M E M O R A N D U M

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Biologics Evaluation and Research

TO: Administrative File STN: 125400/0 (allogenic cultured keratinocytes and fibroblasts in bovine collagen)

FROM: Qiao Bobo, Ph.D., Biologist, CBER/OCBQ/DMPQ/MRB II, HFM-676

THROUGH: Chiang Syin, Ph.D., Chief, CBER/OCBQ/DMPQ/MRB II, HFM-676

cc: Mark Lee, Ph.D., Biologist, CBER/OCTGT/DCGT/CTB, HFM-715
Terrolyn Thomas, RPM, OCTGT/RMS, HFM-700

FACILITY: Organogenesis Inc., Canton, Massachusetts
(License No. 1863; FEI: 1000148471)

SUBJECT: Review Memo – Biologics License Application (BLA) for allogenic cultured keratinocytes and fibroblasts in bovine collagen

ACTION DUE DATE: March 12, 2012

RECOMMENDED ACTION:

I recommend approval of this BLA with a post-market commitment to submit the ----b(4)---- ---------- following the revised protocol you submitted on February 24, 2012 no later than June 30, 2012.

REVIEW SUMMARY:

The recommended action noted above is based on:

- Review of DMPQ-related information included in the Biologics License Application (BLA) and its amendments (STN 125400/0).
- The Pre-license inspection (PLI) that was conducted October 3-7 at Organogenesis' Canton, Massachusetts site.

The original BLA submission has very limited information on the facility and equipment. On July 7, 2011, DMPQ sent a list of deficiencies (Information Request) to Organogenesis through the RPM. On July 20, 2011, Organogenesis submitted an amendment including major revisions to the original BLA in response to the deficiency list. Based on the review of original submission and the amendment submitted on July 20, 2011, I had three additional Information Requests and the responses were acceptable (see **INFORMATION**

REQUESTS Section for details).

Detailed information related to PAI is summarized separately in the 483 Response Memo and the Establishment Inspection Report (EIR).

All review issues and inspection issues have been resolved. Therefore, I recommend the approval of Organogenesis' BLA for allogenic cultured keratinocytes and fibroblasts in bovine collagen, Apligraf (oral) under STN 125400/0.

CHRONOLOGY OF EVENTS:

May 13, 2011	BLA submitted
May 16, 2011	BLA assigned to DMPQ reviews
July 7, 2011	First Information Request (deficiency list) sent from DMPQ through RPM
July 20, 2011	Response to the first Information Request (deficiency list) submitted
January 26, 2012	Telecon with firm discuss additional inspection and review issues-second Information Request from DMPQ, followed by e-mail
February 13, 2012	Telecon with firm discuss additional inspection and review issues – third Information Request from DMPQ followed by e-mail
February 17, 2012	Response to January 26, 2012 telecons e-submission (Copies of the responses were e-mailed to the FDA earlier as the information became available)
February 22, 2012	Response to February 13, 2012 telecon submitted (Copies of the responses were e-mailed to the FDA earlier as the information became available)
February 24, 2012	Follow up response to February 13, 2012 telecon submitted
February 27, 2012	Fourth Information Request from DMPQ for additional information
March 1, 2012	Response to February 27, 2012 Information Request received
March 12, 2012	**Action due date**

INTRODUCTION:

On May 13, 2011, Organogenesis, Inc. (Organogenesis) submitted a Biologics License Application (BLA) for allogenic cultured keratinocytes and fibroblasts in bovine collagen, referred to as Apligraf (oral) in this memo (BLA STN 125400).

Apligraf (oral) is the same final product as the commercially available Apligraf (PMA P950032) but for oral indication. Apligraf is indicated for the treatment of venous leg and diabetic foot ulcers that have not healed within 3 to 4 weeks, respectively, with conventional therapies. The proposed indication for Apligraf (oral) is for the treatment of surgically created gingival and alveolar mucosal defects in adults. Apligraf (oral) is intended for use by periodontists and oral surgeons.

PRODUCT DESCRIPTION:

Apligraf (oral) is a biologic device combination consisting of an upper layer that is made of human keratinocyte (HEP) cells and a supporting lower layer constructed of bovine-derived collagen, human extracellular matrix proteins, and human dermal fibroblast (HDF) cells. The human cells are derived originally from donated human neonatal male foreskin tissue. The layers adhere as one unit to form the product.

Apligraf (oral) is supplied ready for use and intended for application in a single patient. It is kept on a semi-permeable synthetic membrane, which separates it from an agarose nutrient medium within a transparent shipping tray. The final product is packaged within a heat-sealed, heavy-gauge polyethylene transparent bag (polybag) containing an atmosphere of approximately 10% CO_2 at time of packaging. Apligraf (oral) should be kept in the sealed polybag at 68°F to 73°F (20°C to 23°C) in its shipping box with all insulating components intact until use.

ESTABLISHMENT DESCRIPTION:

Two commercial products, Apligraf® (a living bi-layered substitute) and ---b(4)----------
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---------- Apligraf (oral) and does not come into contact with it. Dedicated personnel, gowning, equipment and materials are utilized in the –b(4)--- areas. Apligraf is exactly the same product as Apligraf (oral). It is manufactured using identical materials and processes as Apligraf (oral). ----b(4)----------
----------. –b(4)--- is manufactured at the same location as Apligraf (oral).

Organogenesis manufactures at the 150 Dan Road, Canton, Massachusetts facility the finished product Apligraf (oral) and its starting materials: Type I bovine collagen, HDF and HEP cells. All production related activities, including testing, production, labeling, product release, documentation, and distribution are performed at the Canton, Massachusetts facility.

