CENTER FOR DEVICES
AND RADIOLOGICAL HEALTH
OFFICE OF DEVICE EVALUATION
DIVISION OF ANESTHESIOLOGY, GENERAL HOSPITAL,
RESPIRATORY, INFECTION CONTROL, AND DENTAL DEVICES

U.S. FOOD & DRUG ADMINISTRATION

GENERAL HOSPITAL DEVICES BRANCH
INTERCENTER CONSULT MEMORANDUM

Date: 5/15/2017

To: Thomas Maruna
Regulatory Project Manager
Office of Blood Research and Review
Center for Biologics Evaluation and Research (CBER)

From: Sapana Patel, PharmD
Lead Reviewer/Pharmacist
CDRH/ODE/DAGRID/GHDB

Through: CDR Alan Stevens, Branch Chief
General Hospital Devices Branch

Subject: Consult for BLA125612/ICC1600759

Applicant	Octapharma Pharmazeutika
Indication for Use	For the treatment of acute bleeding episodes (b) (4) in adult and pediatric patients with congenital fibrinogen deficiency, including afibrinogenemia and hypofibrinogenemia
Drug / Biologic Constituent	Human Fibrinogen/Fibryna
Device Constituent	Octajet transfer device Filter (Cleared under (b) (4))

Recommendation:
Approval of the device constituents (Octajet and (b) (4) Filter) for the combination product Fibryna

I. Purpose / Background

The Center for Biologics Evaluation and Research (CBER) requested a consult from CDRH/ODE to review the device constituents of the combination product. The sponsor was notified in the Acceptance to Filing Letter from the Agency dated August 5, 2016 that the product which will be copackaged with a transfer device and a filter is a combination product.

The sponsor is proposing to copackage the following in the FIBRYNA package:
1 single use vial of FIBRYNA concentrate
1 transfer device (Octajet)
1 particle filter (Cleared under (b) (4))

The 50ml Water for Injection used for reconstitution is not provided in the packaging.

In the original submission received on June 9, 2016 the sponsor had noted that the (b) (4) . CBER was (b) (4) .

II. Administrative

Documents Reviewed:

Document Title	**Document Number**	**Date –Version**	**Location**
Final Verification Report-Octajet	120P58_05_08a_03_ FinalVerificationReport	8/24/2016	3.2.P.7
Usability specification and evaluation Octajet Transfer Device	N/A	6/11/2015	3.2.P.7
Medical Devices-Container Closure System			3.2.P.7.2
Compatibility Report Of Filters	Report 012015	6/11/2015	3.2.P.7
Compatibility Report of Transfer Device Octajet	Report 125P58	8/24/2016	3.2.P.7
Usability specification and evaluation Octajet Transfer Device	N/A	8/12/2016	3.2.P.7
(b) (4) Filter	510k submission	3/31/1994	IMAGE (b) (4)

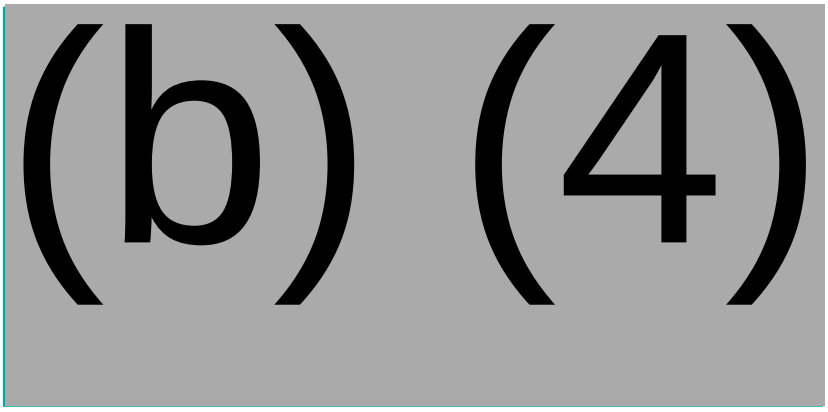
CDRH Review Team:

Team Member	Role
Sapana Patel, PharmD. CDRH/ODE	Lead Reviewer – Pharmacist
Lauren Lilly, Ph.D CDRH/ODE/INCB	Biocompatibility reviewer
Katharine Segars Ph.D CDRH/ODE/INCB	Sterility Reviewer

III. Device Description and Performance Requirements

Indications for Use	For the treatment of acute bleeding episodes (b) (4) in adult and pediatric patients with congenital fibrinogen deficiency, including afibrinogenemia and hypofibrinogenemia
Route of Administration	Intravenous
Intended User	Health Care professionals

Filter:



A letter of authorization has been provided by (b) (4) for review of the 510k for the filter. The filter is cleared under (b) (4) and contains a particle size of (b) (4) and the filter material is constructed of (b) (4). The filter is a (b) (4) filter which consists of a male luer lock and female luer lock side in compliance with ISO 594. The filter is sterilized with gamma irradiation and packaged in a plastic blister with a peel away backing. The following biocompatibility tests were performed on the filter based and classified as USP Class VI Plastics. The following tests were performed on the filter: cytotoxicity, acute systemic toxicity, intracutaneous toxicity, and implantation test.

Performance of the filter was completed under the 510(k). Testing include flow test (flow of water during an established time period), water bubble point (verification of the membrane pore size and integrity of the membrane seal), housing burst test (verification of upper and lower housings), (b) (4) testing (non-pyrogenicity claim), fluid retention (amount of liquid in device after membrane is wetted), bacterial retention of the membrane.

