



Department Of Health & Human Services
Food And Drug Administration
Center for Biologics Evaluation and Research
Office of Compliance and Product Quality
Division of Manufacturing and Product Quality

Memorandum

To: Administrative File for Nycomed BLA 125351/0
CC: Natalya Ananyeva, PhD, Committee Chair, OBRR/DBA/DH, HFM-392
From: CAPT Martha O'Lone, BSN, MRBI/DMPQ/OCBQ/CBER
Through: Carolyn Renshaw, Branch Chief, MRBI/DMPQ/OCBQ/CBER, HFM-675
Deborah Trout, Team Lead, MRBI/DMPQ/OCBQ

Subject: DMPQ review of manufacturing and facility data in BLA.

Reference: Original application BLA 125351/0 (submitted 3/6/2009),
Amendment 125351/4 dated December 21, 2009, and Nycomed's responses to information
requests dated March 12, 18, and 31, 2010.

Action Due Date: 05 April 2010

Recommendation: I recommend approval of the Nycomed TachoSil[®] BLA.

SUMMARY

Nycomed Denmark ApS (Nycomed) is seeking approval to manufacture TachoSil[®], a sterile thrombin-fibrin sealant collagen patch which is indicated for use as an adjunct to hemostasis in cardiovascular surgery. The collagen patch for this product differs from other currently marketed thrombin coated collagen patches due to the equine tendons used to manufacture the collagen patch, and the addition of fibrinogen to the thrombin coating. This combination product (biologic/device) will be the first licensed biological product manufactured in the Nycomed Austria GmbH facility in Linz, Austria. Nycomed has a shared manufacturing agreement with ----b(4)-----to provide the two active bulk substances for TachoSil's fibrinogen/thrombin coating; Human Fibrinogen Active Substance -----b(4)----- and Human Thrombin Active Substance ----b(4)-----

The scope of this review includes all of the product manufacturing and facility related information in the original BLA dated March 6, 2009, the Pre-License Inspection of the Nycomed Austria GmbH facility held on December 10-17, 2009, and the response to CMC questions #22-26 that were provided in Amendment 125351/4 dated December 21, 2009 and Nycomed's responses to information requests dated March 12, 18, and 31, 2010. The

product and stability data in this submission are under separate review by the product office.

Indication for Use

Nycomed states that TachoSil, is a sterile, ready-to-use, degradable thrombin-fibrin sealant collagen patch is indicated as an adjunct to hemostasis in cardiovascular surgery.

Review Narrative

TachoSil® Description

“TachoSil®” is a --b(4)----- sterilized combination product that is described by Nycomed as a “ready-to-use, degradable fibrin sealant collagen patch which is indicated as an adjunct to hemostasis in cardiovascular surgery.” TachoSil’s equine collagen sponge has a yellow coating on one side that is a --b(4)----- suspension which contains two biological active ingredients; human fibrinogen and human thrombin, and Riboflavin -----b(4)----- (Vitamin B2) for the yellow color. TachoSil® is a unique combination product in that the device’s collagen sponge material is manufactured by Nycomed from equine tendons and a second active biological substance used for hemostasis; fibrinogen, has been added to the thrombin coating. -----b(4)-----, provides Human Fibrinogen Active Substance -----b(4)----- and Human Thrombin Active Substance (--b(4)-----) as --b(4)----- bulk in vials for further manufacturing use as per the shared manufacturing agreement between -(b)(4)- and Nycomed. (The details of their December 2001 manufacturing agreement were included in this submission and the --b(4)---- submissions.) ---b(4)----- sources these active substances from human plasma obtained from US licensed centers. -b(4)- manufactures these bulk substances for further manufacturing use with the exact specifications that meet the formulation requirements for TachoSil’s fibrinogen-thrombin coating.

Since there is only one formulation for coating, TachoSil® is produced in only one dosage strength. The dosage of the fibrinogen/thrombin coating on the final TachoSil® collagen sheet is measured in square centimeters for each of these active biological substances; human fibrinogen: 3.6 – 7.4 mg/cm² (target value: 5.5 mg/cm²) and human thrombin: 1.3– 2.7 IU/cm² (target value: 2.0 IU/cm²).

The collagen sponge is a whitish, deformable sponge material in the form of strips. It is used as a carrier for the active ingredients Human Fibrinogen Active Substance b(4) and Human Thrombin Active Substance provided by b(4). The dry matter of the collagen sponge is approximately b(4) of equine collagen in the form of collagen -(b)(4)-. The standard material for collagen sponge production is ---b(4)----- horse tendons. TachoSil sheets are manufactured to be -b(4)-- thick and are cut into 3 different size sheets;

[

b(4)

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

MANUFACTURERSNycomed GmbH in Linz, Austria

TachoSil[®] will be manufactured at Nycomed GmbH in Linz, Austria. Nycomed Austria GmbH is a company in the international Nycomed Group which is headquartered in Zurich, Switzerland. This will be the first Nycomed licensed product at this facility. (Currently Nycomed is licensed as a contract manufacturer of a Pharmaceutical product ProAmatine). CBER conducted a pre license inspection for this TachoSil BLA at this site during December 10-17, 2009. There were no 483 items or other discrepancies noted during the production. (The analytical testing for TachoSil (in-process, release and stability) is also performed at Nycomed.)