Organogenesis also has a facility located at 85 Independence Drive in Taunton, Massachusetts 02780. This facility is designed for the receipt, initial inspection, and storage of incoming raw materials (not including chemicals or tissues) and manufacturing supplies. The Taunton facility manages inventory control per the Canton facility requests. In addition to these activities, the Taunton facility also is responsible for the assembly of shipper boxes. The FDA Establishment Identifier number (FEI) number for the 85 Independence Drive facility in Taunton, Massachusetts is: 3006187899. This facility is currently registered as a Device Establishment and an HCTP establishment.

MANUFACTURING PROCESS AND CONTROL:

The Apligraf (oral) drug product consists of the following components: mature –b(4)-construct (drug substance), agarose shipping medium and carbon dioxide (CO_2). It is a -b(4)------ process therefore the drug substance, the –b(4)-- construct, and its related finished product Apligraf (oral) are manufactured ------b(4)----------
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3 Pages determined to be not releasable:

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PROCESS VALIDATION:

Retrospective Process Validation for Apligraf Manufacturing

Organogenesis conducted a retrospective validation by evaluating –b(4)-consecutive commercial production lots over a 3-month period. All –b(4)- lots met final release criteria for potency and safety. There were no lots rejected for failing to meet release requirements; however, there were some instances of deviations in which in-process specifications were out of range. I would defer the evaluation of process validation to the product reviewer. Prior to final product release and shipment, all in-process samples must be on-test and negative to date. Furthermore, sterility and bioburden samples from final product must also be on-test and negative to date, prior to product release and shipment.

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FACILITY, EQUIPMENT, AND UTILITIES:

Heating, Ventilating, and Air Conditioning Systems (HVAC)

Approximately –b(4)- of the makeup air is –b(4)-- and –b(4)- is –b(4)---------. The makeup air is provided through a ----b(4)---------- which conditions air for room temperature and relative humidity (RH) and delivers the air to various classified spaces through ---b(4)-------- to the ducts. Room temperature and RH are controlled and set to operator comfort with an RH set point of –b(4)- and a temperature range of –b(4)-----. This air is monitored and controlled for temperature and relative humidity by a Building Monitoring Control System (BMCS).

The manufacturing space includes Class ----b(4)---------- cleanrooms and controlled areas. Production activities are limited to the appropriately classified area. **Table 3** lists the room classification for each area from tissue processing to Apligraf (oral) final product packaging.

Table 3 Room Classification for Apligraf (oral) Production

AREA	ROOM CLASSIFICATION
----------b(4)----------	---b(4)---------
------b(4)----------	---b(4)----------

AREA	ROOM CLASSIFICATION
----b(4)----------	--b(4)----
----------b(4)----------	--b(4)-----
-----b(4)----------	--b(4)-----
----------b(4)----------	---b(4)-----

Organogenesis re-certifies terminal High Efficiency Particulate Air (HEPA) filters in cleanrooms –b(4)--- for all Class ------b(4)---------- ------sterility suites, and support areas. Testing includes -----b(4)---------- ----------. All pressure differentials are constantly monitored, recorded by the Building Management and Control System (BMCS) and meet minimal pressure specifications. During the PLI, I verified that Testing and Certifications were performed for the Class ---------- -----b(4)---------- ---------- sterility suites, and support areas ---b(4)------

The HVAC system was qualified and validated based on the rooms (areas) that the air supplies. IQ/OQ and PQs were performed for the HVAC system (s) and environmental monitoring performance qualifications (EMPQs) were performed for specific rooms within the facility.

During the PLI, Organogenesis presented the smoke study DVDs and reports for all Class -b(4)- suites. We found the smoke studies inadequate as cited in **FDA Form 483 Observation 3a** "The smoke study for Class –b(4)- cleanrooms under the dynamic conditions is inadequate in that it did not simulate the actual or worst-case conditions of the production." In response to this observation, Organogenesis has performed revalidation for Class –b(4)- smoke studies under dynamic, worst-case conditions and the results passed the acceptance criteria. The revalidation study reports for all –b(4)-------- suites were submitted on December 30, 2011 and the response is considered acceptable.

During the PLI, I found that the EMPQs for Class –b(4)- and Class –b(4)- cleanrooms were not adequately designed and executed. Specifically, the sampling locations, sites, frequencies and duration for viable and non-viable airborne particles were not scientifically justified. This was cited as **FDA Form 483 Observation 3c**. In response to this observation, Organogenesis performed a retrospective analysis of routine Environmental Monitoring (EM) in the 150 Dan Road production Class –b(4)---------- cleanrooms. The analysis confirmed that additional baseline sampling was required for Class –b(4)- work surfaces to provide a further basis for routine monitoring beyond the original baseline data. The additional studies were performed and submitted on Dec. 31, 2011. This observation is considered closed.

Water Systems

Water for Injection System

The Water for Injection (WFI) system is a PLC controlled ---b(4)----------, located in the –b(4)-- room –b(4)---- of the 150 Dan Road facility. The feed water is from the –b(4)---------- system. The WFI Distribution system is an –b(4)---------- distribution system with a –b(4)- gallon

storage tank and consists of ------b(4)---------- (---b(4)----). There are a total of –b(4)- WFI use-points located in the Class ---b(4)---------- cleanrooms.

----b(4)--------- ----------

WFI is utilized by Manufacturing in the preparation of –b(4)---------- operations, as required by procedure. For routine monitoring, all use-points are sampled and tested at a frequency of b(4) times per b(4), which coincides with the manufacturing schedule for when the WFI system is in use for preparation of –b(4)----------. The WFI system is maintained and tested in accordance with –b(4)---------- WATER FOR INJECTION (**Table 4**). Only action limits are used for WFI system. During PLI, I asked Organogenesis why the alert limits were not established, and Organogenesis said that the alert limits for WFI were being implemented **(Discussion Item #QB-06 in EIR)**. The WFI alert limits have been established since the PLI (see **INFORMATION REQUESTS Section, Subsections February 27, 2012 Information Request Q1** for details).