Filter specifications:

Test Parameter	Limit
Description	
Conformity Marking	CE (b) (4)
Pore Size	(b) (4)
Filtration Area	2.8 cm^2
Material of Construction	Filter Media: (b) (4) Housing: Modified Acrylic
Material Safety	Materials of construction have been evaluated in accordance with United States Pharmacopeia (USP) Biological Reactivity Test, In Vivo <88> (USP Class VI – 121°C Plastics Tests
Requirement	
Operating Pressure (max.)	5.2 bar
Operating Temperatur (max.)	55°C
Sterilization	(b) (4)

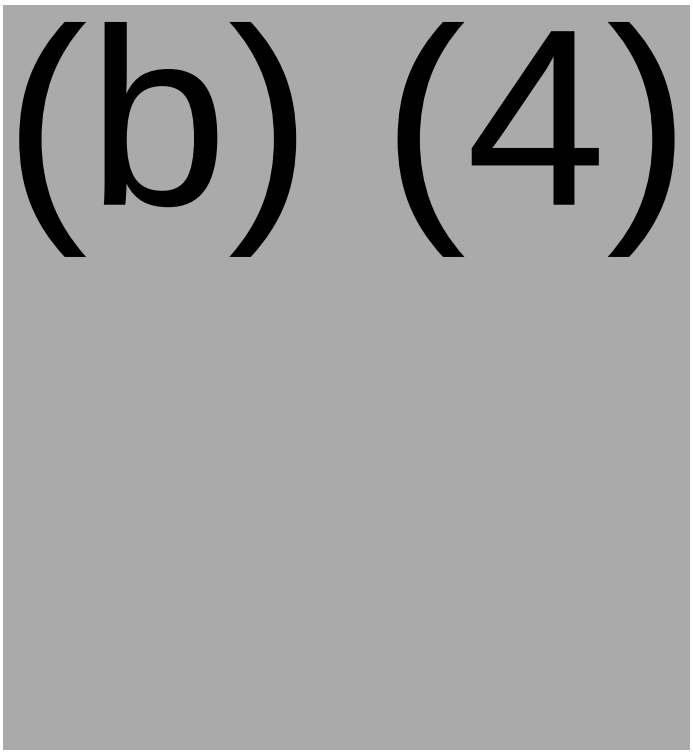
Reviewer Comment:
The sponsor has provided medical device specifications of the proposed filter to be used in the copackaged combination device. The device was reviewed under the 510k clearance and 510k holder had provided testing to support the use of the filter. The sponsor will be asked to provide the in process controls that are in place to ensure that the filters received meet the specifications of the copackaged combination product. The reviewer recommends CBER reviews the final drug product after use of the filter to ensure the drug composition has not changed.

On February 6, 2017 the following IR was sent to the sponsor:
You have provided medical device specifications of the proposed filter to be used in your copackaged combination product. It is unclear of your in process controls that are in place to ensure that the filters meet your specifications when received from your supplier. Please describe the in process controls you have in place to ensure that the device will meet your specifications.

Sponsor Response 2/24/2017: The lot wise Certificate of Quality (see example attached) provided by the supplier is checked to meet the requirements of the product specification. The supplier confirms that the materials of construction have been evaluated in accordance with the United States Pharmacopoeia (USP) Biological Reactivity Test, In Vivo <88> (USP Class VI-121°C Plastics Test). A list of standards applicable to the device is attached. Furthermore, the Certificate of Quality confirms that the criteria for filtration area, operating pressure and operation temperature are met and that the product underwent sterilization by gamma irradiation in the specified dosage range. The quality control performed on every incoming filter lot includes an identification of the material according to the supplier product number and lot number and a visual comparison with a reference sample. The functionality of the combination product is checked by correct fitting of the LUER-LOCK connections.

Reviewer Comment:
The sponsor states a certificate of quality will be provided by the supplier and checked to ensure the filter meets the requirements of the product specification. The sponsor has also provided a summary of applicable standards to the filter. The information provided for the filter is adequate.

Octajet:



Design Control/Design Verification:

Design Specifications:

Test Parameter	Limit
Description	
Conformity Marking	(b) (4)
Requirement	
Water Spike/ Powder Spike	(b) (4)
Luer Lock Cap female	(b) (4)
Distance Ring	(b) (4)
All the materials used meet requirements of the USP Plastic Class VI, ISO 10993 All the materials used meet requirements described in USP for physiochemical testing	
Sterilization	(b) (4)
Vacuum Seal	(b) (4)

Packaging	Blister: (b) (4), transparent ((b) (4)) (b) (4) (b) (4)-Lid: (b) (4)

All the materials used meet requirements of USP Plastic Class VI, ISO 10993
All the materials used meet requirements described in USP for physicochemical testing

Sterilization:
(b) (4)

Reviewer Comments:
In Section 3.2.P.7, the applicant has provided the material requirements for the Octajet. It is stated the water spike and powder spike are composed of the (b) (4) ***material,*** (b) (4) ***.***
On December 21, 2016, an IR was sent to the sponsor requesting additional information on the Octajet. The sponsor had initially stated that the (b) (4) ***. The sponsor was asked to provide the following information in the December 21, 2016 IR:***

(b) (4) Please provide the following information within your BLA submission:

Design Control Inputs to include:

Design Requirement Specifications
Device Verification/Validation Data in the BLA or cross referenced to a master file
Traceability Documentation
Biocompatibility testing based upon the biological evaluation of medical devices.
Sterility testing
Performance requirements of the device constituents including but not limited to leakage testing, flow rate, visual inspection, attachment force, testing in accordance to ISO 594
Lot Release Specifications and Testing
Labeling

Please provide full test reports for all tests performed.