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

---b(4)---

Contract Sterilization:

Collagen Source Material

(The use of these slaughterhouses for the equine material in the collagen sponge is under review by the product office and CDRH reviewers.)

Contract testing laboratories

Riboflavin testing according to b(4) is carried out at --b(4)-----

SITE DESCRIPTION

The site of TachoSil[®] manufacture is Nycomed Austria GmbH, which is located in the Chemie Industrial Park on St. Peterstrasse 25, 4020 Linz, Austria. Although TachoSil[®] will be the first US licensed product for this facility, Nycomed's multiple product facility is currently a contract manufacturer for one US product; ProAmatine[®] (Midodrine Hydrochloride) tablets for Roberts Labs in Eatontown, NJ. Nycomed's site includes three manufacturing operations; API Production, Pharmaceutical Production, and Biological Production. API production occurs in Building b(4). Pharmaceutical Production in Building b(4) occurs on the --b(4)----- are limited to contract manufacture of ProAmatine[®] (Midodrine Hydrochloride) tablets. (The --b(4)----- Pharmaceutical production area in Building b(4) was inspected in 2001 for CDER and was rated VAI for the ProAmatine[®] NDA). Biological production in Building b(4) includes the manufacture of TachoComb for Europe, Japan and Australia on the -b(4)-----, and the use of a dedicated TachoSil production area for the campaign manufacture of TachoSil[®] or TachoSil EU on the --b(4)----- of Building -b(4)-. In 2004, Nycomed added floors -b(4)- on top of Building b(4) and installed ---b(4)----- for the HVAC system to establish the TachoSil production area which is an environmentally controlled core area for TachoSil[®] and TachoSil EU production. There are no other products manufactured on the -----b(4)-- floors. To add a space for a dedicated line for primary and secondary packaging of TachoSil[®], the -b(4)- of Building b(4) was renovated by adding rooms for b(4) separate packaging lines. This allows for a dedicated primary and secondary packaging line for TachoSil[®]. The other building used for TachoSil production is the Building b(4) warehouse which is connected to Building b(4) on -----b(4)----- ----- . It is used for receipt of materials and storage for TachoSil products. It is also used for receipt and storage of materials for Pharmaceutical Production activities at

Nycomed. Final packaged TachoSil is stored in Warehouse b(4) under controlled temperature conditions prior to shipment. Additional buildings at this site that are pertinent to TachoSil production are Building b(4) (waste water treatment plant and cooling equipment for brine) and Buildings --b(4)----- which are Administration buildings.)

This submission provides detailed descriptions of the construction of the rooms, floor diagrams with room numbers, and directional flow arrows for Building b(4) and Building b(4) that indicate appropriate use of the facility for manufacture of TachoSil:

- Product and raw materials;
- Personnel;
- Equipment;
- Waste; and
- Air.

During the CBER pre license facility inspection conducted December 10-17, 2009, no discrepancies were noted with Nycomed's Building b(4) or Building b(4) Warehouse. The production area design, personnel and product flow procedures and policies are accurately reported in this BLA.

Conclusion: The construction and materials used for the floors, walls, and ceilings in the TachoSil production areas in Building b(4) and Building b(4) Warehouse follow the current recommendations for cGMP's. Nycomed has identified all manufacturers used in production and provided evidence of appropriate establishment controls for manufacturing TachoSil[®] at Nycomed.

MANUFACTURING PROCESS

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

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

---b(4)---

23 Pages determined to be not releasable:

b(4)

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

CONTAMINATION/CROSS CONTAMINATION

----- . An additional manufacturing step includes b(4) pH treatment --b(4)-----
----- . Prior to use in production, , the --b(4)----- are tested
for bioburden with an acceptance level which requires a -b(4)--lower bioburden limit from the
initial -b(4)--, before release for the next production step; the bioburden limit for these --b(4)--
----- . After release from bioburden testing, the ---b(4)----- are
ready for the next steps; ---b(4)-----
----- b(4)-----

----- (The selection of the bioburden levels for TachoSil were discussed during this review with Nycomed as noted

under the review of sterilization validation.) Additional components included in the assessment of bioburden were the specification for ---b(4)-----
----- . The -b(4)-----sterilization of TachoSil to an -b(4)----- has been validated and continues to be assessed for pyrogenicity and sterility prior to batch release. In this submission Nycomed also provided validation on cleaning and processing equipment that demonstrate Nycomed's ability to maintain strict environmental and processing controls that contribute to the low bioburden found during manufacture of TachoSil.

