

MEMO TO THE RECORD
BLA 125351.0

DATE: 3/22/10
OFFICE: HFZ-410
DIVISION: DGRD/PRSB
FROM: Biologist
RE: Consult review
APPLICANT: NYCOMED - Fibrin Sealant Patch
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Recommendation: The most important aspects of my review of the collagen sponge material deal with the safety concerns of potential contamination of the material within the host organism or via the manufacturing facility. The collagen sponge material has been demonstrated to be safe in terms of animal sourcing, manufacturing processing and potential viral contamination issues. I confirmed with the DMPQ reviewer who went on the site inspection that the facility's machinery was naïve to other potentially contaminated tissues, e.g., bovine tissues derived from BSE-countries. She assured me that the facility was truly designated for this equine material and that it had not seen other materials. The viral inactivation potential of the manufacturing process is adequate for all hallmark viruses used for evaluation. For 3 of the viruses, the process achieves very high levels of inactivation; for PPV, the extent seen with gamma irradiation can be added to other manufacturing process steps not assessed, e.g., -----(b)(4)-----
-- ----- . No additional information is necessary.

Review:

CBER requested the following consultative review:

Consultative review is requested from CDRH to comment on the following:

- Tendon Supplier Qualification Requirements (should it be also addressed to CVM?)
- Collagen Sponge Manufacturing Process (from (b)(4) Horse Tendons to preparation of Collagen Sponge Strips)
- Implemented Improvements
- Expansion of the Production Capacity
- Control of Collagen Sponge quality (including adhesiveness)
- Adventitious Agents Safety Evaluation
- The Coating Process
- Effect of the (b)(4) on Collagen Sponge characteristics

Tendon supplier qualification requirementsSourcing/animal husbandry and facility issues

The collagen material is described as being produced at NYCOMED, Austria GmbH, Linz. The raw material is obtained from horses “at various -----(b)(4)----- slaughterhouses” which are stated to be “approved by the competent national veterinary authorities”. The sponsor notes that the tendons are retrieved from one -(b)(4)- slaughterhouse in -(b)(4)- and horse-(b)(4)- slaughterhouses in -----(b)(4)------. The sponsor notes that the horse-(b)(4)- slaughterhouses are certified by EU authorities and the ---(b)(4)-- slaughterhouse is approved by EU authorities and is USDA/FSIS certified. The summarized information provided indicates that:

- The slaughterhouses are approved by competent authorities
- Substantial measures for prevention of cross contamination/intermingling of tissues are taken
- Each batch of tendons is accompanied by a veterinary certificate and that the certificate indicates that the horses are free from disease

With regard to potential BSE issues, i.e., --(b)(4)-- slaughterhouse in -(b)(4)-, the following information was obtained from the USDA/APHIS website

(http://www.aphis.usda.gov/import_export/animals/animal_import/animal_imports_bse.shtml) regarding the presence of BSE:

Bovine Spongiform Encephalopathy

Countries/Regions Affected with Bovine Spongiform Encephalopathy (BSE)

Countries in which BSE exists 9 CFR 94.18(a)(1)

Austria	Japan
Belgium	Liechtenstein
Czech Republic	Luxembourg
Denmark	Netherlands
Finland	Oman
France	Poland
Germany	Portugal
Greece	Slovakia
Ireland (Republic of)	Slovenia
Israel	Spain
Italy	Switzerland
United Kingdom [<i>includes Great Britain (England, Scotland, Wales, Isle of Man), Ireland, Northern Ireland, and the Falklands</i>]	

Countries presenting an undue risk for BSE 94.18 (a)(2) *

Albania	Former Yugoslav Republic of Macedonia
Andorra	Monaco
Bosnia-Herzegovina	Norway
Bulgaria	Romania
Croatia	San Marino
Federal Republic of Yugoslavia	Sweden
Hungary	

*Import requirements less restrictive than those that would be acceptable for import into the United States and/or because of inadequate surveillance, present an undue risk of introducing bovine spongiform encephalopathy into the United States.

Countries Considered Minimal-Risk with Regard for BSE

94.18(a)(3)
Canada

Countries with Indigenous BSE Cases that May Export Whole Cuts of Boneless Beef.

9 CFR 94.27

Japan

As noted, even if tissue was obtained from -(b)(4)- slaughterhouses in -----(b)(4)-----, neither country is identified as a BSE concern. In -(b)(4)-, there is “minimal risk” identified, and so, since the abbatoir in -(b)(4)- is -(b)(4)- use, there would be a corresponding level of concern IF the tissues were intermingled. The sponsor does audit (see below) for this concern and -(b)(4)- and the United States have both been considered to present the same level of BSE risk for collagen-based medical device products. Both countries now use measures identified in 2004 regarding potential contamination by BSE:

The Food and Agriculture Organization of the United Nations (FAO) and the World Health Organization (WHO) make the following recommendations:

“All countries should continue to check for the disease and apply precautionary measures, even where BSE has never been found.”