On January 5, 2017, the sponsor provided the requested information in the BLA for review on the device constituent.

Reviewer Comment:
On January 5, 2017 in response to the Agency's Dec 21, 2016 request for additional information on the device constituent, the component material of the Octajet (identified by the device manufacturer) are (b) (4) ***for the water spike and*** (b) (4) ***for the powder spike. The applicant will be asked to clarify the discrepancy as the.***

The sponsor provided the design traceability matrix which included the design requirements (inputs), design control and verification (outputs) and design validation of the device constituents. This included a risk assessment and risk mitigation strategies. The information provided was adequate.

IR to Sponsor on February 6, 2017:

You have provided in Section 3.2.P.7 the material requirements for the Octajet. You state the Water spike/Powder spike is composed of (b) (4). In your response to Question 1 in the information request response on received on January 5, 2017, it is stated in Annex 5 that the water spike material is (b) (4) and the powder spoke is (b) (4). It is unclear if your material requirements are met by the proposed transfer device. Please clarify if your material requirements are met by the supplier of the Octajet. If the materials differ, please provide a rationale to why the device is considered acceptable if the requirements differ.

Sponsor response on February 22, 2017:
The correct materials to be used for the water spike and powder spike are (b) (4) and (b) (4), respectively (see table below). Both materials meet the requirements of USP class VI plastic. Stating of (b) (4) as construction material for the water spike in specification (b) (4) is incorrect. Although it was initially intended to use the same material for water and powder spike, this has been changed during development of the device. We apologize for the mistake in the provided specification. Please find the corrected material specification (b) (4) enclosed in Section 3.2.P.7.

Reviewer Comment:
The sponsor has stated that the correct material specifications are consistent with the specifications of the device manufacturer. The application has been updated to reflect this information. The response is adequate.

Biocompatibility (This section was reviewed by Lauren Lilly Ph.D. (INCB Branch) :

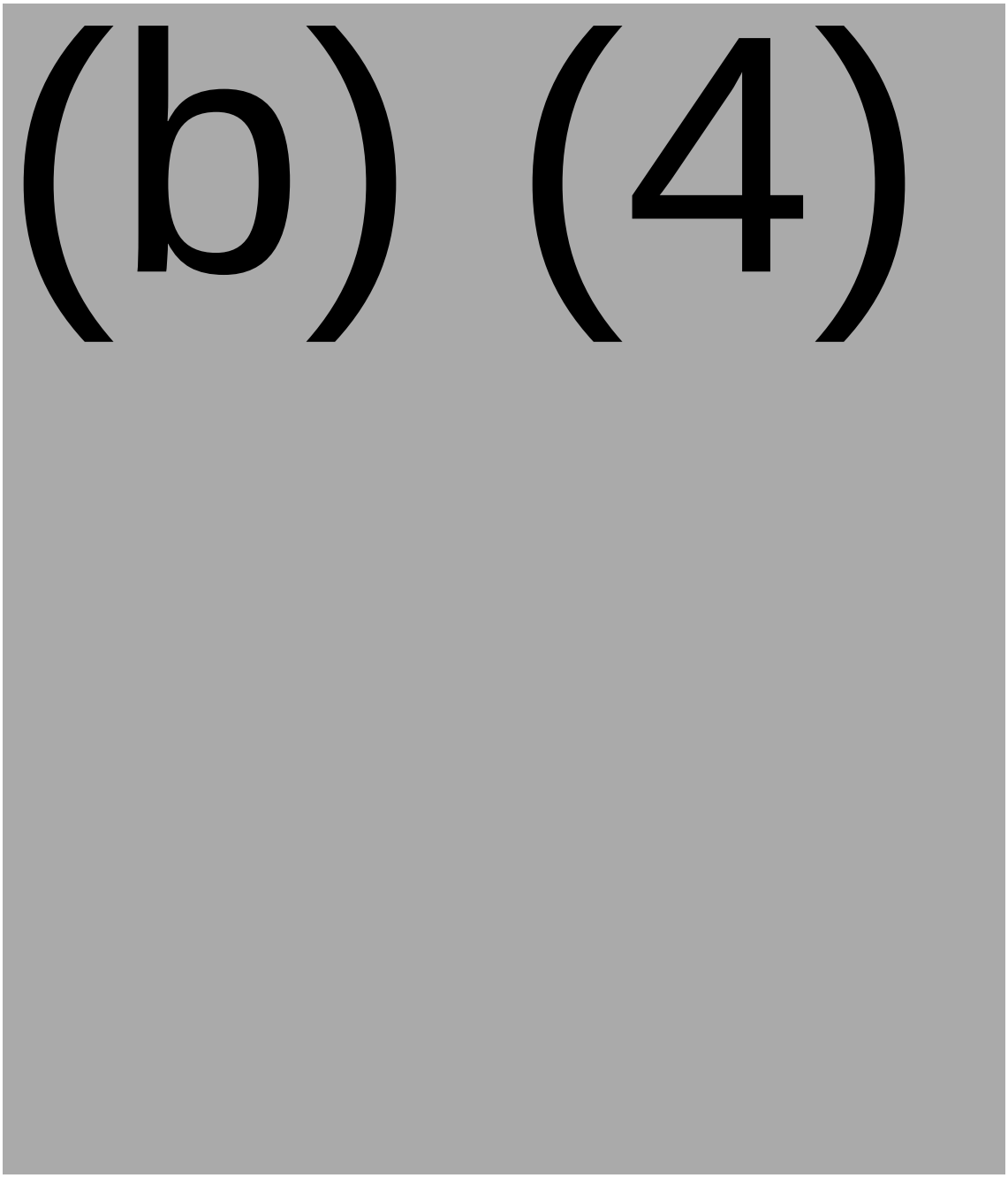
The sponsor did not provide biocompatibility testing as recommended by FDA's #95-1 memorandum and ISO 10993-1 for external communicating, blood path indirect devices. Rather, the sponsor contends that the primary risk of the subject device is the risk of drug vial contamination. In lieu of testing, extractable testing was performed on the final sterile device, in accordance with the European Pharmacopoeia 01/2009 (Ph. Eur.).