Table 4 Routine Tests Performed for WFI System

TEST	LIMITS (ACTION)
Bioburden by -- b(4)--	--b(4)--------
Endotoxin by -- b(4)--	--b(4)-------
TOC by ----b(4)----------	--b(4)----
Conductivity–-------b(4)----------	--b(4)--------

Endotoxin, Bioburden, Total Organic Carbon (TOC), and Conductivity data for WFI in May-July 2011 were provided in the submission and the data appear acceptable.

During PLI, I reviewed the trending analysis reports for WFI for Jan-Dec 2010 and Jan-June, 2011, and found no objectionable conditions.

Purified Water System

The USP Purified Water Treatment System (PW) is a ---b(4)---------- system located in the –b(4)---- room –b(4)---- of the 150 Dan Road facility. The service water is from the ---b(4)----------. PW supply is utilized by Manufacturing and Quality Control for ----b(4)----------

----------. The PW system is maintained and tested in accordance with ---b(4)---------- PURIFIED WATER.

----b(4)------ ----------

There is a total of –b(4)-- PW use-points located in the Class –b(4)- and Class –b(4)- cleanrooms, as well as in other areas of the facility (e.g., QC laboratory). For routine monitoring, all use-points are sampled and tested by Quality Control at a frequency of –b(4)---------. Only action limits are used for PW, but the alert limits were being implemented at the time of inspection. PW system is maintained and tested in accordance with –b(4)- requirements for PURIFIED WATER (**Table 5**). The PW alert limits have been established since the PLI (see **INFORMATION REQUESTS Section, Subsections February 27, 2012 Information Request Q1** for details).

Table 5 Routine Tests Performed for Purified Water System

TEST	LIMITS (ACTION)
Bioburden by b(4)	----b(4)----------
TOC by b(4)	--b(4)-----
Conductivity b(4)	---b(4)----------

Endotoxin, Bioburden, Total Organic Carbon (TOC), and Conductivity data for PW in May-July 2011 were provided in the submission and no excursions were found during that time. During the PLI, I reviewed *FW-UPW2-001, USP Purified Water –b(4)---- System Cleaning and Maintenance (Revision 2.0, Effective Date February 28, 2011)* and verified that the record of changing the –b(4)---------- filters was up to date per FW-UPW2-001. Also, during the PLI, I reviewed the trending analysis reports for PW for Jan-Dec 2010 and Jan-June, 2011, and found no objectionable conditions.

Clean Steam System

A –b(4)---------- Clean Steam Generator is used at the 150 Dan Road facility in order to produce up to –b(4)-- of clean steam (at –b(4)----- from -----b(4)----------. The clean steam is distributed via b(4) stainless steel piping to the points of use, which includes ---b(4)----------

----b(4)----- ----------

---------b(4)-------- ----------

--b(4)---- ----------

The Clean Steam system is maintained and tested in accordance with b(4) requirement for PURE STEAM (**Table 6**). Procedure requires –b(4)--- sampling and testing of –b(4)------ collected from the Clean Steam system. Only action limits are used for Clean Steam. The action limits have not been established due to lack of long term data. Organogenesis stated that the action limits will be established by December 2012 (see **INFORMATION REQUESTS Section, Subsections February 27, 2012 Information Request Q1** for details).. Data collected during July 2011-February 2012 met the acceptance criteria. An inspection follow-up is recommended to verify the establishment of action limits for the Clean Steam system (see **INSPECTION FOLLOW-UP Section**)

Table 6 Routine Tests Performed for Pure Steam System

TEST	LIMITS (ACTION)
Bioburden by –b(4)-	----b(4)-----
Endotoxin by –b(4)-	--b(4)----
TOC by –b(4)-	--b(4)----
Conductivity –b(4)-	---b(4)----------

Liquid Nitrogen (LN_2)

The LN_2 system is designed for the supply of liquid nitrogen (LN_2) to selected use points within the manufacturing and laboratory departments. The LN_2 storage tank located in the back of the facility is an –b(4)---------- control panel with associated valves and instrumentation.

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---------- ----b(4)---------- ----------.

----b(4)---- ----------

--b(4)--- ----------

All acceptance criteria have been met.

Carbon Dioxide (CO_2) Storage and Distribution System

The CO_2 storage and distribution system consists of a tank having a maximum holding capacity of –b(4)- of Liquid CO_2 at –b(4)---------- and feeds a supply of CO_2 gas for all -b(4)---------- within the facility and to the packaging system for final packaging of the drug product.

The distribution system is constructed of –b(4)----------. All points of use are protected by –b(4)----------; the system is compliant with ASME code section B31.3 chemical plant piping guidelines. Pressure in the distribution portion of the system is maintained at –b(4)- psi.

Completion of the IQ/OQ for the Carbon Dioxide Storage and Distribution System was performed according to VFR-302118 and VFR-IOQ-EU- CO_2-01-028. The acceptance criteria and results for the validation are listed in **Table 7** below.