“Keeping the material out of the food chain and not amplifying risk through feeding it back to animals are the principal factors to ensure against the survival of BSE in a country. “

In a statement issued on 12 January 2004 under the heading “BSE controls in many countries are still not sufficient”, sub-headed “FAO urges countries to strictly apply preventive measures”, FAO urged governments and industry to carry out a proper risk assessment and to keep risk animals and materials out of the food chain and to strictly apply the following preventive measures:

- * ban the feeding of meat-and-bone-meal to farm animals, at least to ruminants;
- * strictly avoid cross contamination in feed mills;
- * remove and destroy SRMs (Specified Risk Materials: brain and spinal cord, etc.) from cattle over 30 months;
- * ensure safe practices in the rendering industry, i.e. treatment of the material at 133°C under 3 bar pressure for 20 minutes;
- * apply active surveillance measures within the cattle population and accurate identification of animals and traceability throughout production, processing and marketing;
- * ban the use of mechanically removed meat.

Therefore, FDA/CDRH does not consider --(b)(4)-- bovine tissue to pose any additional risk than U.S.-based animal derived tissues, and U.S. animals are commonly used as source materials for implanted medical devices. The sponsor conducts audits of the slaughterhouses as follows:

Thorough audits are performed on a regular basis by Nycomed to qualify the slaughterhouses whereby the following issues are assessed:

- 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 of species
- Origin of slaughtered animals
- Traceability of materials and animals
- Hygiene and cleaning procedures
- Training of personnel
- Documentation system

In addition, the sponsor has controls in place to guard against tissue cross-contamination, and regarding facility use:

Measures for the prevention of cross contamination and intermingling of species include:

- Batch processing of animals with appropriate monitoring
- Segregation of the animal materials
- Use of dedicated equipment
- Appropriate cleaning procedures

Veterinary inspection of animals:

Each animal is examined by a veterinarian before and after slaughtering. Only tendons from horses which have passed the ante and post mortem inspection are used for further processing.

A veterinary certificate, which is issued by the competent veterinarian at the slaughterhouse, confirms that the horse tendons (animal by-product) satisfy requirements for the manufacture of pharmaceutical products. In addition the veterinary certificate confirms that the horse tendons originate from animals free from notifiable diseases and that the meat obtained from those animals is suitable for human consumption. 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 .

A significant concern that is typically raised when animal tissues are processed in manufacturing facilities in the EU is whether the facility has been used in the past for tissues which were sourced from BSE-contaminated countries. Austria, the manufacturing site, is a BSE-country and therefore there is likelihood that the facility has been previously contaminated. In previous medical device review, FDA/CDRH has determined that there is NO validated method

Manufacturing process

(b)(4)

The manufacturing process regarding the collagen sponge has many steps wherein virus-inactivation can occur. -----(b)(4)-----

In addition, the product is
--(b)(4)-- sterilized with gamma irradiation. The sponsor conducted a viral inactivation validation assessment using the following viruses:

- **Pseudorabies virus (PRV; enveloped DNA virus)**
- **Parainfluenza virus, Type 3 (PI-3; enveloped RNA virus)**
- **Reovirus, type 3 (Reo 3; non-enveloped RNA virus)**
- **Porcine Parvovirus (PPV; non-enveloped DNA virus)**

in accordance with FDA and international guidance recommendations. The sponsor determined that (b)(4)- pH achieved the following log₁₀ reductions in viral titers:

PRV:	≥5,68	(b)(4)
PI-3:	≥5,87	

however, (b)(4)- pH ((b)(4)-) did not achieve significant viral titer inactivation for Reo 3 or for PPV. The sponsor conducted an evaluation of the potential viral inactivation potential of the gamma irradiation sterilization step and found the following results:

The following minimum log₁₀ reduction factors (± 95 % confidence limits) were achieved by gamma irradiation with (b)(4) (data taken from table 01 through 04):

PRV:	≥4,67	(b)(4)
PI-3:	≥3,96	
Reo-3:	≥6,22	
PPV:	2,99	

As noted, there are a number of steps not assessed which could add to the extent of viral inactivation, i.e., -----(b)(4)-----

For 3 of the 4 viruses, (b)(4)- pH and irradiation are sufficient measures to eradicate significant quantities of virus titers. Porcine Parvovirus (PPV) is the only hallmark virus tested which did not show great titer diminishment with either (b)(4)- pH or sterilization. Approximately 3 logs of titer reduction were seen with PPV. It is reasonable to assume a 1-2 log diminishment for the -----(b)(4)----- steps for PPV, not considering -----
(b)(4)----- treatments. Therefore an approximate additional 3 logs titer reduction for PPV is not un-reasonable to estimate, and therefore, the viral inactivation potential of the manufacturing process for the equine collagen, including the animal husbandry oversight measures, i.e., veterinary inspection for ill animals, adequately provides for determination of a safe profile for the collagen sponge. **No additional information is necessary.**

Expansion of the production capacity, control of quality (i.e., adhesiveness, coating process, effect of -----(b)(4)-----

The sponsor cites in-process controls (IPCs), and identified collagen material specifications, as based on their European-approved (2004), TachoSil product. The acceptance criteria proposed are based on:

- -(b)(4)- EU validation batches
- Standards and guidance which include ICH Q6B, Specifications: Test procedures and acceptance criteria for biotechnological/biological products (1999)
- Observed data

The criteria are:

One (1) Page Determined to be Non-Releasable: (b)(4)

Results – collagen specific

[
--(b)(4)--
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The sponsor also conducted a comparison of the material as manufactured, at an expanded level and in the new facility designated for this product. The information demonstrated product consistency. **No additional information is necessary.**

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