Nycomed uses the following slaughterhouses for the equine tendons;

--b(4)-----

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

To address potential TSE or other prion contamination, Nycomed provided information in the submission about these facilities and their audits. The facilities are noted to include ---
-(b)(4)---- equine slaughterhouses and -----(b)(4)----- slaughterhouses. The -
b(4)---- facility is acceptable as it is on the USDA FSIS list; the other facilities are not in known BSE countries. The audit of each facility was up to date during the Pre License Inspection and was reported as satisfactory for;

- Quality system and/or risk management system (e.g. HACCP) in place
- Facilities, equipment and processes for manufacturing of horse tendons
- Measures against cross contaminations and intermingling ---b(4)---
- Origin of slaughtered animals
- Traceability of materials and animals
- Hygiene and cleaning procedures
- Training of personnel and:
- Documentation system.

Nycomed also audits each of the -b(4)- slaughterhouses -b(4)- for prevention of cross contamination (dedicated equipment, appropriate cleaning procedures) and intermingling of the -(b)(4)-. Each batch of horse tendons, which is supplied to Nycomed, is accompanied by a veterinary certificate and by a QA certificate, issued by a quality responsible person of the slaughterhouse. These certificates are provided to confirm that the horse tendons originate from animals free from notifiable diseases. (The certificate also states that the meat obtained from those animals is suitable for human consumption, which is not pertinent to the use of tendons at Nycomed.) The final acceptability of these collagen sources are deferred to the CDRH reviewer for TachoSil. Nycomed has not manufactured any bovine materials in this TachoSil production area. Nycomed also included their sourcing of the -b(4)- Human Fibrinogen and Thrombin for the active substances as being derived from plasma that is only collected from FDA licensed US donor centers. Nycomed's report on potential prion contamination of TachoSil during manufacture is reviewed below.

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

----- The final review of the report on Adventitious Agents Safety Evaluation, test results for potential equine collagen as a viral contaminant and the extent of viral inactivation necessary are deferred to the product office and CDRH reviewers.

Conclusion: The manufacturing processes, virus validation, and monitoring of raw materials contributes to the low bioburden per TachoSil sheet prior to gamma irradiation. The negative test results for sterility and pyrogenicity provide additional information on the ability of gamma irradiation to remove remaining bioburden so that the final packaged TachoSil product is sterile and pyrogen free.

Potential Prion Contamination

TachoSil[®] and TachoSil EU are the only products that have been manufactured on floors - b(4)-- of Nycomed's Building b(4). This TachoSil production area has some Grade b(4)/ISO b(4) areas, but is primarily a Grade -b(4)- environmentally controlled core surrounded by Grade b(4)/ISO b(4) support rooms. The TachoSil production area has limited access, dedicated trained personnel, strict gowning requirements for the Grade b(4) areas, and where possible, dedicated equipment is used to minimize cross contamination between the campaign manufacture of these two TachoSil products. Although Nycomed did manufacture previous versions of TachoSil for Europe (TachoComb H and TachoComb) with bovine thrombin and bovine aprotinin, these products which are manufactured on the -b(4)- floor of Building b(4), are now manufactured without bovine materials to reduce potential prion disease contamination. Since the new production area on the -b(4)----- floors of Building b(4) have not been exposed to bovine materials, Nycomed states that the current potential for prion disease contamination during production of TachoSil is due to the use of non US licensed human plasma and albumin as source materials for the active human thrombin and human fibrinogen in TachoSil EU. In addition to the material, personnel, waste flow and environmental controls in Building b(4) dedicated TachoSil production area that are designed to minimize potential contamination, the two TachoSil products are manufactured on a campaign basis. After manufacture of TachoSil EU, additional inter-campaign changeover procedures are executed designed to minimize the risk of cross contamination for the next batch of TachoSil[®]. To document their control of contamination/cross contamination, Nycomed provided the following reports on their risk assessment for potential prion contamination, changeover activities, cleaning procedures and cleaning validation;

"Contamination/Cross Contamination Issues-US/Document 0903X-AD-0000012"

Nycomed provided this report to describe their risk assessment and activities to address the potential for prion contamination and cross contamination of Building b(4) TachoSil production areas due to manufacture of both TachoSil EU (European Union sourced plasma pools) and TachoSil (Fibrinogen Active Substance b(4) and Human Thrombin Active Substance from U.S. sourced plasma pools). Both the TachoSil and TachoSil EU formulations contain 5.5 mg/cm² fibrinogen and -b(4)----- thrombin. This risk assessment determined the potential worst case material for cleaning and contamination transmission between these TachoSil products to be --b(4)----- was identified as the worst case or lead substance for evaluation of cleaning because of --b(4)-----

----- To limit cross contamination, Nycomed uses dedicated and single use equipment for manufacture of TachoSil where feasible. To reduce the potential for prion transmission with shared equipment, Nycomed cleans with -b(4)- between batches of TachoSil and during changeover after production of TachoSil EU.