Table 7 CO_2 System Validation Acceptance Criteria and Results

ACCEPTANCE CRITERIA		RESULT
Verification of System and Component Installation		Completed
--b(4)----------	--b(4)--- ---------- ---------- ----------	----b(4)----------
--b(4)---------- ----------	--b(4)---------- ----------	---b(4)----------
--b(4)---------- ----------	---b(4)---------- ---------- ----------	---b(4)----------

During the PLI, I requested the firm to provide data for -b(4)- integrity tests for –b(4)- used in all –b(4)---------- within the facility and to the packaging system for final packaging of the drug product. Organogenesis provided the –b(4)-integrity test record for the packaging

system, but no –b(4)- integrity test was performed for –b(4)----------. However, it is noted that all ---b(4)---------- have a –b(4)--- which is certified –b(4)-

Computer Systems

Computerized systems at Organogenesis are used for analytical instrument control, data collection, and data storage in a secured environment. Specific systems are listed below:

- ---------b(4)----------
- -b(4)-- ----------
- --b(4)----------
- --b(4)----------
- --b(4)----------

All systems are validated per approved Organogenesis procedures.

ENVIRONMENTAL MONITORING:

Routine Environmental Monitoring Program

Organogenesis has an Environmental Surveillance Program (ESP) is governed by –b(4)----------, "Environmental Surveillance Program", which specifies the procedures to be followed for testing frequency, investigations, reporting requirements and alert/action limits.

Alert and action levels are set for particle, air and surface microbial samples. **Table 8** shows the Alert/Action Limits (revised after FDA PLI) for viable/nonviable air, surfaces, and personnel in Class –b(4)---------- ---------- areas, as well as frequency of testing in each area under dynamic conditions

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b(4)

[b(4)]

During the inspection, the deficiency in EM program was cited in **FDA Form 483 Observation 2.** In response to **FDA Form 483 Observation 2b**, regarding monitoring of Class -b(4)---, in the final response submitted on Dec. 30, 2011, Organogenesis stated that the company revised the associated SOP *QCP-094 Environmental Monitoring Program-Class –b(4)-------Areas, (Revision 10.0, Effective Date: 29 December 2011)* to initiate routine monitoring of non-viable particulates in Class –b(4)----- at a frequency of –b(4)---------- in accordance with the most current version of ------–b(4)---- However, I found that Organogenesis' SOP *QCP-094 Environmental Monitoring Program-Class –b(4)-------- Areas, (Revision 10.0, Effective Date: 29 December 2011)* was not consistent with

Organogenesis' response to this observation. QCP-094 indicates that the total particle monitoring in –b(4)---------- is monitored –b(4)-------- and that the –b(4)---------- are monitored for total particles –b(4)----------. I asked the firm for clarification during the January 26, 2012 teleconference and, in a follow-up e-mail, I pointed out the title of the SOP did not match the content which includes monitoring of the Class -b(4)----- and b(4). On February 17, 2012, Organogenesis responded with another revision of the SOP defining the –b(4)------- ---------- (for processing of ---b(4)----------) and the –b(4)------ as –b(4)---------- --------- (-----b(4)----------). The revised SOP is now *QCP-094 Environmental Monitoring Program, Class –b(4)- Areas, Class ---b(4)---------- (Revision 12.0, Effective Date: 15 February 2012).*

In response to **FDA Form 483 Observation 2a**, regarding monitoring of Class –b(4)- cleanrooms, Organogenesis revised the associated SOP, *QCP-094 Environmental Monitoring Program, Class –b(4)- Areas, Class ---b(4)----------,(Revision 12.0, Effective Date: 15 February 2011)* to increase the frequency of monitoring of viable and non-viable particles in Class –b(4)- cleanrooms from –b(4)---------- to –b(4)--------- for Class –b(4)--- cleanrooms surrounding Class –b(4)- areas.

Environmental Monitoring Data

Environmental data for the month of May 2011 were submitted for each classified area (---b(4)----------, respectively) for Non-Viable Air, Viable Air, and Surface. A summary of the excursions is presented below.

In Class b(4), there was one (1) action level excursion for a surface (Floor/Suite b(4) Sample No. b(4), 7 cfu; gram (+) rods, *Bacillus cereus*) which occurred on May 4, 2011. Organogenesis stated that a cross-functional meeting was held on the day the excursion was reported to assess potential product impact and corrective and preventive actions. Briefly, affected lots and companion lots held in-house were placed on quarantine pending additional testing, as required by procedure, which includes additional bioburden sampling. As a corrective measure, the affected areas were cleaned and the operator was observed by the supervisor. The preliminary product assessment was that there was no product impact based on all in-process bioburden and sterility samples being negative, including additional –b(4)- samples and b(4) bioburden/sterility samples from the packaging operation. All quarantined lots were released after additional testing was completed and shown to be negative for microbial growth.

In Class –b(4)- there were no action level excursions. In Class –b(4)- there was one (1) action level surface excursion (-b(4)---- Cold Room/b(4); 1 cfu; mold) on May 17, 2011. Organogenesis stated that it was determined that the –b(4)---- Cold Room/b(4) was cleaned the night following sampling and was cleaned again in response to this excursion. There was no product impact.

During the PLI, I reviewed the trending analysis reports for environmental monitoring prepared for Jan-Dec, 2010 and Jan-June, 2011.

For Class b(4)areas during 2010, a total of –b(4)- non-viable air, b(4) viable air, -b(4)- surfaces, -b(4)- equipment (settling plates), and –b(4)- personnel (excluding QC) samples were collected and tested. A total of 8 action limit excursions and 25 alert limit excursions occurred. Investigations were conducted for the excursions and microorganism ID was performed for viable excursions. The overall EM excursion rate based on a total of –b(4)- samples was almost zero.

For Class –b(4)- areas for the 6 month beginning in January 2011, the overall EM excursion rate based on a total of –b(4)- samples was almost zero (totally 3 action limit excursions and 14 alert limit excursions occurred).

