changeover;
   b. Periodic monitoring of thermal fluid and oil; and
   c. SIP cycle.

5. Please review the most current HEPA filter testing for the dry heat depyrogenation oven located in the

6. Volume 97, pages 50 and 51 summarizes the stopper washer evaluation. Stoppers were analyzed for . In addition to these criteria, there should be some evaluation of particulates. Please review these studies and verify that some particulate evaluation was performed.

7. Volume 97, page 55 indicates that . Please review the qualification of personnel performing these evaluations to include control defects with lyophilized product.

8. Volume 97, pages 57 and 58 describe the vial overseal operation in the and visual inspection performed in Please verify that there are time and temperature controls when the final product is transported between buildings.

REVIEW NARRATIVE

Overview - MEDI-493 (palivizumab) is a humanized monoclonal IgG1 antibody directed to the antigenic site A on the respiratory syncytial virus (RSV) F protein. Palivizumab has been shown to neutralize all RSV clinical isolates tested, inhibit RSV-induced cell fusion, and reduce pulmonary RSV titer when given prophylactically to cotton rats. MEDI-493 drug substance (bulk product) is manufactured and tested at MedImmune, Inc. Manufacturing is performed in the Licensable Manufacturing Area (LMA) of the Gaithersburg Manufacturing and Development Facility (GMDF) located at 35 West Watkins Mill Road, Gaithersburg, Maryland. Testing is performed at this site and at the Frederick Manufacturing Center (FMC) located at 636 Research Drive, Frederick, Maryland, 21702, USA.

Manufacturer (Identification, Other Products, Contamination Precautions) - The submission states that the GMDF is a multi-product facility, however, only one product is manufactured. The GMDF consists of five areas: the Licensable Manufacturing Area (LMA), the Development Manufacturing Area (DMA), the Support Area, the Common Area, and the Mechanical/Receiving Area. MEDI-493 cell culture and purification operations are carried out in the LMA which consists of the following areas: Cell Bank Storage Room, Inoculum Expansion Room, Media Preparation Room, Bioreactor Room, Isolation Room, Buffer Preparation Room, Clean Storage Room, and a 4-room Purification Area.

Other products are produced in the DMA which consists of a Cell

Culture Area, a Purification Area, and a Fermentation Room. The LMA and DMA share the Support Area which includes glassware wash, autoclave, depyrogenation oven, tank wash, clean-in-place (CIP), and storage/weighing of raw materials. The Support Area consists of the following areas: Glassware/Tank Wash Room, Dirty Storage Room, CIP Room, Weigh Room, Raw Material Ambient Storage Room, Raw Material Cold Storage Room, Product Storage Cold Room, and DMA Clean Storage Room. The Common Area consists of the following areas: Change Rooms, Rest Rooms, Break Room, Computer Room, and Quality Control (QC) Laboratory. The QC Laboratory supports the environmental monitoring program, raw material release, in-process testing, drug substance and drug product release, and stability testing. The Mechanical/Receiving Area houses the utility systems which include reverse osmosis deionized (RODI) water, clean steam, water-for-injection (WFI), compressed air, process gases (oxygen, nitrogen, and carbon dioxide), and waste treatment. The Mechanical/Receiving Area also contains the Metrology Laboratory, the Gowning Storage Room, and the Loading Dock.

Quality Control Laboratories at the Frederick Manufacturing Center (FMC) - There are four QC laboratories at the FMC: Chemistry, Plasma Screening, Microbiology, and Product Testing. The Microbiology Laboratory carries out testing to support the environmental monitoring program, utilities monitoring program, and in-process control testing. The Chemistry Laboratory supports raw material release, in-process testing, drug substance and drug product release testing, and stability testing. This includes HPLC and spectrophotometric assays. The Product Testing Laboratory is responsible for in-process testing, drug substance and drug product release testing, and stability testing. This includes electrophoretic and immunologic assays. The Screening Laboratory, a laboratory unrelated to MEDI-493, is responsible for testing incoming plasma samples for product specific titers.

Other Products (Shared Areas) - At the current time, there is no plan to introduce other products into the LMA. Shared areas used for LMA (MEDI-493) and Development Manufacturing Area (DMA) operations include the Buffer Preparation Room, the Unloading/Drying Room and the Support Area. The and solution preparation vessels in the Buffer Preparation Room are shared and used to prepare solutions for purification operations taking place in the LMA and DMA.

Solution preparation for other products is separated from MEDI-493 solution preparation by time and procedure. Components and solutions for only one product are present in Room at any time, there is a change-over procedure employed between preparation of solutions for different products, and the procedure for delivery of solutions from Room to the DMA is

also defined. There are several shared areas for processing of LMA and DMA equipment. The CIP station for portable equipment, the glasswasher, the autoclave, and the depyrogenation oven in the Glassware/Tank Wash Room is shared for cleaning LMA and DMA equipment. The Unloading/Drying Room is shared for unloading and drying equipment from the clean side of the pass-through autoclave and depyrogenation oven.

