

RESPONSE TO INFORMATION REQUEST

FDA request received from Martha O'Lone in email dated 15 March 2010

Bioburden

Q (FDA Question): Is there any bioburden testing at Nycomed on receipt of Fibrinogen or Thrombin from (b)(4)? (If CoA is verified, that is acceptable, just checking information)?

R (Nycomed Response): The bioburden test results are taken over from (b)(4) Certificates of Analysis.

Q: When is the last in process test for bioburden and what test is performed and parameters (range, action/alert level)?

R: The last in process test for bioburden is performed with TachoSil (b)(4) according to (b)(4) is performed with an action limit of (b)(4) and an alert limit of (b)(4) (b)(4)

Q: Is there any routine testing for bioburden (b)(4) sterilization performed at Nycomed or contracted out from separate lab?

R: Yes, please see above response. The bioburden testing of TachoSil (b)(4) is performed by Nycomed (b)(4). Usually the product is sent (b)(4) Based on stability programs performed with TachoSil (b)(4) (validation batches and conformance batches) a maximum hold time of (b)(4) months (at 2-8°C) was set.

Q: The final release bioburden specifications for TachoSil in 3.2.P.3 are listed as (b)(4) Your current or usual levels documented in the submission for release, sterilization validation and stability testing are (b)(4) The use of (b)(4)

(b)(4) for your specification does not appear to be an appropriate reflection of your current manufacturing capabilities. This level should be lower based on your sterilization validation as noted in discussion of sterilization below. This parameter should be adjusted to agree with your observed levels. Please provide a justification or a lower level. This level should be appropriate for release, sterilization, and stability testing. Please provide your alert and action levels. Please explain if there is any evaluation or planned evaluation at the alert level.

R: Compared to its predecessor products the action limit for US TachoSil was reduced already from (b)(4). The limit of (b)(4) was chosen due to the newly implemented inhouse packaging for US TachoSil and the few batch analytical data available so far. According to (b)(4) an average bioburden up to (b)(4) is adequate for a minimum sterilization dose of (b)(4). An internal alert limit of (b)(4) was set already in awareness of the actual low bioburden load of TachoSil (b)(4). This alert limit was based on the highest bioburden of (b)(4) (overall batch average (b)(4)) obtained in (b)(4) TachoSil (b)(4) sheets determined in sterilization Validation Studies (0903X-VB-000006.01) and rounded up to the next log level, resulting in (b)(4).

Nycomed will closely observe the bioburden values of US TachoSil (b)(4) during manufacture of the first commercial US batches, e.g. the (b)(4), and intends to then adjust the alert limit accordingly.

Sterilization

Q: In review of your irradiation summary sterilization validation report; Please provide a justification for the bioburden sterilization specification of (b)(4) (Section 3.2.P.3 page 1) when your sterilization data indicates that the bioburden tested during sterilization validation has been (b)(4).

R: Please refer to response above.

Q: Please explain the purity limit cited on page 49 of 2.3 Quality Summary where it states- Purity A limit of (b)(4) bacterial load guarantees the microbial quality of Collagen

R: The limit of (b)(4) reflects the limit for the Collagen Sponge (b)(4) (b)(4). One TachoSil (b)(4) size sheet (b)(4) consists of approx. (b)(4) collagen sponge which reflects approx. (b)(4) of one collagen sponge strip. For details please refer to 3.2.P.4.4, Justification of Specification for Collagen Sponge and to 3.2.P.3.4 Justification of Specification TachoSil (b)(4).

R: Nycomed plans to perform the next sterilization dose audit with the manufacture of the first commercial US TachoSil batches which at the same time are the first US TachoSil batches manufactured in 2010.

R: Revalidation in January 2010 was not performed as commercial production was not yet started. For clarification, the adjusted dose of (b)(4) is the standard irradiation dose and there are no intentions to change this dose. The standard irradiation dose is substantiated during the (b)(4) sterilization dose audit.

Q: Please provide the alert/ action level for bioburden testing (b)(4) sterilization. IF there were none, please provide information on how this will be addressed.

R: Please see above (action limit: (b)(4) alert limit: (b)(4)).

Packaging

Q: Other than the microbiological and sterility tests performed during sterilization validation and PQ for packaging, is there any test of final packaging physical integrity testing after sterilization or in your shelf life/ stability testing? In addition to visual inspection, the list of mechanical package integrity testing described in the submission during on line packaging and in sterilization validation appears to be (b)(4). Please provide/identify any packaging standards that are followed for the packaging tests, the parameters, and the action/alert levels, please clarify if they were included in Process Validation. If no standard test is used, please provide brief test method summary, acceptance criteria, ranges/parameters and action/alert levels. (Please provide brief information as to method, not the full testing).

R: Table 1 gives an overview of mechanical parameters for testing the integrity of TachoSil packaging during routine production.

The table indicates the acceptance criterion, the document where the test is described in detail (short method description is given below the table) and whether the test was performed during Process Validation.

The Packaging Process Validation in addition contained a series for testing the (b)(4) strength after irradiation. This test is not performed routinely because results of the validation (b)(4).

Page 3 redacted for the following reason:
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(b)(4)