For Class b(4) areas during 2010, the overall EM excursion rate based on a total of –b(4)- samples was 0.1% (totally 4 action limit excursions and 29 alert limit excursions occurred).

For Class b(4) areas for the 6 month beginning in January 2011, the overall EM excursion rate based on a total of –b(4)- samples was 0.1% (totally 13 action limit excursions and 8 alert limit excursions occurred).

The data appear acceptable.

EQUIPMENT

-----b(4)----------

----b(4)---- ----------

----b(4)--- ----------

Controlled Temperature Environments

Multiple refrigerators, incubators, cold and warm rooms, and freezers including liquid nitrogen storage tanks are installed throughout the 150 Dan Road facility. All units provide controlled and monitored conditions for cell bank storage, product storage, sample storage, reagent storage, and manufacturing operations. The use, maintenance, and validation of the units are defined in approved procedures and protocols.

1 Page determined to be not releasable:

b(4)

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Autoclave

---b(4)---- ----------

---b(4)--- ----------

Autoclaves are monitored ---b(4)--- ----------

IQ/OQ validation of all autoclaves (--b(4)----------) has been completed as per their specific equipment protocol. The autoclave performance qualifications were designed particular to the load being sterilized. Sterilization was verified with a combination of Biological Indicators (BI's) and thermocouples placed in challenge locations within the load using half cycle approach.

During the inspection, I reviewed the performance qualification reports for all –b(4)- production autoclaves and no objectionable conditions were found. I also reviewed the validation report for establishing hold time of autoclaved products during the PLI. The study supports up to b(4)days sterile hold time.

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b(4)

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CROSS CONTAMINATION PRECAUTIONS

Cleaning and Sanitization

Organogenesis has procedures in place for cleaning of cleanrooms and equipment. The disinfect effectiveness study (ORGANO-001 “Disinfectant Study Using –b(4)--------
------- for Organogenesis, Inc”) was performed using b(4) disinfectants---b(4)----------
---------- representative surfaces ---b(4)---------

---------- microorganisms were used in this validation including –b(4)-ATCC microorganisms per ----b(4)----------
---------- “in-house” isolates representing flora in the Organogenesis facility. All acceptance criteria were met for all disinfectants relative to microbial log reduction –b(4)---- on all surfaces after contact time exposure for all tested microorganisms.

During the PLI, I verified that all disinfectants listed in routine sanitization procedure –*b(4)------- Clean Room Sanitization Process (Revision 7.0, Effective Date July 2, 2011)* were included in the disinfectant effective study.

During the PLI, we observed the manufacturing process and found the operators did not follow aseptic practice which resulted in **FDA Form 483 Observation 1a** as below:

"Observation 1. Procedures designed to prevent microbiological contamination of drug products purporting to be sterile are not strictly followed. Specifically,

a. During the packaging process of the final product in Class b(4) cleanroom, operators were observed repeatedly touching their hands and resting their arms on the working bench where aseptic processing was performed without sanitization."

Organogenesis responded with revised SOP that requires sanitization of gloves, performance of QA auditing and implementing Aseptic Training Program revision. The response is acceptable.

Area Clearance and Changeover

Organogenesis stated that cleanrooms and production equipment are cleaned after completion of manufacturing. Equipment such as –b(4)----------. is also cleaned before use. Line clearance is performed before each manufacturing process using line specific check lists to ensure that the manufacturing area is free of materials from the previous lot. Line clearance also includes verification of cleaning procedures for production equipment and premises.

Prior to use in production, the identity of raw materials is verified and the release status is checked. In addition, the identity and cleanliness status of equipment used in manufacturing process are verified and documented. Before packaging commences, the identity of the container/closure system components is verified and documented. Personnel conducting area cleaning and clearance procedures are trained accordingly.

Any deviations that occur during area cleaning are addressed, investigated, and documented. Personnel are trained in procedures that prevent cross-contamination, including proper gowning procedures, material and product flow, aseptic handling, handling of product waste, etc. Gowning and personal sanitization procedures are in effect and are followed by all personnel entering the manufacturing area.

The procedure for line clearance is –b(4)-------00521, "General Clearance Control Procedure," which describes line clearance requirements for a work station prior to and after each manufacturing lot is processed. The procedure that details segregation controls is *–b(4)------00903, "Segregation Controls for Processing Study Material*," which describes the requirements for segregation of a work station prior to and after each non-clinical or clinical manufacturing lot is processed.

Containment

----b(4)----------

------b(4)----------

----b(4)----------

-----b(4)-----

----b(4)----

ENVIRONMENTAL ANALYSIS:

Organogenesis is claiming categorical exclusion under 21 CFR 25.31(c), for Biological License Application (BLA) of Apligraf (oral). Section 25.31 (c) provides for a categorical exclusion regarding an action of a BLA, for substances that occur naturally in the environment when the action does not alter significantly the concentration or distribution of the substance, its metabolites, or degradation products in the environment. In the case of Apligraf (oral), Organogenesis stated that the product is comparable to the occlusive dressings used for the current and intended indications and its degradation products are environmentally innocuous and typically found in normal human waste streams. The primary component of Apligraf is –b(4)---------- and all other components are derived from natural sources in an unaltered state. This product is readily and completely biodegraded.

A separate Categorical Exclusion memo is added to the file.

INFORMATION REQUESTS:

<u>July 7, 2011 Information Request (Deficiency List):</u>

The original BLA submission has very limited information on the facility and equipment. On July 7, 2011, DMPQ sent a list of deficiencies to Organogenesis through the RPM. On July 20, 2011, Organogenesis submitted an amendment including major revisions to the original BLA in response to the deficiency list. The responses to this deficiency list are not itemized here as the information was massive and incorporated into different sections of the submissions. All the requested information was submitted. Requests for additional information based on review of the original BLA and this amendment are included in **Subsections January 26, 2012 Information Request , February 13, 2012 Information Request and February 27, 2012 Information Request**.

