DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

DISTRICT ADDRESS AND PHONE NUMBER	DATE(S) OF INSPECTION
555 Winderley Place, Suite 200 Maitland, FL 32751 (407) 475-4700 Fax:(407) 475-4768 Industry Information: www.fda.gov/oc/industry	06/25/2012 - 07/11/2012* FEI NUMBER 3002719998

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT ISSUED

TO: Caroline Hartill, Executive Vice President, Chief Scientific Officer

FIRM NAME	STREET ADDRESS
RTI Biologics, Inc.	11621 Research Circle
CITY, STATE, ZIP CODE, COUNTRY	TYPE ESTABLISHMENT INSPECTED
Alachua, FL 32615-6825	Human Tissue and Medical Device Manufacturer

This document lists observations made by the FDA representative(s) during the inspection of your facility. They are inspectional observations, and do not represent a final Agency determination regarding your compliance. If you have an objection regarding an observation, or have implemented, or plan to implement, corrective action in response to an observation, you may discuss the objection or action with the FDA representative(s) during the inspection or submit this information to FDA at the address above. If you have any questions, please contact FDA at the phone number and address above.

DURING AN INSPECTION OF YOUR FIRM WE OBSERVED:

OBSERVATION 1

Environmental conditions existed in which contamination or cross contamination of HCT/Ps or equipment could occur, and environmental conditions were not adequately controlled.

Specifically,

a) Gram negative organisms and fungus were recovered during routine environmental monitoring in your Deval area, Class 5 processing/packaging areas identified as rooms numbered (b) (4) on the following dates.

- On 1/6/2011 - 160 CFU's were recovered in **room** (b) (4) and identified as Gram negative rods.
- On 1/26/2011 - 26 CFU's were recovered in **room** and identified as Gram negative rods.
- On 4/11/2011 - 4 CFU's (alert level) identified as fungus, sampled from **room** (b) (4)
- On 5/4/2011 - 3 CFU's (alert level) identified as fungus, gram negative rods and Micrococcus species were cultured in the routine environmental monitoring scheme for **room** (b) (4)
- On 5/31/2011 - 20 CFU's identified as fungus, gram negative rods and Micrococcus species were sampled from **room** (b) (4)
- On 6/28/2011 - 32 CFU's identified as gram negative rods and recovered from **room** (b) (4)
- On 6/30/2011 - 128 CFU's identified as gram negative rods and recovered from **room** (b) (4)
- On 9/27/11 and 10/2/11 - action level of 40 CFU's, 48 CFU's and 8 CFU's identified as gram negative rods and coagulase negative Staphylococcus were recovered from **room** (b) (4)

Initial/primary processing of donor tissue is conducted in this Deval area. After primary processing and BioCleanse sterilization, the tissue is returned to this primary processing area (**rooms** (b) (4) for final aseptic packaging without a terminal sterilization process. The aseptic processing and packaging of the OC allografts also takes place in this Deval area.

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b) Pseudomonas species identified below were recovered from the following sampling points of the firm's (b) (4) water system located in RTI West on the following days:

- 6/1/2011 sampling point WV-B-POU-132-1 - Pseudomonas fluorescens
- 6/15/2011 sampling point WV-B-POU-124-1 - Pseudomonas species
- 6/15/2011 sampling point WV-B-POU-126-1 - Pseudomonas species
- 6/27/11 sampling point of use 124 & 127 - too numerous to count
- 7/7/2011 sampling point WV-B-POU-124-1 - Pseudomonas fluorescens
- 7/12/2011 sampling point WV-B-POU-126-1 - Pseudomonas fluorescens
- 7/25/2011 sampling point WV-B-POU-124-1 - Pseudomonas fluorescens

In addition, data requested and provided to the investigators indicate the (b) (4) system had findings of Pseudomonas fluorescens and other Pseudomonas species identified from a period of 6/1/2011 to 1/23/2012, although not always at your specified action and alert levels.