Processing of LMA and DMA equipment in these areas is separated by time and procedure to prevent potential cross contamination. Equipment for only one product is present at any time in each of the rooms, there is a change-over procedure employed between processing of equipment for different products. There are additional procedures in place for control of the equipment cleaning areas. For MEDI-493, cell culture glassware is decontaminated and washed in the cell culture Media Preparation Room . It is then covered in bags and transported to Room via for autoclaving. Cell culture equipment is not mixed with purification equipment in Rooms , and there is an area change-over between processing cell culture and purification items. The Weigh Room is used for dispensing components of solutions to be prepared in the GMDF, except for cell culture components which are weighed within the cell culture areas. Weighing of components for other products is separated from MEDI-493 weighing operations by time and procedure. The components for only one product are present in Room 408 at any time, there is a change-over procedure employed between weighing of components for different products. The raw material storage Rooms house materials for both the LMA and DMA.

The Product Storage Cold Room is used to hold the MEDI-493 and DMA products. MEDI-493 is stored in a locked cage within Room Similarly DMA materials are housed within locked cage(s) separate from MEDI-493. Corridors and are shared. The flow of materials and equipment are controlled by time and procedure.

Containment and Contamination Precautions - The product manufacturing areas and personnel are dedicated on a single product campaign basis. Separate gowning-in areas are provided for cell culture and purification. The production equipment (e.g., glassware, bioreactors, columns, and tanks) in the LMA are dedicated to MEDI-493. Portable product contact equipment are identified with product-specific labels. The equipment is cleaned according to validated procedures and visually inspected prior to use. The status of each piece of equipment is clearly labeled throughout the operations. The sterilization of process equipment and cell culture medium are also performed according to validated procedures. After product contact, the cell culture process glassware are decontaminated and cleaned within the Cell Culture Area prior to transport to the Support Area for autoclaving. Equipment from cell culture and purification are processed separately in the glassware wash area with change-over procedures between these operations to prevent cross contamination.

Master Cell Banks - The MEDI-493 production cells were cultivated in serum-free culture medium, which contains

All were certified free from bovine viruses bovine viral diarrhea (BVD), infectious bovine rhinotracheitis (IBR), and parainfluenza 3 (PI-3). The components were obtained from US/Canadian suppliers and have traceable histories. The liquid medium was prepared by dissolving the powdered components in U.S.P. Water for Injection (WFI) and prior to use.

Selection of a cell line, suitable for large-scale production, was based on expression level, growth rate, and stability. The , and subsequently subjected to two rounds of single-cell cloning (limiting dilutions) in

Cells from the spinner flask cultures were centrifuged and resuspended in a serum-free freezing medium to

establish a The freezing medium was composed of The MCB was created on and the lot number designated and the remaining vials are stored in a secured cGMP liquid nitrogen freezer at the MedImmune Gaithersburg Manufacturing and Development Facility.

Working Cell Bank - Each MCB vial can be used to prepare a Working Cell Bank (WCB).

End of Production Cells (EPC) - The End of Production cells (EPC) were collected aseptically at the end of the cell culture production process from the production bioreactor. The EPC were characterized for identity, quality, safety, and stability. The characterization was performed as recommended in FDA's Points to Consider. The EPC test results from the 3 consistency lots were evaluated. No evidence of viral contamination was found in the mouse antibody production (MAP) test, in vivo assay, and in vitro assay for adventitious viruses. No evidence of microbial or mycoplasma contamination was found in the sterility and mycoplasma tests.

Culture Medium - Osmolarity and pH data from all medium lots lots) and prepared for the Phase III production campaign were collected and used to establish Proven Acceptable Range (PARs). The PAR for

Medium is prepared at three different scales: for inoculum expansion, for the expansion bioreactor, and for the production bioreactor. Nutrient feed is prepared for th production bioreactor ir batches. Medium and nutrient feed preparation were validated for

Cell Growth and Harvesting - The media preparation, inoculum expansion, and bioreactor operations are conducted in Rooms , respectively. These production rooms are Class and positively pressurized against the Cell Culture Gowning Room Open manipulations are performed in a Class Small scale media filtrations are performed in a laminar flow hood in Room Large scale media filtrations are performed at the receiving

bioreactors in Room ——— Clean-in-place (CIP) and steam-in-place (SIP) procedures are employed to ensure the cleanliness and sterility of equipment. The vessels are equipped with steam-sterilizable ports for aseptic sampling and addition of inoculum, media, and nutrient feeds. expansion bioreactor and the production bioreactor is steam-sterilized in place prior to transferring the culture. The inlet (headspace and sparger) and exhaust gases are sterilized by a 0.2 μm hydrophobic filters. The integrity of the 0.2 μm filters are verified after each use.

Prior to entry into the Cell Culture Area, personnel put on hair covers, face masks, gloves, sterile gowns and shoe covers in the gowning room. The air and surface cleanliness of the area is routinely monitored. MEDI-493 is produced in ——— A vial of cells from the WCB is expanded through a series of ——— From the ——— , the cells are pooled and inoculated into a ——— expansion bioreactor. The culture is transferred into a ——— production bioreactor for the final stage of cell culture production where ——— Bioreactor cultures are aseptically sampled and microscopically examined for microbial contaminants. For all production bioreactor runs, in-process controls include measurement of ——— The operating parameters of the bioreactor ——— are also controlled and monitored during cultivation.