Below is the deficiency list from DMPQ sent on July 7, 2011 (in bold).

The information submitted in the Appendices 3.2.A.1 Facilities and Equipment and Sections relevant to manufacturing processing and processing control are considered significantly deficient. We recommend you reference FDA *Guidance for Industry: content and format of Chemistry, Manufacturing and Controls Information and Establishment Description Information for a Vaccine or Related Product* (January 1999) for the content and format to be submitted in this section. The following are some specific items that you should include in the submission.

1. **Establishment Description**

    a. **Water systems and clean steam system**

    - **Submission should include a validation summary of water systems and clean steam system. The summary should contain:**
        - **A narrative description of the validation process (or protocol) including acceptance criteria**
        - **Certification that installation qualification (IQ) and operational qualification (OQ) have been completed**
        - **The length of the validation period**
        - **The parameters monitored and tests performed**
        - **The frequency of monitoring each point of use during the validation period**
        - **A validation data summary**
        - **An explanation of all excursions or failures, including deviation reports and results of investigations.**
    - **Submission should include a narrative description of the routine monitoring program for your water systems and clean steam system, to include:**
        - **The tests performed**
        - **The frequency of testing**
        - **The alert and action limits used**
        - **A summary of actions to be taken when limits are exceeded**

- **Routine water monitoring data and summary.**

b. Heating, ventilation and air conditioning systems (HVAC)

- **In addition to validation summary, the submission should contain:**
  - **The number and segregation of the air handling units (AHU) including a legible diagrams showing the AHU segregation, room classification and pressure differential in the processing area**
  - **Whether air is single-pass or recirculated**
  - **Any containment features and air change rate**
  - **Description of HVAC system qualification process, action and alert limits, routine monitoring program, and corrective actions when limits are exceeded**
  - **Validation results, protocol number and summary on HVAC system**
  - **Results, protocol number and summary on cleanroom and Class ------ b(4)----- qualification**
  - **Data, protocols and summary of routine environmental monitoring.**

c. Liquid Nitrogen, CO_2 and BMC systems

- **The submission should contain data, protocol number and summary of these utility system validations.**

d. Contamination/cross-contamination issues

- **A detailed list of equipment, including single-use and reusable, dedicated and shared for manufacturing and QC test should be submitted (information can be included in the Equipment section).**
- **For dedicated equipment, cleaning procedures and methods should be submitted, including information on the validation procedures for the removal of product and cleaning agents, as well as the sampling methods and analytical methods.**
- **For shared equipment: the submission should contain:**
  - **A brief description of the cleaning procedures and cleaning reagents**
  - **A rationale for the cleaning procedures chosen which addresses their effectiveness for the residual products to be removed**
  - **A validation report describing the cleaning validation procedures for removal of product residues and cleaning agents. The report should identify the sampling and analytical methods used and address their sensitivities and specificities**
  - **Validation data, protocol number and summary of cleaning and sanitization of the cleanroom and equipment.**

- **Containment features such as air pressure differentials, airlocks, and segregation of air handling units should be submitted.**

- **Organogenesis stated that multiple products are manufactured in the facility, and the -----b(4)---------- Please specify whether multiple products will be produced on a campaign or concurrent basis. Please provide a description of the in-process controls, physical and procedural controls performed to prevent or identify contamination, cross-contamination and mix-up.**

- **Protocols (such as changeover and line clearance) should be submitted.**

- **For cell banks, the submission should contain the locations of cell line storage, identification and segregation of cell lines, and validation of integrity of storage vials or ampoules.**

e. Sterilization and depyrogenation:

- **The submission should contain:**

  - **A description of the sterilization and depyrogenation equipment and process**

  - **Data, protocol number and summary of qualifications for autoclave and depyrogenation.**

  - **Relevant Performance qualification reports.**

f. Equipment

- **The submission should contain data, protocol number and summary of manufacturing and QC equipment qualifications.**

g. Computer systems

- **Submission should contain information on computer systems that control critical manufacturing processes. Information should include:**

  - **Developer of the system**

  - **List of computer-controlled manufacturing steps**

  - **Description of the validation process and validation summary**

  - **Deviation reports and explanation of failures, including investigations**

  - **Validation data, protocol number, and summary.**

2. Manufacturing Process and Process Control

a. The manufacturing process flow chart should contain:

- **In-process holding steps, including time and temperature limits**

- **Methods used in product transfer between steps or between equipment, areas, or buildings**

- **Computer-controlled steps should be identified**

b. The submission should contain a list of all in-processing endotoxin and bioburden tests with sampling procedures, test methods and acceptance criteria

c. The submission should contain a summary of method validation and qualification for the microbiological assays such as sterility, endotoxin, bioburden, and preservative effectiveness studies.

3. Container/Closure System

a. The submission should contain a summary of methods and results of the following studies:

- **Container closure compatibility with the drug product**
- **Biocompatibility, toxicity and biological tests**
- **Container closure integrity testing**
- **Leachable and extractable studies**
- **Validation report for sterilization of primary and secondary packaging materials**

4. Environmental Assessment

You claimed a Categorical Exclusion from an Environmental Assessment under 21 CFR 25.24(e)(4). The referenced regulation is no longer effective. A request for a Categorical Exclusion with the basis as outlined in 21 CR Part 25.31(a), (b) or (c) should be submitted.