In assessing the risk of cross contamination, Nycomed used the -b(4)- dose criterion and limit determination to evaluate the potential cross contamination risk for shared equipment. Nycomed calculated that the sum of the shared equipment surface areas in TachoSil production equals -b(4)-. Nycomed calculated the -b(4)----- dose of -(b)(4)-----

----- size TachoSil patch as --b(4)-----; however Nycomed calculated the maximum daily dose as b(4) patches to add an additional safety margin. In addition to the -b(4)--- dosing premise of pharmaceutical carryover “not more than -b(4)- of the normal therapeutic dose of any product will appear in the maximum daily dose of the following product,” Nycomed also evaluated “not more than -b(4)- of any product will appear in another product.” When applying both of these calculation approaches, the result was that --b(4)----- was calculated as the limit of carryover determined for --b(4)-----.

Conclusion: The choice of --b(4)----- appears to be an appropriate choice as worst case material for cross contamination. (As noted below in the review of the cleaning validation reports, Nycomed has also evaluated other potential sources of contamination such as bioburden, endotoxins, and potential contamination of product due to residuals from cleaning materials. -----b(4)----- Routine cleaning for both products is performed with ---b(4)----- the carryover of these materials is evaluated by measurement of -b(4)-----

--b(4)-----

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

Cleaning Procedures

The cleaning agents in TachoSil production are limited --b(4)--- -----
------. As noted below
in the review of the cleaning validation, -b(4)----- was identified as the worst case challenge
to cleaning during TachoSil production. All equipment (direct and indirect product contact)
is cleaned -b(4)----- of TachoSil according to the automatic or manual cleaning
procedures. Additional cleaning is performed --b(4)-----
----- where appropriate. Only personnel who have been trained in procedures used for
cleaning are authorized to clean in the production areas. The cleaning procedures used in
TachoSil production are classified into -b(4)----. Of these cleaning procedures described
below, cleaning -b(4)- is the only method that is automated.

-b(4)-----

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

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

--b(4)-----

--b(4)-----

1 Page determined to be not releasable:

b(4)

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Equipment cleaning is documented in the room equipment log and batch record and verified by the supervisor.

Equipment Categorization for Cleaning

Equipment used in manufacture of TachoSil is categorized for cleaning and changeover as to direct product contact, indirect product contact that has the potential for cross contamination and no potential for contamination, single use and multiple use equipment. Dedicated or single use equipment is used, if possible, when there is direct product contact. Equipment that can withstand the requirement for use of -b(4)--- in changeover cleaning is categorized as multiple use equipment. In the submission the manufacturing equipment was

identified by usage dedication and cleaning type. The equipment used for TachoSil is noted to be primarily custom manufactured with ---b(4)------. During observation of the cleaning process during inspection I noted that other than the coating apparatus or “--b(4)-----” which has -b(4)--- tubes for -b(4)----- the active substance suspension, the equipment surfaces and materials do not appear to have areas that are difficult to access during cleaning of the --b(4)----- surfaces. The cleaning suite has developed a --b(4)----- with special cleaning procedures after ---b(4)-----

[
b(4)
]

b(4)

Cleaning Validation

Nycomed executed --b(4)---- cleaning validation protocols after production of the -b(4)-- TachoSil Standard Sheet conformance lots to support the effectiveness of the cleaning procedures in the TachoSil production area on the ---b(4)---- -----

----- that is dedicated to TachoSil production. For both protocols, --b(4)----- was identified as the worst case or lead substance for evaluation of cleaning because of its --b(4)----- compared to --b(4)----- is --b(4)----- in the standard TachoSil batch formulation, and --b(4)----- has a ---b(4)----- ----- . To evaluate the potential for cross contamination of equipment shared between TachoSil and TachoSil EU, Nycomed determined that -b(4)--- was the sum of all direct product contact surfaces. This measurement was used to determine the potential product carryover and used as the basis for the categorization of equipment for the type of manual cleaning. Using the -b(4)-- dose of -b(4)----- present, Nycomed calculated the limit of carryover and the potential for cross contamination of a patient who was treated with b(4) pieces of standard size TachoSil, which would exceed the maximum recommended patient exposure of 7 pieces. -----(b)(4)----- difference between TachoSil and TachoSil EU formulations are the -----(b)(4)--- source, cleaning validation was limited to evaluation of cleaning after production of TachoSil.

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

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b(4)

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

-b(4)-

-b(4)-

Facility Cleaning of Building b(4)

Cleaning of Building b(4) was noted on inspection to be appropriately documented for the TachoSil production areas.