Harvest - The cells and debris are removed from the culture using ——— and the ——— of the resulting cell-free conditioned medium are adjusted. The operating parameters of the ——— unit used for the harvest process ——— are controlled and monitored during the operation. The integrity of the ——— filter modules and the ——— filter are tested after use. For the conditioned medium, bioburden (agar plate incubation); endotoxin, and antibody concentration are measured. The operating parameters (temperature, pH, and agitation speed) of the harvest tank are also controlled and monitored during the conditioned medium storage. ——— with a ——— . The influence of wall shear rate and transmembrane pressure (TMP) on processing time and product recovery were examined. The effect of antifoam concentration on membrane fouling was also examined. Increases in wall shear rate (feed flow rate) resulted in shorter processing times and higher product recovery. Increases in ——— resulted in a higher permeate flow rate, and thus shorter

processing time, however product recovery was also reduced. High concentrations of simethecone-based Antifoam C resulted in significant fouling of the membranes and a rapid decline in clean water flux.

Purification - LMA purification operations are carried out in five environmental rooms (Rooms each with an air classification of 10,000 and terminal HEPA filtration. The air handling system is validated and the pressure differentials are designed to isolate process steps according to cleanliness level. Process operations are also segregated according to cleanliness level, and pre-and post-viral clearance procedures. The five rooms include a buffer preparation room a pre-viral clearance through the staging area (Room and purification room (Room a post-viral clearance staging room (Room and purification room (Room Room is equipped with a Class 100 laminar flow hood for the bulk filtration. Daily, weekly, monthly and quarterly cleaning procedures which incorporate rotation of phenolic cleaning agents are used to maintain cleanliness and to minimize potential for contamination. The rooms are routinely monitored for air quality and surface bioburden. This includes measurement of viable and non-viable air particles, and room and equipment surface bioburden. Full gowning is required for personnel in the LMA purification suite and consists of a sterile clean room gown, boots or shoe covers, hair cover, gloves, and face mask. In addition, a full hood and double sterile gloves combined with alcohol application are required for bulk filtration operations which are carried out in a Class laminar flow hood. A one-way flow pattern is followed for personnel working in Rooms and clearance steps. In this case, personnel are not permitted to return to Room and other LMA purification rooms without exiting the LMA via regowning in

MEDI-493 is purified from the medium using a series of chromatography and filtration steps including:

- The first step in the purification of MEDI-493 is the column step. This exchange step uses for the selective capture of MEDI-493 from harvested cell-free conditioned medium. Effective binding of MEDI-493 depends on the pH and conductivity of the adjusted conditioned medium. The critical parameters for this step are

and reduction of The performance of this step is based on evaluation of step yield, product purity, and reduction of Endotoxin is monitored as an indicator of the effectiveness of column preparation and cleaning.

- An treatment step is used for in the MEDI-493 purification process. This step was implemented because small which are removed by the subsequent chromatography steps. The critical operating parameters for this treatment include incubation time at The performance of the step was evaluated by of the preformulated drug substance. The results indicate that using the parameters specified in the in the MEDI-493 preformulated drug substance is No exceptional conditions occurred during this study.

- The is followed by . This step uses a selectively bind MEDI-493. The bound protein is washed with and equilibration buffer to remove process contaminants. The MEDI-493 product is eluted with a low pH buffer. Throughout clinical development, several were used and each has exhibited different properties. Because the is prepared with a high ligand density, elution properties of the MEDI-493 are different for this gel and considerable reoptimization was required. Laboratory data indicated that the optimal loading capacity for this gel compared to and as a result, the eluted product is more concentrated. During the optimization of the step using this gel, it became apparent that the product eluted with the he criteria for the Moreover, the product could not be titrated to the low pH without causing aggregation. For this reason, a separate is included after but before the The critical parameters for the . Performance of the step is based on and in the product.

- The in the MEDI-493 purification uses the

. This filter is effective for the removal of viruses greater than The critical parameters for this step include transmembrane pressure and cartridge capacity as well as product concentration. The performance of this step is based on

. This step was implemented in order to meet the criteria of the conditions for viral inactivation. For this step, the is titrated to .

