



**DEPARTMENT OF HEALTH & HUMAN SERVICES**

Food and Drug Administration  
Center for Biologics Evaluation and Research  
Office of Compliance and Biologics Quality  
Division of Manufacturing and Product Quality

**Date:** July 31, 2009

**To:** Natalya Ananyeva, Visiting Scientist, OBRR/DH/LH, HFM-392, Committee Chairperson for BLA 125351/0

**From:** Joyce Rockwell, CSO, CBER/OCBQ/DMPQ/MRB1, HFM-675  
CAPT Martha O'Lone, BSN, CBER/OCBQ/DMPQ/MRB1, HFM-675

**Through:** Carolyn Renshaw, Branch Chief, CBEROCBQ/DMPQ/MRB1, HFM-675

**CC:** Jie He, Regulatory Project Manager, CBER/OBRR/DBA, HFM-380

**Subject:** **Filing Memo for STN 125351/0 for Fibrin Sealant TachoSil, Nycomed Danmark ApS, dated 22 May 2009.**

**Recommendation:** We recommend filing this BLA.

**Summary:** Determining technical merit of the submitted information was not performed as part of this initial assessment.

**Highlight of issues requiring further information / clarification**

**Questions for Nycomed**

1. Environmental Assessment: Please note that you have claimed **two** categorical exclusions; under 21 CFR § 25.31(a) and 25.31(c). Based on the information provided, it appears to CBER that 25.31(c) is the more appropriate exclusion. Please re-evaluate your claim for categorical exclusion and communicate your determination, including rationale for selection, to the agency.
2. Raw materials / reagents: Please provide details about determinations of country of origin for all raw materials and reagents.  
Is your facility manufacturing with non U.S. human plasma?  
Please provide more information on the incoming requirements for your equine materials.

3. Cleaning: Please provide a justification for the use of ----(b)(4)---- as a cleaning agent for removal of potential prion contamination.
4. Release criteria: What are the Endotoxin limits on final finished product?  
Please provide an explanation of the test method and a summary that includes actual test results for all conformance batches.
5. Change in equipment used for -----(b)(4)----- of coating suspension: Section 3.2.P.2.3, Pharmaceutical Development of Manufacturing process, page 10 states the ---(b)(4)--- device for the preparation of the fibrinogen suspension was changed from -----(b)(4)----- . Please clarify the currently used ---(b)(4)--- device since the former ---(b)(4)--- device is stated in major process equipment list (section 3.2.A.1, page 14).

**This application included the following sections on facility and equipment:**

Location	Description of Information
1.12.14	Environmental Assessment
2.3, 2.3.A., and 3.2.A.1. General Information	Establishment Description <ul style="list-style-type: none"> <li>• Site</li> <li>• Building -(b)(4)-</li> <li>• Production Areas / Floors</li> </ul>
1.4.4	Cross-Reference Information <ul style="list-style-type: none"> <li>• -----(b)(4)----- ----- -----</li> </ul>
3.2.P.2.4 3.2.P.7 3.2.P.8.3	Container / Closure System
3.2.A.1	HVAC
3.2.A.1	Water Systems (WFI and HPW)
3.2.A.1	Facility and Floor Diagrams: site, production areas (- (b)(4)-----), packaging area No diagrams for ground floor which is used for final packaging
3.2.A.	Flow Diagrams: product, materials, personnel

Location	Description of Information
----------	----------------------------

3.2.A.1	Contamination/Cross-Contamination <ul style="list-style-type: none"> <li>• Air classifications</li> <li>• In-Process controls</li> <li>• Changeover for production areas shared between US and rest of the world (ROW)</li> </ul>
3.2.A.1, and General Information (2.6)	Major Process Equipment <ul style="list-style-type: none"> <li>• Detailed list by process step/area: equipment name/description, identification number, room number</li> </ul>
3.2.A.1	Computer Systems
3.2.A.1	Cleaning Validation <ul style="list-style-type: none"> <li>• Categorization, dedicated equipment, change-over procedure, cleaning procedures and intervals, cleaning validation, containment features</li> </ul>
3.2.P.3.5	Process Validation <ul style="list-style-type: none"> <li>• Transport (Shipping)</li> <li>• Packaging</li> <li>• Sterilization (Gamma Irradiation)</li> </ul>
Information to be requested	Analytical Methods Validation <ul style="list-style-type: none"> <li>• Sterility</li> <li>• Endotoxin</li> </ul>
3.2.P.2.5	Microbiological Attributes <ul style="list-style-type: none"> <li>• Bulk Drug Substance --- (b)(4) --- controlled; release criteria established: ----- (b)(4) ----- -----</li> <li>• TachoSil: Pyrogen test (----- (b)(4) ---), Sterility (-(b)(4)- -----)</li> </ul>
3.2.P.3.3	Sterilization <ul style="list-style-type: none"> <li>• Gamma-irradiation of product in secondary packaging</li> <li>• Dry ----- (b)(4) ----- sterilization (equipment)</li> </ul>
3.2.R	Packaging <ul style="list-style-type: none"> <li>• Method Validation</li> </ul>
3.2.P.3.1	Analytical Tests not performed by Nycomed <ul style="list-style-type: none"> <li>• Sterility, Purity, General Safety Tests</li> </ul>