Conclusion: Although FDA is unaware of any established methods, including use of (b)(4)-, to reliably decontaminate or sterilize articles potentially contaminated with prions, the use of (b)(4)- ----- during automated cleaning in Cleaning (b)(4)- ----- is a rigorous decontamination step for the post production cleaning of the (b)(4)- equipment (b)(4)- ----- . During the inspection there was no visual or indirect evidence that the quality of the (b)(4)- ----- and other materials used in the TachoSil manufacturing equipment had been damaged or (b)(4)- by exposure to the levels of (b)(4)- used in Nycomed's changeover procedure and cleaning. Nycomed has demonstrated in their audits

of incoming materials, control of bioburden during production, use of dedicated equipment where possible, changeover procedures, and in validation of their cleaning and sanitization programs an appropriate use of current contamination and cross contamination controls during manufacture of TachoSil. The final review of the use of shared equipment in this facility where non US donor blood products are used in manufacture is deferred to the product office.

ENVIRONMENTAL MONITORING

HVAC/EM

Building -b(4)- dedicated TachoSil production area on the --b(4)----- is a contained environment with limited key card access for personnel who are appropriately gowned and trained for this Biological Production Area. The air-conditioning system for the -b(4)----- floors was constructed in 2004 as a circulating air system --b(4)----- with a constant part of filtered external air -b(4)----. The system is based on b(4) separate air handling units (AHU's Unit --b(4)-----). In the submission Nycomed provided drawing and descriptions for the areas covered by each of these AHUs. (The qualification of the production area according to --b(4)----- and the EU Guidelines to GMP for medicinal products-Annex 1 primarily includes the use of Grades -b(4)---- in the TachoSil production areas. All clean room Grade b(4) areas and all locks, connecting GMP and clean room Grade b(4), are equipped with ---b(4)-----

----- All areas classified as GMP, and all airlocks connecting non
classified areas with GMP areas, are equipped with ---b(4)-----
----- Where special conditions apply, for
example in high humidity areas or cold rooms, additional air handling units are provided to
supply and control the local conditions specified. The exhaust air is removed through
volume flow rate controlled exhausters, in the TachoSil manufacturing areas Grade b(4) air is
generally supplied through ---b(4)-----

----- air flow. The air -b(4)- have filters where particles are generated by a production step such as the ---b(4)-----

The pressure cascade in the production area is permanently controlled, Grade b(4) rooms are --b(4)----- overpressurized compared to the surrounding area classified as “GMP”. In case of violation of the specified differential pressure, temperature or humidity limits, an alarm is given by independent monitoring systems.

The -b(4)--- packaging area for TachoSil (primary packaging area room -b(4)---) and (-b(4)-- secondary packaging area room -b(4)-) is equipped with a --(b)(4)-- ventilation system to ensure proper conditions for primary packaging lines (Grade b(4)) and the secondary packaging line (Grade b(4)). The pressure cascade in the rooms and over the open areas for packaging TachoSil are designed to reduce the risk of contamination and to protect critical process operations. An overpressure of ---b(4)----- in each lock (either personnel or material lock) ensures properly separated rooms of different status. For the supply air

filters of grade --b(4)----- are used, the exhaust air is filtered through an b(4) filter.

After IQ for the individual air handling units in the TachoSil production area was completed, OQ included successful testing of all terminal filters with -b(4)-----
----- for leak-proof construction, filtration efficiency, verification of air change rates per area, recovery times and measurements of particles at rest were performed during the OQ phase. (Re-testing for these rooms is repeated -----b(4)-----
-----.) PQ for Air Handling Units --b(4)----- were documented in a combined report. During the initial qualification of the Grade b(4) rooms, Nycomed reported problems with differential pressure and air rates not meeting acceptance criteria. In December 2006, a final PQ for the HVAC system was performed and the Grade b(4) rooms were qualified using smoke studies with no further deviations. In 2009 a successful requalification with no deviations was performed after changeover procedures were modified prior to Process Validation 2 for TachoSil conformance batches.

The pressure cascade in the TachoSil production area is designed to reduce the risk of contamination and to protect critical process operations. The production environment for TachoSil on the -b(4)-- floors is generally described as a Grade b(4) or ISO Class b(4) during operations. The coating area is supplied by --(b)(4)-- air handling units and is called a “Grade b(4)” by Nycomed but is essentially meets an ISO Class b(4) or Class -b(4)- in operation with strict gowning requirements that are more commonly found in Grade b(4) or ISO Class b(4) or Class b(4) environments; face masks, full jumpsuit, gloves, and booties. The air flow is positive pressure -b(4)- to Grade b(4) rooms. Again the number of air changes per hour (ACH) in the TachoSil production area exceeds the requirements for Grade b(4) and Grade b(4) rooms. The coating area is set for b(4) ACH, material locks to the coating area are b(4) ACH, the TachoSil cutting rooms are b(4) ACH and dispensing and storage has b(4) ACH. Grade b(4) classification is used for personnel movement between process areas and clean gowning is used in these areas.