Device material:

(b) (4)

Briefly, (b) (4) finished and sterilized devices were mounted on an infusion bottle according to the device instructions. A volume of 50 mL of WFI freely flowed through each device into collection vessel. All (b) (4) extracts (b) (4) for the tests, i.e. (b) (4) extracts were used for testing of (b) (4). The average leachate time was (b) (4) min. Test results of WFI and the (b) (4) extract were compared with limits of the Ph. Eur.

The Extractable Analysis report is provided as Exhibit 15A of the 510(k) submission. The results are below:



The sponsor did not provide any biocompatibility testing as recommended by FDA's #G95-1 memorandum or ISO 10993-1. Rather, the sponsor performed a leachable study according to European Pharmacopoeia 01/2009 (Ph. Eur.) to demonstrate that no harmful leachables are generated by the device. The sponsor indicates that the leachables from the subject device conform to the specifications of European Pharmacopoeia 01/2009 (Ph. Eur.). It should be noted that the leachable study provided varies substantially from the recommendations of ISO 10993-12 and ISO 10993-18. For extractable and leachable testing, we typically recommend that testing is performed using a traditional polar and nonpolar solvent, under conditions of exhaustive extraction at 50C for 72 hours. After extraction, a risk assessment with calculated margins of safety for all chemical residues identified from the extractable and leachable testing, including the organic, inorganic, organometallics, metals, and other residues should also be

provided. In contrast, the testing provided by the sponsor had a leachate time of (b) (4) minutes. However, the typical use of this device will be 30 to 45 seconds; therefore the extraction time is reasonable. The extract was then analyzed according to European Pharmacopoeia 01/2009 (Ph. Eur.).

Based on European Pharmacopoeia testing, the sponsor also claims that the materials used in manufacturing of the subject device are USP Class VI and are pharmaceutical grade. To support that claim, the sponsor should demonstrate that the subject device does not transfer any adulterants to the drug. As such, the sponsor should **perform USP <661> testing** to demonstrate that the subject device meets pharmaceutical standards. As an alternative, the sponsor may claim that the European Pharmacopoeia 01/2009 and USP<661> are comparative. If the sponsor claims that the European Pharmacopoeia 01/2009 is comparative to USP<661>, a comparison between the European standard and USP <661> should be performed.

FDA Biocompatibility Deficiency #1: You have provided justification as to why biocompatibility testing was not performed on the subject device. In the absence of biocompatibility testing, you indicate that testing according to European Pharmacopoeia 01/2009 was performed. However, to demonstrate the pharmaceutical quality of a device, we recommend testing according to USP <661> Containers-Plastics. Therefore, the provided justification is incomplete and additional information is needed to assess the safeness of device. To demonstrate that your device is inert and will not alter the drugs transferred, please provide testing according to USP <661>. Alternatively, if European Pharmacopoeia 01/2009 is comparative to USP<661> testing and specifications, you may provide a thorough comparative analysis between European Pharmacopoeia 01/2009 and USP <661>. The comparison should include justification on how the results obtained from European Pharmacopoeia 01/2009 testing compare to the standard requirements of USP <661>.

Sponsor's response (dated February 14, 2017): *Testing according to USP <661> is not considered applicable due to the following reasons:*
USP <661> Containers-Plastics is for (b) (4) *based plastic packaging systems of pharmaceuticals. It is not applicable to the Octajet device as the Octajet is not used as a packaging container for pharmaceutical products nor made of* (b) (4) *. Packaging materials have long-term contact with the respective medical articles, whereas the Octajet is a transfer device which has only a few seconds contact with the diluent and with the mixed drug during removal by the Luer lock syringe (< 1 minute total time). This very limited contact time and the fact that all device components which have direct contact to the drug are made of USP class 6 compliant material eliminates the need for further biocompatibility testing. This is also supported by the results of the Extractable Analysis study (previously provided as Exhibit 15A-see enclosed), which shows that no hazardous materials are extracted from the sterile device during its use. During this study, the extract was in contact with the device for over* (b) (4) *, which is at least* (b) (4) *times the expected contact time during actual usage. The Octajet is shown to be biologically safe for its intended use.*

FDA Comment to sponsor (sent on 2/16/17): You have provided justification as to why biocompatibility testing was not performed on the subject device. In the absence of biocompatibility testing, you indicate that testing according to European Pharmacopoeia 01/2009 was performed. To demonstrate the pharmaceutical quality of the device, we have requested testing according to USP <661> Containers-Plastic in lieu of traditional biocompatibility testing. However, in your response to the Agency, you have stated that your device will only have a few seconds of contact with the fluid/medication. Please be aware that your device is likely to have repeated use, resulting in cumulative exposure to the patient. As such testing is needed to demonstrate that your device is safe for repetitive, indirect patient contact. Therefore, the provided justification is incomplete and additional information is needed to assess the safeness of device. To demonstrate that your device is inert and will not alter the

drugs transferred, please provide testing according to USP <661>. Alternatively, if European Pharmacopoeia 01/2009 is comparative to USP<661> testing and specifications, you may provide a thorough comparative analysis between European Pharmacopoeia 01/2009 and USP <661>. The comparison should include justification on how the results obtained from European Pharmacopoeia 01/2009 testing compare to the standard requirements of USP <661>.