Data obtained from laboratory studies indicated that titration below potentiated aggregation. The critical parameters for this step include pH and incubation time. The acceptance criteria are based on the time course of viral inactivation indicated that 6-7 logs of inactivation of Psuedorabies and Xenotropic Retrovirus occurred at Although low pH treatment could be carried out for longer times minutes was chosen to accommodate the time needed for transfer of larger volumes at increased manufacturing scale. The is a flowthrough step using . The column capacity is based on PAR data from the Phase III production campaign which indicated an average of 81 g Additional laboratory studies were carried out to challenge the

as initially used as a polishing step for removal of trace levels of process contaminants. For this column step, the is adjusted to prior to binding and eluted with The should not exceed because of the potential for aggregation. till

MEDI-493 in the non-bound fraction, and without any effect on step performance. The critical parameters for this step are

Diafiltration, Concentration, and Formulation - The step uses a concentration at . At the conclusion of the last the product is recovered and the protein concentration is adjusted to the final concentration using a The initial buffer exchange is designed to remove The subsequent into is required for concentration of the product to greater than a formulation buffer suitable for lyophilization. The critical parameters for this step include the The concentrated product was The final concentration of the product was

The purified product is formulated in 25 mM histidine, 1.2 mM glycine, 3% mannitol, pH 6.0 buffer. The resulting formulated bulk MEDI-493 is 0.2 micron filtered into 5-L or 7-L Stedim 38 film, BioPharm XL bags and stored at 2-8°C until final filtration, fill, and lyophilization at an offsite contract manufacturer.

Removal of Process Contaminants - Process validation studies included in-process analysis to evaluate the removal of and These components include Removal of components added during the purification include Removal of residual was also evaluated. reduced to release specification levels after the . Levels of meet release specifications after the Note that the . product is assayed following the step. In addition, the purity specification of as judged by high performance size exclusion chromatography (HPSEC), was achieved after the

Container System - The container for the MEDI-493 filtered bulk product is a [redacted] These [redacted] are manufactured by [redacted] The [redacted] contain an inlet port, an outlet port and two sample ports. The [redacted] are supplied with a [redacted] Each [redacted] is individually subjected to an air leak test. The product contact surface is composed of a proprietary polyethylene blend which passes U.S.P. plastics Class 6 Tests, U.S.P. Physico-Chem Tests, as well as in vivo and in vitro testing for systemic toxicity, cytotoxicity, and cell lysis. The results of these studies indicate that under a variety of extraction conditions no toxicity has been observed in any of the test systems. The [redacted] have also been tested for chemical resistance and mechanical strength. The formulated bulk MEDI-493 is [redacted] filtered into the bags and stored at [redacted] until a second [redacted] filtration and fill is carried out at an offsite contract manufacturer. Studies have been undertaken to evaluate the stability of the filtered bulk product in the [redacted]. The analyses include [redacted]

Stability - Drug Substance Stability Studies Stability protocol SP-0004 outlines the stability conditions used for evaluation of [redacted] For this study, MEDI-493 drug substance is stored in [redacted] stainless steel containers as scaled down simulations of the [redacted] used to store the Phase III material following formulation. During the study, material is stored [redacted] and is removed aseptically at the required time points. The [redacted] temperature was selected to represent the condition for storage of MEDI-493 drug substance prior to fill/finish. MEDI-493 [redacted] material was formulated in 25 mM histidine, 1.6 mM glycine, 3% mannitol, pH 6.0 at a protein concentration of [redacted] Data to date [redacted] demonstrate that MEDI-493 drug substance has maintained its purity, potency and strength. Purity assessed by HPSEC was > 99.0% indicating that the material is free from aggregate or lower molecular weight degradation. Assays for biological activity, [redacted] and all other assays pass specifications.

Consistency Lot Drug Substance Stability Studies - Stability studies for the [redacted] are being conducted under Stability Protocols [redacted] In protocol [redacted] MEDI-493 drug substance is placed in [redacted] as scaled down versions of the [redacted] that will be used to store and transport MEDI-493 drug substance prior to fill/finish. The [redacted] are stored at [redacted] and [redacted] and test samples are removed aseptically at [redacted] The [redacted] temperature

was selected because it is the storage temperature used prior to fill/finish. The ——— temperature was selected to evaluate the potential effect of temperature excursions which may occur during shipping or storage of MEDI-493 drug substance. This condition is being assessed to assure that slight increases in temperature during shipment or storage do not affect the quality or integrity of the product indicating that MEDI-493 is stable under these conditions for at least these time periods. Storage of MEDI-493 drug substance at an accelerated temperature demonstrated that the molecule can withstand elevated temperature conditions for ——— days (all assay results passed specifications). The data also show similar stability profiles for MEDI-493 prepared from different size bioreactors. Data compiled, and summarized here, indicate that MEDI-493 drug substance, ——— or lyophilized formulation (up to 6 months), is stable when stored at 2-8°C.

The container/closure system for the MEDI-493 lyophilized vialed product consists of 5 cc Schott, U.S.P./EP type I borosilicate (Purform) glass vials with a 20 mm neck opening, 20 mm 4405/50 gray butyl rubber stoppers, and 20 mm flip-off aluminum overseals with a green button. QC testing includes in-process, lot release, stability, and comparability tests; as well as tests to support raw material release, environmental monitoring, utility monitoring, and validation. Each lot of MEDI-493 drug substance and drug product are tested for identity, potency, purity, and microheterogeneity, as appropriate, with respect to the Working Reference Standard

Master specifications are defined for lot release, stability, and comparability criteria. Similarly there are specifications for raw materials, environmental monitoring sites, and utility sampling sites. Three lots of MEDI-493 material produced in the Gaithersburg facility have been used to date as Working Reference Standards for release of clinical, consistency, and commercial manufacturing lots. Working Reference Standard lots are qualified by comparison to the existing Working Reference Standard with respect to identity, potency, purity and microheterogeneity; and the stability of all standard lots are monitored.