The (b) (4) water is used to manufacture (b) (4) and (b) (4) saline products which are not autoclaved prior to use in product processing. The (b) (4) water is also used to clean the RTI West facility's tissue processing areas and to rinse black sprayers, which are used for cleaning processing and packaging areas in the RTI East and West facilities.

c) On 4/28/11, Pseudomonas was found in samples collected from black sprayers cleaned in RTI WEST and rinsed with the (b) (4) water. The black sprayers are used to clean all areas of the firm including the Class 5 areas used for tissue processing and packaging.

OBSERVATION 2

Environmental controls do not provide for adequate cleaning and disinfecting of rooms and equipment to ensure aseptic processing.

Specifically,

a) In April 2011 the cleaning process of the black sprayers was (b) (4) (by an outside contractor) to (b) (4) This process was changed within approximately (b) (4) Pseudomonas species were

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cultured in the black sprayers as early as 4/28/2011. The use of (b) (4) in place of (b) (4) was then investigated in May and implemented in June 2011. However, written cleaning procedures were not established for these black sprayers until 9/22/11 with SOP "Disinfection of Black Sprayers", Document # 6478. The black sprayers are used to dispense the cleaning solutions and rinse water used for cleaning the tissue processing areas in RTI West and RTI East facilities.

b) SOP "Disinfection of Black Sprayers", Document #6478, dated 9/22/11, is inadequate in that, Section 5.11 indicates that the (b) (4) can be reused (which is the current practice); however, the (b) (4) manufacturer's labeling for cleaning/sanitizing indicates "may not be reused as a cleaner/sanitizer".

c) The gram negative rod isolates cultured from the Class 5 area over the period of January 2011 to January 2012 indicated an increase during that time frame. The current cleaning procedures have not been evaluated for disinfection adequacy with the increased levels of contamination that continue to be observed as recently as May of 2012.

d) Pseudomonas species were isolated in the Water for Injection system, including Pseudomonas aeruginosa, on at least 16 occasions in 2011 and 8 occasions in 2012, although, not necessarily meeting its action or alert levels. An additional occurrence of Pseudomonas fluorescens dated 5/1/2012 is currently being investigated.

OBSERVATION 3

Corrective actions relating to core CGTP requirements did not include both short term corrective actions to address the immediate deficiency and long term corrective actions to prevent recurrence.

Specifically,

a) The addition of potential contamination to all stages of receiving, processing, and packaging, and its effect on the validated sterilization (BioCleanse) process has not been addressed to ensure it has not been compromised beyond it's capabilities.

b) In March 2011 an investigation (CAR-00064) was opened due to an increase (7 cases between 1/2011 and 4/1/2011) of (b) (4) failures for the "Bio DBM boats". Also numerous isolates of

environmental contamination were cultured including Bacillus species, Pseudomonas aeruginosa (2 occurrences) and Serratia species. The corrective action of removing the mouse pads from the BGS processing suites failed to adequately address the ongoing environmental conditions within the suites as demonstrated by the continued sporadic failures from December 2011 until June 2012.

c) Prior to March 2012, gram negative rods isolated from the Class 5 Deval area were not identified, preventing a thorough investigation of the tissue failures occurring concurrently throughout the facility. The records (Alert and Action record for **room** (b)(4) dated 5/31/11) indicated that no corrective action was taken after reviewing cleaning records, water and air results. Also Alert and Action record for **room** (b)(4) dated 9/2/11 and 10/2/11 stated, "Corrective Action none. Spike with no impact on tissue safety."

d) On 4/28/11, Pseudomonas was found in samples collected from black sprayers cleaned in RTI WEST and rinsed with the (b)(4) water from that building. No investigation was opened prior to June 2011 (CAR-00088) that considered the black sprayers as a source of contamination.

