

From: Do.Yu
To: Joan.robertson@grifols.com
Subject: Information Request (Response Due by Tuesday, October 17, 2017): Original BLA, BL 125640/0, Fibrin Sealant (Human), Instituto Grifols, S.A.
Date: Friday, October 13, 2017 3:26:41 PM
Attachments: [image007.png](#)
Importance: High

Dear Ms. Robertson:

We are reviewing your original November 3, 2016, submission to BLA 125640 for Fibrin Sealant (Human). We determined that the following information is necessary to continue our review:

1. In your response to Information Request dated February 6, 2017, regarding the preparation of glass syringes and stoppers, you indicated that IG performs endotoxin testing on the syringes and stoppers purchased from (b) (4). Please indicate the frequency of testing (i.e., every lot or every specified number of lots) and the sample size tested.
2. In regard to your (b) (4) membranes, please specify the maximum time frame within which the membranes may be held (stored) prior to recleaning. Information provided should include time and temperature and summary of qualification data to support. Please note that if you are using manufacturer's recommendations for storage conditions, qualification is not required. Additionally, please indicate if you are performing Normal Water Permeability (NWP) testing to detect membrane fouling; if not, please implement a plan to perform NWP testing or provide a justification for not performing.
3. In regard to your manual cleaning of product contact equipment, please indicate your routine monitoring program. If you do not perform routine monitoring, revalidation every (b) (4) is not sufficient. Please provide an updated requalification schedule or implementation plan for routine monitoring.
4. In regard to the cannula applicator, please indicate if you are performing any incoming testing to verify sterility. If not, please provide justification.
5. Please note that a supplement is required to be submitted for review, regarding the new (b) (4) machine after pending BLA approval.
6. In regard to room classification and acceptance criteria tables that were provided for HVAC and environmental monitoring (including Media fills), the values and classifications indicated for Class (b) (4) and Class (b) (4) seem to be consistently incorrect. These instances include, but are not limited to, the following:
 - a. On page 9 of the document Facilities and Equipment 3.2.A.1, the following was indicated:

Grade (b) (4) (Class (b) (4)): Filling rooms area (surround filling laminar flow equipment), rooms of the aseptic area, and room for sterility testing

Grade (b) (4) (Class (b) (4)): Rooms where the product is handled during its purification, rooms where auxiliary solutions are prepared, rooms for washing final product containers and closures, rooms for autoclave loading, and microbiological control laboratory areas.
 - b. In Table 6 in IG_VS_001545, Class (b) (4) is designated as (b) (4), and Class (b) (4) is designated as ((b) (4)) with particulate limits that do not match those in the FDA guidance. According to FDA guidance, Class B is 1000, while Class C is 10,000.

- c. In Table 1 (Limits to be applied in operative conditions) provided in document IG_MSP-001018_ING - Class (b) (4) ISO (b) (4), the particulate limits do not match those in the FDA guidance.
- d. In the updated Report IG_VS-001533 Validation of the Aseptic Filling (provided in response to Information Request dated April 26, 2017), the table for the Environmental Monitoring acceptance criteria had incorrect particulate limits for Class (b) (4).

According to FDA guidance, the acceptance criteria for the room classifications are indicated as follows:

Clean Area Classification (0.5 µm particles/ft ³)	ISO Designation ^b	= 0.5 µm particles/m ³	Microbiological Active Air Action Levels ^c (cfu/m ³)	Microbiological Settling Plates Action Levels ^{c,d} (diam. 90 mm; cfu/4 hours)
100	5	3,520	1 ^e	1 ^e
1000	6	35,200	7	3
10,000	7	352,000	10	5
100,000	8	3,520,000	100	50

Please indicate if the instances noted above (in addition to other instances not included) with regard to classifications and acceptance criteria for Class (b) (4) and Class (b) (4) are typographical errors. If these are not typographical errors, please provide a justification for the particulate limits indicated.

The review of this submission is ongoing, and issues may be added, expanded upon, or modified as we continue to review this submission. Please submit your response as an amendment to this file by October 17, 2017, referencing the date of this request. If you anticipate you will not be able to respond by this date, please contact the Agency immediately so a new response date can be identified.

If we determine that your response to this information request constitutes a major amendment, we will notify you in writing.

The action due date for this file is November 3, 2017.

Please acknowledge receipt of this request and contact me at (240) 402-8343 or Yu.Do@fda.hhs.gov if you have any questions.

Sincerely,

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