Stability studies were carried out on Phase I, II, and III clinical lots to monitor the stability of the product used during the course of clinical studies, evaluate the stability indicating assays, assess the stability of MEDI-493 following simulated excursions in storage or shipping conditions, compare clinical lots produced by varying manufacturing processes and determine the product shelf-life. These studies demonstrated that MEDI-493 is a robust and stable molecule when stored at for at least two years, and that minor excursions in temperature do not affect the purity or potency of the molecule. Information gained from these studies was used to support condition selection for studies using consistency lots. Process control is monitored by a comprehensive testing program, and demonstrated by validation studies. Quality programs are in place to provide ongoing assessment of the facility (Environmental Monitoring Program), raw materials (raw material control programs), and performance of the process (process testing). Classified areas are routinely monitored for air quality and surface bioburden. This includes measurement of viable and non-viable air particles, measurement of room and equipment bioburden, and identification of viable contaminants. For raw materials there are specifications, inventory management, and testing procedures. In addition, routine monitoring is performed on water, clean steam, and compressed air used in the GMDF. In-process testing is carried out on culture media and purification process solutions. The product stream is monitored through the cell culture, harvest, purification and formulation steps. The validation program encompasses the facility, equipment, process operations, and analytical test methods. Major utilities (e.g. heating-ventilation-air conditioning, clean steam, water, compressed air, CIP system); facility equipment (e.g. glass washer, autoclave, depyrogenation oven); and process-related equipment (e.g. bioreactors, chromatography controller, laminar flow cabinets, cold storage areas, tanks, pressure cans) were validated. Performance qualifications for process solution and product contact equipment include validation of cleaning procedures. Process validations were performed on cell culture, harvest, purification, and formulation process steps; as well as, supporting procedures such as preparation of cell culture medium, and purification or formulation process solutions. Additional purification process validation studies include demonstration of adequate removal of process derived contaminants such as . Validation studies were performed on analytical test methods that support in-process, lot release and stability assessment; as well as, tests supporting the environmental monitoring program, raw material testing, and cleaning qualifications. The is also validated.

Final 0.2 Micron Sterile Filtration, Fill, and Lyophilization - The filtered bulk product is transported at to an offsite contract manufacturer for final sterile filtration, filling, lyophilization, labeling and packaging.

Microbial retention studies were undertaken to test the ability of the to retain *Brevundimonas diminuta* in the presence of the MEDI-493 drug substance. The study was designed based on a recirculation flow rate of MEDI-493, and using a bacterial challenge consisting of 1 x 10^7 *Brevundimonas diminuta*/cm^2. Under these conditions, the minimum flow rate is maintained at with a range of to simulate product/filter contact under pressure for a time in excess of the time actually required for the filtration of the drug substance. Three lots of After the recirculation portion of the experiment, control filters (0.45 micron) were added downstream from the test filters but prior to the collection vessel. Both the control filters and the fluid from the collection vessel were plated, incubated 7 days and observed for evidence of bacterial growth. Lack of bacterial growth in both cases confirm the sterility of the system. Additional control studies indicated that MEDI-493 is not inhibitory to the growth of *Brevundimonas diminuta* and it does not inhibit the ability of the organism to pass through the 0.45 micron control filter. Challenge bacteria were also stained for evaluation of cell morphology, size and purity. The acceptance criteria are that all of the test organism is retained by the in the presence of MEDI-493. The test system must also remain sterile as demonstrated by absence of growth on the plated control filter and in the collection vessel fluid. In addition, the growth conditions for *Brevundimonas diminuta* must yield cells which pass through the 0.45 micron control filter but are retained by the 0.22 micron test filter.

Environmental Assessment - MedImmune requests an exemption under a categorical exclusion in accordance with 21 CFR Part 25.

Fill/Finish Manufacturer - MEDI-493 drug substance manufactured at MedImmune is 0.2 μm filtered into sterile plastic and transported for final sterile filtration and filling into 100 mg vials.

Container/Closure System - The container/closure system for the MEDI-493 lyophilized vialed product consists of vials, stoppers and overseals. This container/closure system was used for Phase II-III clinical studies. The vials are 5cc, Schott, U.S.P./EP type I borosilicate glass. The neck opening is 20 mm D

with blowback design. The product number is and the drawing number is The vials are tubing glass vials manufactured by . The stoppers are 20 mm D stoppers composed of 4405/50 gray butyl rubber formulation in an mold. The product number is and the drawing number is The stoppers are . The stoppers meet U.S.P./EP specifications for extraction characteristics and biological reactivity testing.