Pseudomonas was isolated in the (b)(4) water system as early as June 2011, but no investigation was opened until 10/20/2011 (Min-00128) to address increases in the water and chemical bioburden for the (b)(4) water system located in RTI West/(b)(4) t processing area. There was a failure to identify the potential relationships between the investigations of the presence of Pseudomonas within the (b)(4) water system and Black Sprayers, the elevated environmental monitoring within the Class 5 processing/packaging areas, and the increase packaging culture failures throughout 2011.

e) On November 30, 2011, an investigation (MIN-00144) was opened in response to a spike in soft tissue final release testing resulting in the recovery of yeast, non beta hemolytic Streptococcus, Serratia liquefaciens, Raoultella planticola, gram positive rods, Bacillus species, and coagulase negative Staphylococcus. These products were packaged in **room #**(b)(4) of the Deval area. Although operations were suspended in **room #**(b)(4) where the packaging cultures were sampled, the sign-off comment that no corrections are necessary as current controls detected the issue and appropriate disposition of the affected tissue took place is inadequate. These packaging and destructive companion tissue samples are relied upon for final release.

CAR-00110 was subsequently opened 1/27/12 due to inadequate corrective action implemented in response to the failed cultures identified in MIN-00144 described above. The inadequate corrective action was the inadvertent release of two donors' tissue (eight pieces). Donor (b)(6) had a positive

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post-processing swab culture, while donor (b) (6) has a positive post-processing destructive culture. This release of tissue was reported to FDA as two HCTP deviation reports. This CAR addresses the fact that this release of finished product that failed the finished product cultures was due to the firm's lack of an automated QC Hold function within the LIMS system. The Root Cause recorded in the CAR states "Process controls failed to detect positive culture results and prevent distribution of affected graft." which implies human error due to absence of an automated system; however, this human element is not directly stated or addressed in any way throughout the investigation.

OBSERVATION 4

Processes with results which could not be fully verified by inspection and tests, were not validated and approved according to established procedures.

Specifically, fresh osteochondral (OC) allografts are processed aseptically, including the use of a bioburden-reducing (b) (4), and procedures addressing how to process the OC allografts have not been validated.

OBSERVATION 5

Environmental controls do not provide for adequate control of temperature and humidity.

Specifically,
The temperature and humidity within the classified core areas, where tissue processing and final packaging take place, are not currently controlled.

OBSERVATION 6

Failure to process and package HCT/Ps in a way to prevent the introduction, transmission, or spread of communicable diseases.

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Specifically,

a) There were 70 incidents of finished product packaging swab culture failures in its Sports Medicine products which were identified by the firm's laboratory as Pseudomonas species, including one incident of the pathogenic species of Pseudomonas aeruginosa, from 1/1/2011 to 6/30/2012. Within the same time period there were 23 (b) (4) failures detected in the destructive sterility test (release testing) for the Sports Medicine/soft tissue products. The packaging is performed primarily in rooms (b) (4) and # of the Deval area (a Class 5 processing/packaging area containing rooms numbered (b) (4) There were in excess of 33,000 tendons distributed between 2011 and 2012.

Additional cultures found during the same time period include gram negatives such as Serratia liquefaciens, (21 occurrences, swab and (b) (4) and Bacillus species, other unidentified gram positive rods, yeast and molds (4 occurrences of fungus).

There was a failure to adequately address the processes to ensure that the tissue processed and packaged in the Class 5 area has not been contaminated prior to distribution. In addition, an aseptically processed Osteochondral (OC) allograft product that does not go through a terminal sterilization process prior to distribution is also processed and packaged in this area. There have been in excess of 400 OC grafts distributed in 2011-2012.

b) During the time period from December 2011 through June 2012, the aseptically processed "Bio DBM boats" were found to exhibit (b) (4) culture failures with the following organisms having been detected, but not limited to, Bacillus species, coagulase negative Staphylococcus and fungus. There were in excess of 10,000 BGS Boats distributed in 2011 and 2012.