<u>January 26, 2012 Information Request:</u>

On January 26, 2012, DMPQ and the product office had a telecon with the firm to discuss inspection related and review related questions. The firmed submitted the responses on February 17, 2012. Below is a list of review related DMPQ questions (in bold), summaries of firm responses (in plain text) and DMPQ comments (in bold and Italic).

DMPQ Question 1a:

1. Your heat sealer validation runs consisted of ----b(4)---- ----------
----

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a. For CO_2 composition, please clarify how the CO_2 composition was verified to meet specification of –b(4)-------- How was the test sensitivity established?

Summary Response to Review Question 1a:

CO_2 composition was verified by ----b(4)----------:

[b(4)]

[b(4)]

-----b(4)--- ---------- ----------

DMPQ Comment: The information provided assurance that other CO_2 measures are in place in ---b(4)----------. The response is acceptable.

DMPQ Question 1b:

b. For seal integrity, you stated that ---b(4)---------- ----------. How was the test sensitivity established? The test should be sensitive enough to detect minute leaks.

----b(4)----------

----b(4) ----------

----b(4)---- ----------

DMPQ Question 1c:

c. For sterility test, please provide information supporting microorganism growths under the same condition as the ---b(4)--- ----- ----------

Summary Response to Review Question 1c:

Organogenesis will develop and execute a protocol to demonstrate microorganism growth under the same condition as –b(4)----------. This study will be conducted post approval.

DMPQ Comments: This response was not acceptable. During the telecon on February 13, 2012, I told Organogenesis that this study should be performed before the BLA approval. Organogenesis agreed with DMPQ position, conducted the study and submitted the study report on February 24, 2012. The data were reviewed and considered acceptable (see <u>February 13, 2012 Information Request</u> Section Q1 for details).

DMPQ Question 2:

2. **Regarding the cleaning validation for your ---b(4)----------, please clarify what soils and cleaning reagents were used? Please demonstrate that the soils used represented the worst case situation and the –b(4)- locations represented the worst case locations? Please justify why the conductivity and visual inspection were not included in the validation acceptance criteria. Please justify using –b(4)--- as one of your validation acceptance criteria. In addition, please provide the acceptance criteria and most recent data (3 months) for routine monitoring of the ----b(4)----------**

----b(4)- ----------

-----b(4) ----------

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----b(4)----------

---b(4)--- ----------

1 Page determined to be not releasable:

b(4)

----b(4)------ ----------

DMPQ Question 3:

3. **Your description of microbial challenge study for –b(4)------ packaging did not specify the –b(4)---------- of the positive control. Please provide more information on the positive control. Please note that test sensitivity should be established for container closure integrity studies to ensure minute leaks can be detected. Please submit the study report for the container closure integrity study.**

-----b(4)--- ----------

---b(4)----- ----------

----b(4)----- ----------

DMPQ Question 4:

4. **Please provide monitoring data for WFI and PW for May, June and July, 2011 including bioburden results.**

Summary Response to Review Question 4:

An electronic copy (i.e., Excel spreadsheet) of the monitoring data for water for injection (WFI) and purified water (PW) for the period of May 2011 through July 2011 is provided with this response.

During the period of 14 June 2011 through 22 June 2011, there were bioburden excursions on two (2) sample dates during which time the PW system was quarantined. The PW system was released for use after having –b(4)---------- days of acceptable results as required by procedure.

DMPQ Comment: The reason I requested these data is because Organogenesis submitted data only for May 2011, and I noticed during the PLI that some excursions happened in June, 2011. I felt like I need to take another look focusing on the 3

months data. The data are acceptable.

DMPQ Question 5:

5. **During the inspection, we suggested that the revised shared equipment list and additional information related to segregation of Apligraf (oral) with -b(4)---- be submitted to the BLA. If you have not submitted the information, please do so as soon as possible.**

DMPQ Comment: Organogenesis has submitted the updated Section 3.2.A.1. In the response, they pointed out the relevant sections that were updated. The response is acceptable.

DMPQ Question 6:

6. **Please provide the registration information for you facility located at 85 Independence Drive in Taunton, Massachusetts 02780.**

Summary Response to Review Question 6:

The FDA Establishment Identifier number (FEI) number for the 85 Independence Drive facility in Taunton, Massachusetts 02780 is: 3006187899. This facility is currently registered as a Device Establishment and an HCTP establishment.

DMPQ Comment: During the initial review of the BLA, I found out Organogenesis also has a facility located at 85 Independence Drive in Taunton, Massachusetts, which is 20 miles away from their main facility located at 150 Dan Road, Canton, Massachusetts. This facility is designed for the receipt, initial inspection, and storage of incoming raw materials (not including chemicals or tissues) and manufacturing supplies. In September 2011, I suggested that the firm register this facility with the FDA district office. This location is now registered with the FDA.

February 13, 2012 Information Request

On February 13, 2012, I had a telecon with the firm to discuss inspection related and review related questions. The firm submitted the responses on February 22 and 24, 2012. Below is a list of DMPQ questions (in bold) and summaries of firm responses (in plain text) and DMPQ comments (in bold and italic).

DMPQ Question 1:

1. **Regarding your response to Question 1c in 26 January 2012 Information Request, you stated that "Organogenesis will develop and execute a protocol to demonstrate microorganism growth under the same condition as the ---- b(4)---------- We suggest you conduct the study before the BLA approval.**

Summary Response to Question 1:

---b(4)----- ----------

----b(4)---- ----------

DMPQ Comment: The study approach and results demonstrated microorganism growth under the same condition as the ----b(4)----------. The response is acceptable.