Contamination Precautions for Drug Product Manufacturing - The MEDI-493 bulk drug substance is delivered to for final sterile filtration, filling and lyophilization. The sterile filtration uses a filter which is similar to the filter used for the bulk filtration of the drug substance by MedImmune. Sterile filtration occurs in a HEPA filtered Class 100 hood within the filling core. Pre and post use integrity testing of the filter is performed. For filling operations, the components are prepared and sterilized according to validated procedures for the vial washer, autoclave and depyrogenation oven. Product contact items and filling machine parts are dedicated to MEDI-493 and sterilized according to validated procedures. Media fill validations are performed semiannually on each filling line and trained filling personnel perform operations according to validated procedures. Container/closure integrity is validated for the MEDI-493 components using microbial immersion techniques. Sterility testing is carried out in compliance with 21 CFR 610.12 for bulk drug substance and drug product. Air sampling for viable and non-viable particulates is carried out, contact plates are used for surface monitoring and personnel gowning monitoring is performed. Personnel gowning includes a sterile gown, full hood, mask, boots, gloves and goggles.

Description of Methods - Manufacturing is carried out in the Process Development Unit (PDU). The drug product is stored in the PDU,

Sterilization of Bulk - Containers of MEDI-493 bulk are transferred into Component Preparation Room where the bulk is transferred into a sterilized bulk tank in a laminar air flow unit. After sampling the bulk for prefiltration bioburden, the bulk tank is moved to a laminar flow unit located in Equipment Washing Room The filter and tubing are passed out from to the Equipment Washing Room inside the laminar air flow unit through a wall port. The

sterilizing filter is integrity tested in the Aseptic Filling Room. The bulk is then passed through the 0.2 μm filter using nitrogen overpressure into a sterilized bulk tank located in the Aseptic Filling Room. A second integrity test on the sterilizing filter is performed following the filtration. The sterilized bulk is then held in the Aseptic Filling Room until filling begins. Validation of the filter used for sterilization was conducted. Analysis of the product specific bubble point compared to water yielded a bubble point ratio of 1.01, indicating that the MEDI-493 did not alter membrane bubble point properties. Microbial retention testing was conducted using *Brevundimonas diminuta*.

Aseptic Filling - Sterilized stoppers are loaded into the stopper hopper. The sterilized filling syringe and valve assembly are installed in the filling machine. The sterile bulk tank is attached to the filling machine using sterilized tubing. Fill volume checks are performed and any necessary adjustment made. The vials are then filled with sterilized bulk, a stopper is partially inserted into each vial, and the filled vials are discharged into lyophilizer trays. Weight checks are performed as each lyophilizer tray is filled. At the completion of the filling operation, a product reconciliation is performed.

Lyophilization - As each lyophilizer tray is filled with partially stoppered product vials, it is loaded into the prechilled freeze dryer. After all the filled vials have been loaded into the lyophilizer, the door is secured and the freeze drying cycle is begun. At the end of the lyophilization cycle, 0.2 μm filtered medical grade nitrogen is bled into the chamber. The stoppers are fully inserted into the vials by hydraulically raising the lyophilizer shelves.

Detailed Description of Manufacturing Areas at Operations are conducted in multiproduct areas which are licensed for biological product manufacturing under

Component Preparation - Vials and stoppers are washed and prepared in The vials are loaded into a double-doored dry heat depyrogenation oven, and are unloaded directly into The stoppers are loaded into a double-doored steam sterilizer, which is also unloaded into the Aseptic Filling Room. The product is filled into vials, partially stoppered, and lyophilized in Aseptic After lyophilization, the vials are fully stoppered, removed from the lyophilizer, and passed into Finishing for oversealing. Vials are then stored at prior to inspection and labeling.

HVAC - Room Air Supply Air handler PH-3 in the supplies temperature-controlled and humidity-reduced air to the aseptic filling area. Rooms served include Gowning Sterile Filling, Air Lock 123, Equipment Washing Room and Component Preparation. Outside air enters the air handler through prefilters. Room air is supplied through ceiling-mounted terminal HEPA filters. Air is recirculated through low level return ducts. Humidity is reduced by passing incoming air through a chilled water coil to remove moisture. Humidity is reduced to≤60% and is monitored in the return air duct. Room air temperature is maintained at 18-25 ±5°C using hot supplied to heating coils to reheat the chilled air. The temperature in Rooms is maintained at 2°C.

Area Classification - Rooms are designed to meet Class 100,000 conditions. Gowning Room and Aseptic Filling Room are designed to meet Class 10,000 specifications. Within room is a sterile core that provides Class 100 conditions for aseptic filling and loading of the lyophilizer.

From the airlock, personnel may enter either Aseptic Filling Room or the component preparation area. Personnel working in Aseptic Filling Room enter from Gowning Room. The Gowning Room is divided into less clean and clean areas by a bench. In the Gowning Room, operators don sterilized gowning consisting of a face mask, hood, jumpsuit, shoe covers, sterile gloves, and goggles. Personnel working in the component preparation area don clean lab coats, hair covers, shoe covers and enter directly into Component Preparation Room.

Environmental Monitoring - Environmental monitoring is performed by Quality Assurance personnel in the aseptic filling area, component preparation area, and the Gowning Room according to "Environmental Monitoring Procedure." Monitoring includes routine air sampling for viable and non-viable particulates and routine surface microbial sampling in critical areas. Viable and non-viable air particle counts, and surface counts are obtained in conjunction with each fill. Monitoring in the Aseptic Filling Room includes sampling of the gowning of fill room operators. Alert limits are established for all sites and are described in SOP QN017.