c) The 4th quarter 2011 bioburden (in-process) culture samples collected during Deval/Soft Tissue processing resulted in elevated CFU counts for Aerobes and Fungi tests. Two of these elevated in-process/bioburden cultures, tested 12/8/2011, were identified as Pseudomonas fluorescens; this organism was not identified on the pre-processing tissue cultures performed on these two donors (#(b) (6) and (b) (6)

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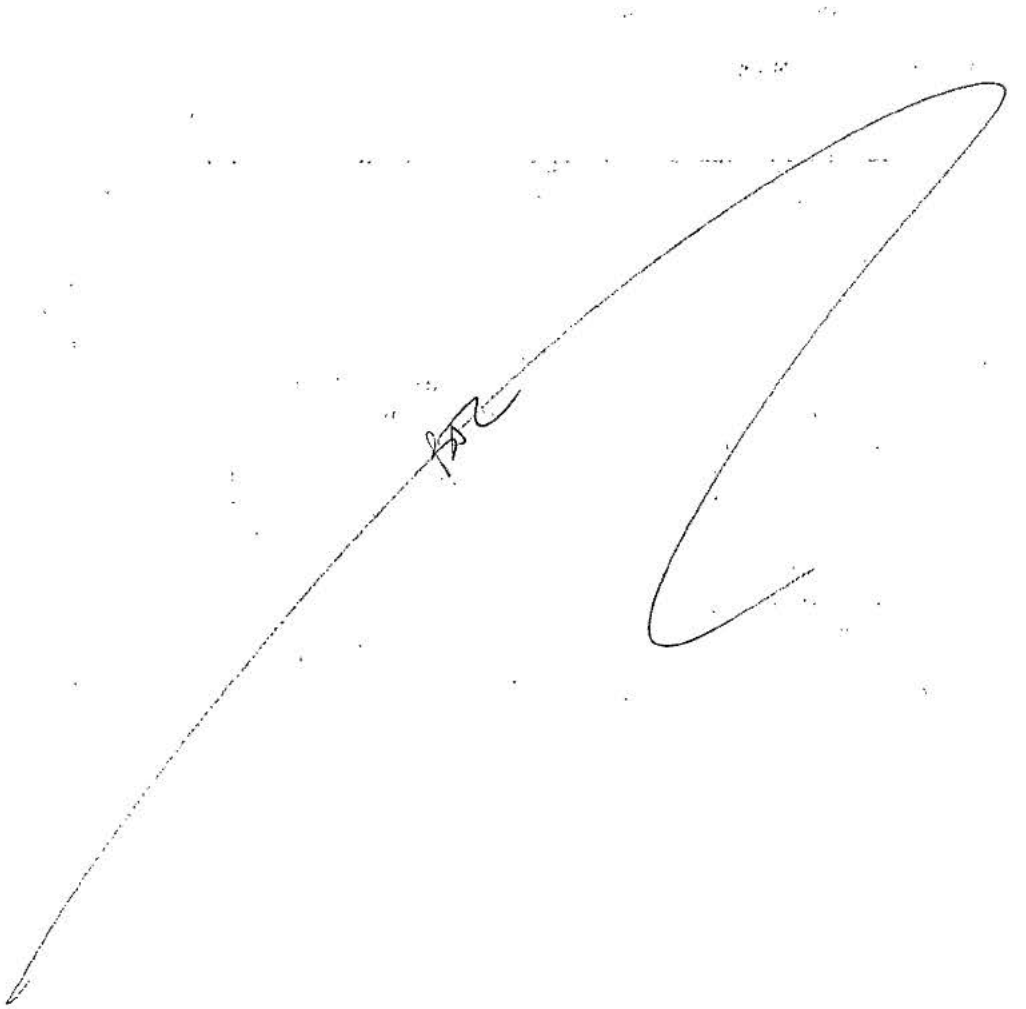
*** DATES OF INSPECTION:**
06/25/2012(Mon), 06/26/2012(Tue), 06/28/2012(Thu), 06/29/2012(Fri), 07/11/2012(Wed)



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