Sponsor's response (sent in documents received on March 7, 2017):

Response:

Biocompatibility testing has been performed on the individual parts of the device (please refer to the already provided document "*15_Biocompatibility*"). This includes:

- Certification according to USP Plastic Class VI, which guarantees that neither injection of different extracts of the device nor implantation of the latter have any toxic effect (please refer to Table 15A of document "*15_Biocompatibility and Table 2 below*).

- Certification according to ISO 10993 which confirms the biocompatibility of the device (please refer to Table 15B of document "*15_Biocompatibility*).

- A simulated extractable study on the sterile device has been carried out (please refer to "*Exhibit 15A Octajet Extractable Analysis*").
  Study description: since WFI is the main solvent that comes in contact with the Octajet device WFI has been used as solvent for extraction. (b) (4)
  (b) (4)
  Test methods: (b) (4)
  (b) (4)
  Test results: the test results show that the extract, i.e. the WFI complies to all quality requirements demanded by Ph.Eur. and thus prove that the device is inert, that it will not add any contaminants to the drug product and that it will not alter the drugs transferred.
  The tests demanded by Ph.Eur. are exhaustive and equivalent to the tests listed in USP <661> Containers-Plastics, USP 37. For the sake of clarity, the following table is presented comparing the extent of tests covered by both Ph.Eur. and USP <661> Containers-Plastics, USP 37. Equivalent tests are marked by different colors.

Table 1: Comparison of tests required by both Ph.Eur. and USP <661> Containers-Plastics, USP 37. Equivalent tests are marked by different colors.

(b) (4)

The overview of tests demanded by both Ph.Eur. and USP <661> Containers-Plastics, USP 37 presented in Table 1 shows that all the tests that are required by USP <661> Containers-Plastics, USP 37 have been performed on the Octajet device according to Ph.Eur. and that all the test results are compliant.

In the following, two tests that have not been carried out are listed and their omission is justified:

(b) (4)

Table 2: Materials used for the production of Octajet

Component	Material
Water spike, Cover, Distance ring	(b) (4)
Powder spike	
Vacuum Seal	
Blister pack	
(b) (4) Cover	

- Biological tests: biological testing of the Octajet device is covered by (b) (4) .

Ph.Eur. does not require measurement of the (b) (4) however, it does demand measurement of the equivalent (b) (4) . In addition to this, Ph.Eur. requires analysis of (b) (4)
(b) (4)
(b) (4) cover this parameter adequately. All parameters were compliant.

Compatibility of the device with the product has been confirmed, please refer to the document, *125P58_05_08b_00_OctajectCompatibility*.

We believe that the aforementioned test results give evidence of the safeness of the Octajet device for its intended use.

In regards to a likely repeated use of the Octajet please note that the Octajet is a single-use device and any reuse is a disregard of the user manual (please refer instruction of use). A reuse would anyway be impossible: by removing the distance ring and pressing down the WFI vial a membrane is disrupted thus enabling the transfer of the WFI into the product vial. Once this membrane is disrupted a reuse of the Octajet for reconstitution is not possible anymore. A further use of the device would then lead to a vacuum loss of the product vial by impeding the transfer of the WFI.

FDA comment to sponsor (sent on 3/28/17): In the Response to Information Requested on February 06, 2017, in response to FDA question 22, you state the following:

Certification according to ISO 10993 which confirms the biocompatibility of the device (please refer to Table 15B of document "15_Biocompatibility).

However, based on the information provided, biocompatibility testing according to ISO 10993 was not performed. Rather, a European Standard test method (i.e. European Pharmacopoeia 01/2009) was performed. Therefore, the meaning of the above statement is not clear. Please clarify.

Sponsor's response (sent in documents received on April 1, 2017):

It is correct that rather a risk assessment and alternative approach for evaluation of the suitability (in terms of biocompatibility) than a biocompatibility testing according to ISO 10993 were performed. We apologize for the misleadingly formulated answer.

The risk assessment of the Octajet device performed by the manufacturer/supplier (b) (4) (b) (4) in accordance with EN ISO 14971:2012 concludes that an alternative approach to ensure biocompatibility is more appropriate (a comprehensive justification is provided in document, *Section 15 Biocompatibility* and *Exhibit 15B Biocompatibility Evaluation).*

- No direct patient contact and extremely short contact time between the device and the drug for reconstitution and transfer for further application (transient/short term contact/non invasive)
- Materials (USP class VI) used to fabricate the Octajet are commonly used in the manufacture of other disposable, single use, sterile medical devices, such as catheters, that have direct and longer-term contact with the patient.