DMPQ Question 2:

2. **Regarding your response to Question 2 in 26 January 2012 Information Request, it seems no visual inspection or routine monitoring is performed for your ----b(4)----------. What are the cleaning procedure and the preventative and maintenance program and record for -b(4)----------? How do you ensure that there is no breakdown of interior, no microorganism growth or material build-up –b(4)----------**

----b(4)----------

----b(4)------- ----------

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----b(4)---- ----------

-----b(4)----- ----------

-----b(4)--- ----------

DMPQ Question 3:

3. **During the inspection conducted in October 3-7, Organogenesis committed to repeat the –b(4)---------- validation study following the corrected protocol because –b(4)---------- study was omitted in the validation protocol during the first –b(4)---------- validation study. Please complete the study prior to BLA approval.**

Summary Response to Question 3:

---b(4)---- ----------

---b(4)--- ----------

----b(4)--- ----------

DMPQ Comment: The response is acceptable and it is agreed that Organogenesis submit the –b(4)---------- validation report no later than June 30, 2012 as a post market commitment (see <u>RECOMMENDED ACTION</u> Section)

DMPQ Question 4:

4. **Your glasswasher validation studies have –b(4)- samples tested for –b(4)----------samples tested –b(4)-. Please justify why the validation studies did not include both the testing of –b(4)- samples and –b(4)- for each washer.**

Summary Response to Question 4:

----b(4)--- ----------

---b(4)-- ----------

DMPQ Comment: The justification plus Organogenesis' commitment to utilizing –b(4)---------- samples for future cleaning validations is acceptable.

DMPQ Question 5:

5. **Please provide an overview of your bioburden, BacT/ALERT and USP sterility tests in your in-process and final products. Please describe the different method used and the rationale for choosing different tests at different stages of process. Please specify the tests that are used for product release.**

Summary Response to Question 5:

In-Process Testing:

Sterility safety testing is performed at all critical in-process steps of Apligraf (oral) production. The primary sterility testing method for liquid, in- process samples is performed using the BacT/ALERT 3D Rapid Microbial Detection System (QCP-002).
----b(4)--- ----------

- ---

---b(4)--- ----------

Product Release:

Prior to final product release and shipment, all in-process samples must be on-test and negative to date. Furthermore, sterility and bioburden samples from final product must also be on-test and negative to date, prior to product release and shipment.

Final product is tested using –b(4)- USP <71> sterility test (QCP-002) and –b(4)---------- ---------- Please refer to BLA Section 3.2.P.5.2.3 for a description of the Sterility analytical method and Section 3.2.P.5.2.4 for a description of the Bioburden analytical method.

---b(4)---- ----------

---b(4)--- ----------

---b(4)--- ----------

DMPQ Comment: The overview provided a better understanding of the numerous sterility and bioburden tests performed throughout the manufacturing process, although much of the information is submitted through out different sections of the BLA. The response is acceptable.

<u>February 27, 2012 Information Request</u>

On February 27, 2012, I contacted the firm for additional information by e-mail. The firm submitted the response on March 1, 2012. Below is a list of DMPQ questions (in bold) and summaries of firm responses (in plain text) and DMPQ comments (in bold and italic).

DMPQ Question 1:

1. **During the pre-license approval inspection, Organogenesis indicated to me that the alert limits for Water-For-Injection, Purified Water and Clean Steam systems were being implemented. Please provide the newly established alert limits, and the rationale for limits established.**

Summary Response to Question 1:

The PW and WFI data collected (---b(4)----------, respectively) from January to June, 2011, were trended and analyzed using Individual Measurement Charts. The alert limits for TOC and Conductivity for PW and WFI were established based on the upper control limits. The statistical upper control limits were calculated based on ---b(4)---------- (data from January – June 2011). For bioburden, alert limits were established based on the highest observation

in the range during the review period. These alert limits are reflected in *QCP-043, Water* for *Injection, Purified Water, and Clean Steam Sampling Procedure (Revision 15).*

The evaluation of alert limits for the Clean Steam system is –b(4)----------(December 2012). No data were available for the 6-month period from January - June 2011 to establish alert limits (Deviation 11-8072, see **Subsection February 27, 2012 Information Request** Q2 for more details). There have been no excursions reported for the period from July 2011 to present (February, 2012).

Table 16 below includes the established action/ alert limits and rationale for establishing the alert limits for PW and WFI.

[b(4)]

DMPQ Comment: The response verified that the WFI and PW action limits have been established since the PLI based on data trended and analyzed. The action limits for Clean Steam system are not established due to lack of long term data, --b(4)----------No excursions have been reported from July 2011 to February 2012. The response is acceptable. However, ---b(4)----------

DMPQ Question 2:

2. **Please provide Clean Steam monitoring data for May-July, 2011 including bioburden data.**

Summary Response to Question 2:

Clean Steam data are not available for the months of May and June 2011 (Deviation 11-8072). Deviation # 11-8072 relates to the finding in April 2011 that the Clean Steam procedure –b(4)---00330, Sampling Procedure for Clean Steam was not followed as required. Specifically, sampling was not performed on a –b(4)--------- basis. An impact assessment was performed and concluded there was no product impact. Corrective actions were implemented in July 2011 and included procedural revisions and personnel training. In addition, internal Quality audits now include verification of the clean steam operation

and sampling procedures. The Clean Steam system has since been routinely monitored for TOC, Conductivity, bioburden and endotoxin ----b(4)----------

Clean Steam data collection from July 2011 until present (February 2012) were provided and all test results were within the specifications. No significant trends or excursions have occurred during this monitoring period.

DMPQ Comment: Organogenesis identified the problem and implemented corrective action. Data collected from July 2011 to February 2012 met the acceptance criteria.

INSPECTION FOLLOW-UP:

I recommend the items below to be followed-up during the next GMP inspection.

1. ---b(5)---------- ----------
2. ---b(5)---- ----------