Stopper Washer - The stopper washer, located in Component Preparation Room is an automatic washer that cleans stoppers prior to siliconization using a hot Water for Injection (WFI) soak, followed by a detergent wash, and rinsing with WFI. Excess water is removed by spinning. Validation of the washing

procedure included three consecutive washing runs, in which rinse water samples were collected and tested for residual detergent, and a sample of the washed stoppers was taken for bioburden and endotoxin testing. After the washing procedure, the stoppers were siliconized, and additional samples of the stoppers were taken for bioburden and endotoxin testing. Washed and siliconized stoppers showed a bioburden of not more than 5 CFUs/stopper, and an endotoxin level of not more than 0.06 EU/stopper. Rinse water samples contained not more than 1 ppm of residual detergent.

Siliconizer - The stopper siliconizer, located in Component Preparation Room is used to siliconize stoppers using medical grade silicon after washing of the stoppers and prior to sterilization. After development of the siliconization process, the process was validated by preparing three consecutive batches of each stopper size by washing, siliconizing and sterilizing the stoppers. Three simulated filling operations were conducted with each stopper size and the machinability of the siliconized stoppers was found to be acceptable.

Steam Sterilizer - Siliconized stoppers are sterilized in a double-doored steam sterilizer which is loaded in Component Preparation Room and unloaded directly into Aseptic Filling Room The sterilization cycle for the stoppers used for MEDI-493 was validated using three temperature distribution/heat penetration runs with a full chamber using biological challenges (spore strips) and thermocouples distributed throughout the load. Biological challenges showed no growth at the end of exposure, and positive controls (untreated spore strips) yielded expected growth.

Vial Washer - Vials are washed in the vial washer located in Component Preparation Room prior to depyrogenation. The wash cycle consists of alternating hot and cold WFI rinses to the inside of the vials followed by a hot WFI rinse to the inside and outside of the vials simultaneously. Rinses are followed by a 0.2 μm filtered air purge. Washing of vials was validated with three consecutive cleaning runs. Prior to each validation run, a predetermined quantity of vials were spiked with polystyrene microspheres After each cleaning run the pre-spiked, cleaned vials were tested for particulates. Pre and post-run vials were also submitted for microbial and endotoxin testing. The post-rinsed vials showed a greater than 3 log reduction in the number of particles by the washing cycle. The vials showed no detectable endotoxin, and a bioburden level of

Dry Heat Depyrogenation Oven - Vials are depyrogenated in a double-doored dry heat oven which is loaded in component Preparation Room and the depyrogenated vials are unloaded directly in Aseptic Filling Room The depyrogenation cycle for the vials was validated using three consecutive temperature distribution/heat penetration runs. Not less than 9 thermocouples were placed at the corners of the chamber and at the controller Resistance Temperature Device (RTD) to record temperature distribution. Sixteen thermocouples were distributed through the load at the slowest-to-heat points. Endotoxin challenges were performed during the loaded chamber runs using challenge vials located at each of the heat penetration thermocouples. The results obtained from the temperature distribution and heat penetration runs were within the described thermal limits providing the operation with a high degree of sterility assurance. Endotoxin challenges indicated at least a three log reduction in activity.

Filling and Stoppering Machine - Product contact equipment used for aseptic filling of MEDI-493 is either product dedicated or disposable. Product contact equipment includes bulk tanks constructed of 316L stainless steel with sanitary fittings, and 316L stainless steel filling syringes. The filling machine is a single head machine which fills one vial at a time. After each vial is filled, a stopper is automatically partially inserted into each vial. Cleaning of the reusable filling parts is performed manually. The filling parts are then sterilized in the steam sterilizer. Cleaning was validated by taking swab samples after cleaning for residual protein testing, and collecting rinse water samples for residual protein, residual detergent and endotoxin analysis. Swab samples were tested for residual protein using the and protein testing in rinse water samples was conducted using the Lowry Residual detergent was determined using conductivity and total organic carbon (TOC) analysis . Endotoxin testing was conducted by LAL All swab samples were below the detection limit of the Rinse water samples were negative for the presence of protein by the Lowry Peterson assay. Conductivity was ≤ 5 μS/cm, with not more than 1.0 ppm TOC. Endotoxin was not detectable.

Lyophilizer - The lyophilizer is a unit constructed with surfaces of 316L stainless steel designed for lyophilization of aseptically filled product in vials. At the end of the lyophilization cycle, the stoppers are fully inserted into the vials by hydraulically raising the shelves while the chamber is filled with a nitrogen atmosphere. The lyophilizer

chamber is cleaned manually using a series of hot WFI rinses. After cleaning, the unit is steam sterilized in place. The lyophilizer is a multiproduct unit used for other marketed and clinical products in addition to MEDI-493. The cleaning of the chamber for removal of all proteins has been validated using the fluorescamine assay. Validation involves performing a production cycle with product vials and, after unloading the product vials, placing liquid formulated product on specified areas of the lyophilizer shelves, running a shortened cycle to dry the product onto the surface, cleaning the chamber according to Manufacturing Production Record MPR I-1906, then taking swab samples and testing for residual protein using SOP QI156. The cleaning procedure has been shown to remove all detectable protein. Validation of the sterilization cycle for the lyophilizer included three empty chamber temperature distribution runs with biological challenges of *Bacillus stearothermophilus*. The results obtained from the temperature distribution runs were within the defined limits. No viable challenge organisms were recovered from the post-sterilized spore strips; positive controls (untreated spore strips) gave expected growth.