EM

Environmental monitoring is performed routinely during manufacturing of each batch of TachoSil. The differential pressure is monitored continuously and the computerized alarm system is set for the parameters and acceptance criteria for each classification are outlined in the table below:

[b(4)]
---	------	---

[b(4)]

Nycomed monitors certain Grade b(4) areas to a higher standard than required (---b(4)-----
-----). These areas are for production operations where the product is deemed to be at greater risk. In addition to routine monitoring of the coating and packaging areas, during batch production when product or intermediates in these Grade b(4) areas are exposed to the environment, Nycomed performs monitoring of both viable/non viable airborne particles and surface -b(4)----- is carried out and recorded in the master batch record. During production in the Grade b(4) TachoSil cutting room; -----(b)(4)----- monitoring of particulates for this Grade b(4) area is performed in addition to routine monitoring and is also documented in the batch record. For rooms where product is in closed containers or no product is manufactured, -b(4)-----monitoring is performed. If an action limit is exceeded, Nycomed performs a deviation investigation.

Nycomed performs the following routine monitoring for nonviable particles;

[b(4)]

[

b(4)

]

Nycomed performs microbial monitoring using a risk based approach which is described with specifics for the production activities in the Grade b(4) areas;

[

b(4)

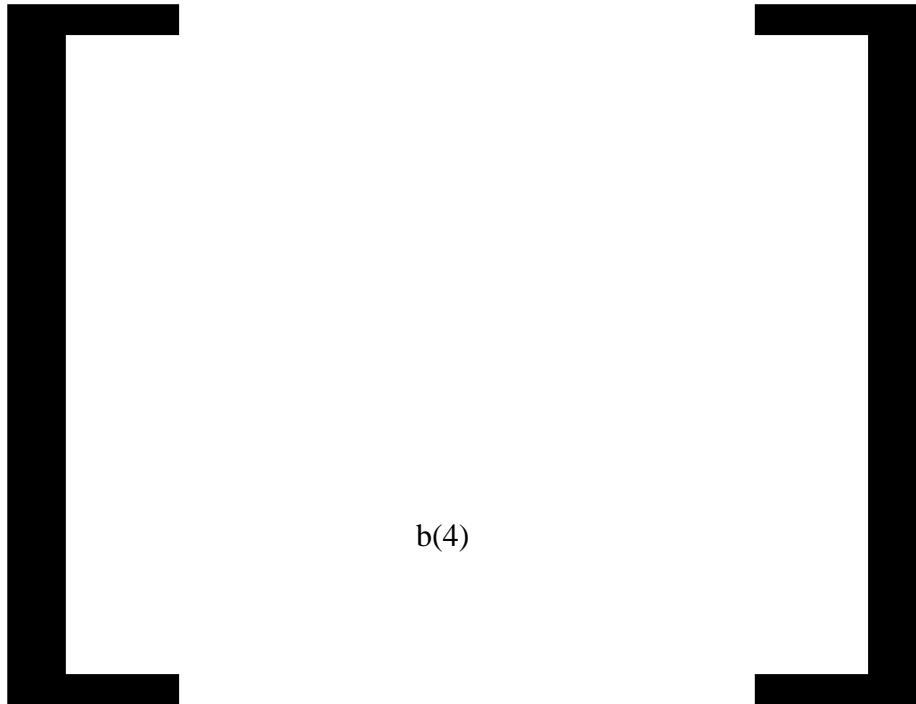
]

[b(4)]

Environmental Monitoring Validation

Nycomed provided TachoSil environmental monitoring performed during both of the two validations for TachoSil. It was noted that the air borne particles in Validation 2 were lower than those in Validation 1. Both validation batches met the acceptance criteria with no deviations. Since Validation 2 captures monitoring performed after implementation of the changeover cleaning from TachoSil EU, these results are most relevant to current TachoSil manufacture. The following summary of the passing monitoring results for the three validation batches of TachoSil Standard Size that were provided in the submission were verified during the inspection by reviewing the original data;

[b(4)]



Conclusion: Nycomed has provided evidence that they have appropriate environmental controls for Class b(4) and Class b(4) during TachoSil manufacture.

UTILITIES

Water Systems

Performance qualification of the two water systems was successfully conducted in three phases. In the submission, Nycomed reported that the acceptance criteria were met, all occurring deviations could be successfully resolved through assignable cause and corrective actions and no seasonal trend could be detected. The current routine monitoring schedule for each system was derived from the testing performed during of the final PQ testing.