Therefore, Octajet manufacturer (b) (4) decided to perform instead a simulated extractable test to evaluate the impact of the sterile device on WFI as solvent under exaggerated contact time condition (in accordance with the European Pharmacopoeia 01/2009, please refer to document *Exhibit 15A Octajet Extractable Analysis).* Please also refer to response of question 22 of information request dated February 06, 2017. Since no hazardous materials were extracted from the product-contacted material from the device, it can be concluded that the device is biocompatible for its intended use.

Final FDA comment to record: The above deficiency (i.e. the original deficiency #1) was sent to confirm that the device is indeed pharmaceutical grade (and therefore controlled for impurities). In the (b) (4) BLA application, the sponsor indicated that testing was performed according to a European standard and not USP 661 (which is typically recommended to demonstrate impurities levels of a drug container closure system). As such, the sponsor was asked to provide a comparison between the standard employed and USP 661. In the above response from the sponsor, the sponsor demonstrated that the test methods are similar. Moreover, the employed method is similarly as vigorous as the USP 661. As such, the provided testing supports the sponsor's claim that the patient contacting components are pharmaceutical grade.

After continuous discussions with Team Lead, it was decided that based on the transient contact, and the pharmaceutical grade status of the device, testing according to ISO 10993 is overly burdensome and not needed for this device. Moreover, based on discussions with the lead reviewer, it was indicated that CBER will not request extractable and leachable testing used the intended biologic (i.e. human fibrinogen). This issue was also discussed with Team Lead. As stated above, the device is intended for only transient contact. Moreover, the device is pharmaceutical grade and therefore has been demonstrated to have a specified level of impurities. Therefore, E&L testing with the biologic was not and will not be requested.

Collectively, the information provided by the sponsor is acceptable.

FDA Biocompatibility Deficiency #2: We have observed that you have provided (b) (4) testing to demonstrate that the device contains acceptable levels of bacterial endotoxins. However, it is not clear whether it is your intent to make non-pyrogenic claims. To support non-pyrogenic claims, bacterial endotoxins and material-mediated pyrogenicity should be evaluated. To evaluate material-mediated pyrogenicity, we recommend USP <151> rabbit pyrogen testing be performed. Therefore, if it your intent to label your device as non-pyrogenic, please provide rabbit pyrogenicity testing according to USP <151> Pyrogen Test.

Sponsor's response (sent to lead reviewer on 2/16/17): It is not intended to claim non-pyrogenicity for the Octajet.

Final FDA comment to record: This issue was discussed with branch during the 510(k) submission. Based on the pharmaceutical grade of the device and the assessment of bacterial endotoxins, additional material mediated pyrogenicity was not and will not be requested. This response is acceptable and this deficiency is resolved.

Sterility (This section was reviewed by Katharine Segars Ph.D. (INCB Branch) :

Sterilization Method: (b) (4)

(b) (4)

Reviewer Comments:

- *terility test reports were provided separately in Exhibit 14A from Amendment #0034. The sterility test reports appear to be appropriate. Exhibit 14A is described in greater detail later in this consult memorandum (under FDA Question 21).*
- *oburden test reports were provided separately in Exhibit 14B from Amendment #0034. Exhibit 14B is described in greater detail later in this consult memorandum (under FDA Question 21).*

2) Stability Test Plan: (MA0019929879S709-03-PVP):

Purpose: "to determine the expiration period based on the results of a stability study."

The sponsor's requirements for testing were provided as follows: (b) (4) sterilization will be performed by the contract sterilizers (b) (4), respectively. The device primary packaging is (b) (4) blister + overlap with (b) (4) label. The required expiration period is a minimum of 12 months, with subsequent extensions to (b) (4). Storage conditions are 2-25°C at (b) (4) relative humidity. The device should be monitored for changes in color in the powder spike component. Accelerated aging and real time stability studies will be performed. Prior to completing the stability studies, the device will undergo functionality testing, bioburden testing, and sterilization using (b) (4)

(b) (4). Partial validation reports will be provided at various time intervals. Three batches will be tested: Batch (b) (4). (b) (4) units will be tested for bioburden from each batch, (b) (4) units/batch will be tested for sterility and (b) (4) units/batch will be tested for stability. Sterility is to be determined at time zero and again at intervals of (b) (4) of accelerated aging. Accelerated aging will comply with ASTM F1980.

3) Stability Test Report: (MA0019929879S709-03-PVR):

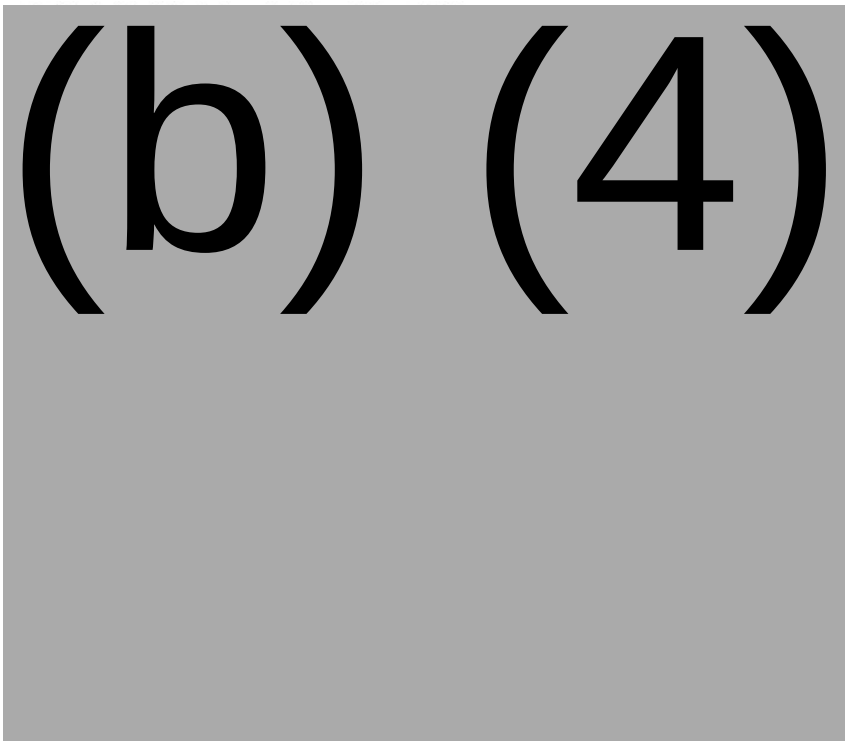
Purpose: To determine the expiration period on the basis of the results of a stability study.