Cleaning and Changeover Procedures - The Aseptic Filling Room and the associated Gowning Room and airlock are sanitized before each fill. Sanitization is performed by operators who are properly gowned, using QA approved sanitizing agents. The filling machine and the barriers surrounding it are sanitized according to Manufacturing Production Records The aseptic filling area of the PDU is used for the aseptic filling of multiple products. Product changeover is conducted according to Only one product may be processed in the Aseptic Filling Room at one time, except that one product may be filled while a second product is isolated in the lyophilizer. At the completion of the filling operation, all materials are removed from the room and the clearance is documented.

Areas for Oversealing and Inspection - Stoppered, lyophilized product vials are passed from Aseptic Filling Room to Finishing Room by conveyer, where overseals are applied. The oversealer is located in Finishing Room and is used to apply crimp type aluminum overseals to glass vials after full insertion of the stoppers. The oversealer is adjustable to apply seals to a variety of vial and stopper sizes. The oversealer was validated by filling depyrogenated product vials with sterile media. The vials were stoppered and then overseals were applied using the established pressure settings. The quality of the overseal was first checked by visual inspection, then the oversealed vials were submitted for testing by a microbial immersion test Following immersion in the microbial bath, the vials are incubated. At the end of the incubation

period, the test vials showed no growth. Visual inspection of the finished vials is conducted in the CMF in Particle Inspection Room 156. Environmental Monitoring Oversealing, labeling, and packaging areas are unclassified and are not included in the environmental monitoring program. Product vials are closed before entering these rooms.

Description of Methods - After the stoppers are fully inserted into the vials, the vials are removed from the lyophilizer. Operation of the oversealer is checked, then vials from each lyophilizer tray are loaded on the accumulator in the Aseptic Filling Room and fed out to the oversealer located in Finishing Room. The oversealed vials are loaded into trays which are labeled with filling tray number, lot number, and date oversealed. The labeled trays are loaded into cages, which are then locked. The outside of each cage is labeled with the product name, lot number and date. A vial reconciliation is performed at the end of the oversealing operation. The cages are then stored at until inspected. For inspection, the cages are removed from storage and moved into Particle Inspection Room in the CMF. Each vial is inspected against a white and a black background for defects. Defective vials are removed. The inspected vials are placed back into the cages and the cages are stored at 2-8°C until labeled.

Areas for Storage Prior to labeling, product can be stored in the PDU, CMF, or V Warehouse. PDU Unlabeled finished products are stored in trays in locked metal cages or cartons sealed with tape. The trays are labeled with lot number, date of fill and tray number. The cages and cartons are numbered consecutively and labeled on the outside with product name, lot number and date of fill. Each lot of product has an inventory control sheet. The cages and cartons are stored in locked 2-8°C walk-in refrigerators in the manufacturing area.

Areas For Labeling and Packaging - Labeling and packaging are performed in the PDU in Finishing Room and Product Cartoning Room. Gowning required in the labeling and packaging rooms includes a plant uniform and a hair cover. Upon receipt from approved labeling vendors, printed packaging materials are sampled, inspected, counted, and approved by the Quality Control Raw Materials Department. A label inventory form is generated for each item of labeling that tracks the amount of labeling issued to Manufacturing. The labeling is stored in a locked area in the CMF labeling area under the control of Quality Assurance. Labels are applied to product vials by the Avery labeling machine. The machine prints the lot number and expiration date on the labels and then applies the label to the vial. A 100% inspection of labeled vials is performed on-line by Manufacturing, and a statistical sample of product vials is inspected by Quality Assurance. Labeling reconciliation and final product vial reconciliation are done concurrently to assure

that all labels are accounted for. Stringent changeover procedures incorporate documented line clearances that are double checked both before and after labeling operations. Labeling is compared to an approved copy of the labeling and its part number before operations commence. Packaging is performed using approved printed packaging materials in PDU Product Cartoning Room 128.

- Unlabeled finished products are stored in trays in locked metal cages or cartons sealed with tape. The trays are labeled with lot number, date of fill and tray number. The cages and cartons are numbered consecutively and labeled on the outside with product name, lot number and date of fill. Each lot of product has an inventory control sheet. The cages and cartons are stored in a locked, limited access walk-in refrigerator (Room in the manufacturing area.

The is a GMP warehouse used for receipt of incoming goods and storage of raw materials, intermediates, and final product prior to shipment. Segregated areas are provided for quarantined and released goods. Controlled temperature storage for formulated bulk MEDI-493 and for lyophilized product vials are provided.

cc: Anderson, HFM-591