Water for Injection (WFI)

---b(4)----- by a separate WFI loop system. WFI is mainly used as --b(4)-----
----- during equipment cleaning. A small amount is used to prepare the --b(4)-----
----- WFI is prepared by
distillation from highly purified water by a -----b(4)-----
----- to Building b(4)

Highly Purified Water

Highly Purified Water (HPW), which is used for ---b(4)-----
----- it is prepared from --b(4)-----, which is supplied
by the --b(4)----- . HPW is produced by ---b(4)-----
----- . Each plant consists of ---b(4)-----

----- HPW is distributed via -b(4)- independent distribution systems
throughout the building; one of these supplies the production area for TachoSil. A -b(4)-
HPW storage and distribution system is installed for the Collagen Sponge and TachoSil
production area in the -b(4)-- floor. The HPW is stored in an ---b(4)-----
----- .

The loop is equipped with --b(4)----- sensor in the return of the loop.
The quality of PW is routinely monitored for bioburden, TOC, and conductivity and meets
the current -b(4)- requirements for Purified Water. Performance qualification was conducted
in three phases.

In phase I and phase II, lasting -b(4)----- accessible point of use and
sampling point were monitored -b(4)- for microbial count and bacterial endotoxins, -(b)(4)-
--b(4)----- . In addition chemical and physical parameters were
determined using testing b(4) times week. In phase III, lasting -b(4)----- accessible
point of use and sampling points were monitored --b(4)----- for
microbial count and bacterial endotoxins, and --(b)(4)-- of use was monitored --b(4)-----
for chemical and physical parameters. The monitoring schedule in phase III was taken over
into routine monitoring. Microbiological deviations during the initial PQ phases I and II
resulted in a changed sanitization scheme by ---b(4)-----

----- After implementation of this corrective and preventive action PQ phases I
and II were successfully completed in April 2005. Nycomed states that the acceptance
criteria were met; all occurring deviations could be successfully resolved assigning causes
and corrective actions. No seasonal trend could be detected. During PQ phase III of the
HPW storage and distribution system serving the TachoSil area, the HPW generation system
was renewed and released for production in September 2006 following the successful
completion of PQ I and II testing. SOPs have been established to govern the actions
necessary in case warning or action limits are exceeded.

Water for Injection

--b(4)----- is supplied by a separate WFI (Water for Injection) loop system. WFI is
mainly used as --b(4)-----

Water for Injection is prepared by distillation from highly purified water by a -b(4)-----
----- . The
storage and distribution system of WFI consists out of ---b(4)-----

-----, one of these serving the area of production of TachoSil. The loop is equipped with an --b(4)----- . The circulating water volume is --b(4)----- . Storage and circulation temperature: approx. -b(4)- with the temperature at point of return: approx. -b(4)-. The quality of the water is continuously monitored using conductivity and temperature --b(4)----- return and meets current -b(4)- requirements for WFI. Performance qualification for WFI was conducted in three phases. In phase I and phase 2, lasting -b(4)----- point of use and -(b)(4)- sampling point were monitored b(4) for microbial count and bacterial endotoxins (in summary -b(4)-). ----b(4)----- the sampling points in the WFI supply and return line were tested for chemical parameters. In phase III -----(b)(4)----- sampling points was monitored -b(4)- for microbial count and bacterial endotoxins and b(4) point of use -----(b)(4)---- for chemical and physical parameters. The monitoring schedule in phase III was taken over into routine monitoring. The acceptance criteria were met, all occurring deviations were stated to be resolved through assignable cause and corrective actions and no seasonal trend could be detected. SOPs were established which govern the actions necessary in case warning or action limits are exceeded. In the submission Nycomed provided a summary of the monitoring data for PQ which included the microbial data. This data met the acceptance criteria. During the Pre License Inspection, no trends were noted with the water system.

PRODUCTION EQUIPMENT

Nycomed describes the major production equipment for TachoSil in two categories; collagen or coating production. During the filing review, Nycomed was asked to clarify the equipment used for --b(4)----- of coating suspension. The firm responded that the device for the preparation of the fibrinogen suspension was changed from ----b(4)----- . Although this is the correct name, Nycomed stated in their response that “the -b(4)----- is a description used in the summary of manufacturing equipment that is meant to cover all types of --b(4)----- devices in the coating areas, regardless of the brand name. The unambiguous identification of the individual devices is achieved by the equipment number.” Nycomed also stated that they had “installed the new -b(4)- equipment or --b(4)----- after opening the new TachoSil production area. This equipment was used in the qualification, process validation and stability studies with TachoSil EU product. Subsequently, all US TachoSil batches have been manufactured using the ---b(4)-----

Although the equipment numbers have not been consistently used for descriptors in the submission, the following equipment used in the TachoSil production area on the -b(4)----- -----of Building b(4) at Nycomed were verified as completing IQ/OQ during the inspection;

[b(4)]

[b(4)]

In the submission, the process validation study for coating included the PQ for TachoSil production equipment, which met their acceptance criteria in the triplicate testing.