- This document was revised on April 8, 2016 to add "the results of sterility." The partial report includes evaluation of the accelerated aging for (b) (4), which is equivalent to a (b) (4) shelf life. Bioburden was determined on August 17, 2015 and stress tests were completed on January 5, 2016. Stress test results were provided; however, device performance testing is outside the scope of this sterility consult.
- The test report includes confirmation that real time stability testing is being conducted in parallel. This is appropriate.

Method: Bioburden was determined (b) (4) by (b) (4). Sterility testing was performed (b) (4). The protocol for sterility testing could not be located.

Results:

- The bioburden test results from August 17, 2015 do not appear to be included in this test report.
- Sterility test results:



Reviewer Comments: The information provided in Stability Test Report: (MA0019929879S709-03-PVR) was not clear. The information provided appears to state that bioburden testing was conducted (b) (4) *and sterility testing was performed* (b) (4). *However, the results of the referenced bioburden testing could not be located and the protocol for sterility testing was not included. The sponsor*

was asked to clarify this test report and provide actual test results for bioburden testing. The sponsor should also provide the test method that was used to conduct sterility testing. The sponsor provided adequate information in their response.

This attachment also includes evaluation of color change and functionality testing at the end of the proposed shelf life; however, this information is outside the scope of a sterility review.

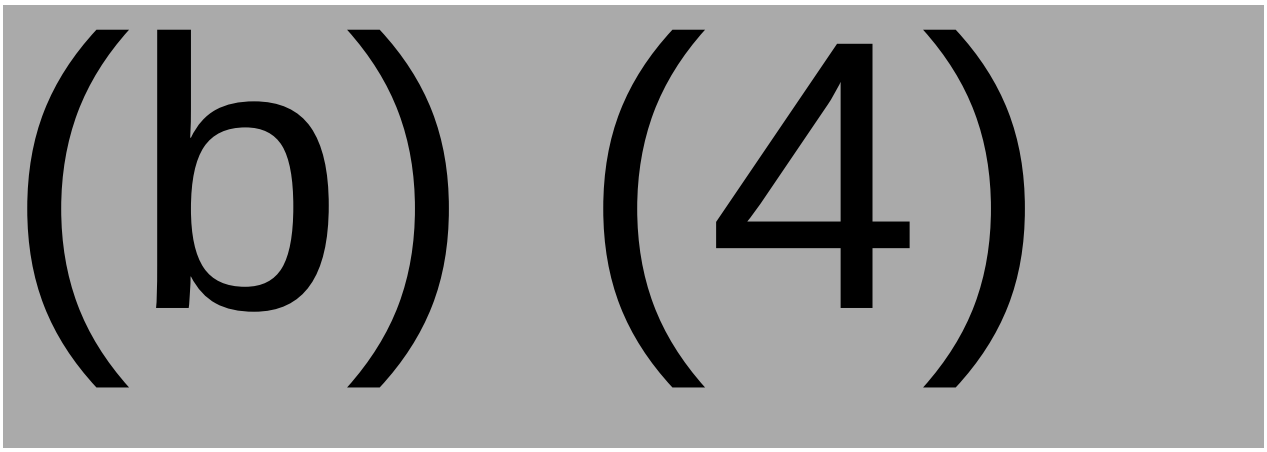
4) Packaging Transport Validation report – (MA001992989S709-02-PVR)

Reviewer Comment: Dr. Patel provided email confirmation on 3/22/2017 that the packaging transport validation test report is specific to device functionality and as such, is outside the scope of this sterility consult.

Deficiency to sponsor: *The stability test plan and report (MA0019929879S709-03-PVP and MA0019929879S709-03-PVR, respectively) are provided in your submission. Furthermore transportation and handling testing was conducted demonstrating that the packaging remained in a satisfactory condition with no evidence of damage to the primary packaging. Please find enclosed the Packaging Transport Validation report, MA001992989S709-02-PVR.*" However, the information that you provided is not sufficient to support a (b) (4) year shelf life claim. Please address the following concerns:

a) You have not provided package integrity testing to demonstrate that the device packaging maintains a sterile barrier throughout the claimed shelf life. Please consider conducting the most appropriate package integrity testing for your package type, seal integrity, and barrier performance as referenced in ANSI/AAMI/ISO 11607-1:2006/(R)2010, Packaging for terminally sterilized medical devices – Part 1: Requirements for materials, sterile barrier systems, and packaging systems. We recommend that your testing include bubble leak or dye penetration according to ASTM D2096, Standard Test Method for Detecting Gross Leaks in Packaging by Internal Pressurization (Bubble Test) or ASTM F1929-15, Standard Test Method for Detecting Seal Leaks in Porous Medical Packaging by Dye Penetration, respectively. Testing should be conducted on the final, packaged device at the end of the claimed (b) (4) shelf life, and should be conducted separately for (b) (4) sterilized devices. Please ensure that you conduct real time aged testing in tandem with testing on accelerated aged devices.