COMPUTER SYSTEMS

Nycomed has two computer systems used for production of TachoSil. The first system is the “-b(4)-” which is a Distributed Control System manufactured by --b(4)-. It controls certain production steps ---b(4)-----.

The IQ and OQ of the system was documented in their respective reports 4271-IQB-0059-01 and 427-OQB-0057-01. PQ was performed for the system as part of the qualification studies for the controlled equipment. Change control of the system infrastructure is covered by the IT department change control procedure; SOP 0100K-SOP-00003. The change control procedures include the following steps: change application, change evaluation including definition of measures to maintain validation, decision (authorization to proceed), change execution, change authorization related to production. There were no discrepancies related to this system noted during the Pre License Inspection.

The second system is the b(4) which is an integrated Enterprise Resource Management (ERP) System that is widely used throughout the site. It was developed by --b(4)-. The ERP/MES system consists of several modules/sub-modules supporting different business processes such as Material Management, Production Planning, Quality

Management, Sales and Distribution and Plant Maintenance. Validation testing has been performed as part of the implementation at the central site. Local PQ has been performed to ensure correct operations of the system and processes as used on-site. Material Management has several sub modules that were reviewed during the Pre License Inspection. These sub-modules include the use of the system for Inventory and Management of product and materials in the Building b(4) Warehouse. SAP also includes Material Master Maintenance, Batch management and traceability. Production Planning functionality is supported by a sub module; "Production planning- Process Industry" which is involved in the generation of batch numbers. Quality Management (QM): Supporting Quality Control activities (batch release via usage decision) and material status for procured materials. Status changes can only be initiated by the Qualified Persons and the Head of QC. Sales and Distribution (SD): Supporting the Order Management Processes, including Customers, Customer order, Delivering and Invoice.

Plant Maintenance (PM): Supporting periodic and general maintenance of production equipment and environment, such as calibration and maintenance management. Validation testing has been performed as part of the implementation at the central site. Documentation is located with the Central IT Department in Konstanz, Germany. Local PQ has been performed to ensure correct operation of the system and processes as used onsite. The change control procedures include the following steps: change application, change evaluation, change execution, and closure. Change execution for this system includes performance of tests in a Validation Environment followed by transport to the productive system. There were no discrepancies related to this system noted during the Pre License Inspection.

Any deviations that occurred in the course of the validation of the system that was reviewed during the inspection have been addressed by attributable cause and resolved by corrective action. No discrepancies were noted with the computer system or the plan for change control during the Pre License Inspection.

ENVIRONMENTAL ASSESSMENT

Nycomed requested the following categorical exclusions; as outlined in 21 CFR Part 25.31(a), (c) and 25.15(d). Refer to separately prepared Environmental Assessment memo contained in Electronic Document Room (EDR).

References

AAMI/ ISO 11137-1: 2006: Sterilization of Health Care Products- Radiation- Part 1: Requirements for development, validation, and routine control of a sterilization process for medical devices.

AAMI TIR33: 2005 Sterilization of health care products- Radiation- Substantiation of a selected sterilization dose- Method VDmax.

FDA “Guidance for Industry and FDA - Current Good Manufacturing Practice for Combination Products (Draft Guidance),” September 2004.

FDA “Draft Guidance Cooperative Manufacturing Arrangements for Licensed Biologics,” November 2008.

FDA “Guidance for Industry: For the Submission of Chemistry, Manufacturing and Controls and Establishment Description Information for Human Blood and Blood Components Intended for Transfusion or for Further Manufacture and For the Completion of the Form FDA 356h “Application to Market a New Drug, Biologic or an Antibiotic Drug for Human Use,” May 1999.”

FDA Guidance “Sterile Drug Products Produced by Aseptic Processing — Current Good Manufacturing Practice,” September 2004.

FDA “Draft Guidance for Industry: Amendment (Donor Deferral for Transfusion in France Since 1980) to “Guidance for Industry: Revised Preventive Measures to Reduce the Possible Risk of Transmission of Creutzfeldt-Jakob Disease (CJD) and Variant Creutzfeldt-Jakob Disease (vCJD) by Blood and Blood Products,” August 2006.

FDA “Draft Guidance for Industry: Current Good Tissue Practice (CGTP) and Additional Requirements for Manufacture of Human Cells, Tissues, and Cellular and Tissue- Based Products (HCT/Ps),” January 2009.

FDA “Guidance for Industry: For the Submission of Chemistry, Manufacturing and Controls and Establishment Description Information for Human Plasma-Derived Biological Products, Animal Plasma or Serum-Derived Products,” May 1999.

FDA “Guidance for Industry: For the Submission Documentation for Sterilization Process Validation in Applications for Human and Veterinary Drug Products”, November 1994.

PDA August 1998 Technical Reference 29 “Points to Consider for Cleaning Validation.”