Sponsor Response: The below mentioned testing and sampling plan are considered for (b) (4) aged and real time aged Octajets. Both studies are being conducted in parallel and shall verify the minimum time where the Octajet remains sterile, functional and without any visible material cracks. Regarding the requested package integrity testing, Peel test according to ASTM F88/88M and Dye Penetration test according to ASTM F1929 are considered. Both tests are performed for (b) (4) sterilized devices for the real time stability study and for the (b) (4) sampling period. For detailed information a revised Validation Plan, MA001992989S709-03- PVP will be provided until appr. April 20, 2017.



Plan for Real time Stability Study for three batches Octajet			
Sampling/expiration period [years]	**Conducted Tests at each sampling period[1]**	**Test description** *Validation Plan, MA001992989S709-03-PVP*	**Reporting on conducted tests**
1	Sterility Test Discoloration check Functionality Test Stress Test **Peel Test** **Dye Penetration Test**	Chapter 7.8.1 Chapter 7.8.2 Chapter 7.8.3 Chapter 7.8.4 Chapter 7.8.5 Chapter 7.8.6	*Validation Report, MA001992989S709-03-PVR_Part5*
2			October 2017
(b) (4)			October 2018

[1] Determination of Bioburden on all three batches is considered (b) (4)

Based on the finalized (b) (4) *equivalent to* (b) (4) *expiration period) and 1 year real time aged stability study a shelf life of* (b) (4) *is claimed, please refer to respective tables below. Data on the requested package integrity testing by e.g. Peel test and Dye Penetration are available for the 1 year real time sampling period and will be performed acc. to Validation Plan for the other real time sampling points, 2* (b) (4) *. Additional testing's were considered for the* (b) (4) *sampling point of the accelerated stability study, please refer to the tables below. More detailed information on data/results, will be provided in revised Validation Reports, Accelerated Stability Study for* (b) (4) *MA001992989S709-03-PVR_Part 3 and Real Stability Study for 1 year MA001992989S709-03-PVR _Part 5 respectively until appr. April 20, 2017.*

(b) (4)

Data on Real time Stability Study for three batches Octajet		
Sampling/expiration period [years]	**Conducted Tests**	**Test Results** *Validation Report, MA001992989S709-03-PVR_Part 5*
1	Sterility Test	Sterile, refer to chapter 2.4.1
	Discoloration check	Passed, refer to chapter 2.4.2
	Functionality Test	Passed, refer to chapter 2.4.3
	Stress Test	Passed, refer to chapter 2.4.4
	Peel Test	**Passed, refer to chapter** 2.4.5 (4)
	Dye Penetration Test	**Passed, refer to chapter** 2.4.5 (5)

[1] Bioburden was successfully determined within specified limits on all three batches (b) (4)

Concluding, package integrity testing is considered throughout the claimed shelf life of (b) (4)*. Peel test according to ASTM F88/88M and Dye Penetration test according to ASTM F1929 are conducted in tandem for the* (b) (4) *real time stability study for* (b) (4) *sterilized devices.*

Reviewer Comment: The sponsor provided an (b) (4) **aged stability study in MA001992989S709-03-PVR. Devices were sterilized by** (b) (4) **prior to** (b) (4) **of** (b) (4) **aging to represent the** (b) (4) **shelf life. Peel test, dye penetration, and visual evaluation was conducted at the end of the** (b) (4) **aging. The results of the peel test, dye penetration test, and label readability were reported in the "Stability Report** (b) (4) **." The reports indicate that the protocol was executed without deviations and the acceptance criteria were met for both tests. The sponsor confirmed that testing was conducted in accordance with ASTM F88/88M and ASTM F1929.**
Additionally, the table copied above entitled " Plan for Real Time Stability Study for three batches Octajet" confirms that the sponsor is currently conducting peel and dye penetration testing on real time aged products. The provided information and testing is appropriate to support the (b) (4) **shelf life.**

b) It is not clear how the information in the stability test plan and report (MA0019929879S709-03-PVP and MA0019929879S709-03-PVR) supports your claimed shelf life. The test reports alternate between multiple languages and are difficult to interpret. The test report indicates that bioburden testing was conducted (b) (4) and sterility testing was performed (b) (4). However, the results of the bioburden testing could not be located and the protocol for sterility testing was not included. Additionally, it is not clear how this information is intended to validate that your device will remain sterile throughout a (b) (4) shelf life. Please clarify how bioburden testing (b) (4) and sterility testing (b) (4) supports your claimed (b) (4) shelf life. Please also update your test

reports to include the complete protocols and test results for bioburden and sterilization of both the (b) (4) sterilized devices.

Sponsor Response: A more reader friendly stability test plan and report concerning multiple languages including results of bioburden testing and information on sterility testing (and also in regards to question 1) is currently being prepared and will be provided until appr. April 20, 2017.

Determination of bioburden was conducted (b) (4) *acc. to Working and Control Instruction No. LS-PKP.MA001992989S709 to release batches for conducting stability study and represents start point, time 0 "T0". Please find enclosed in total* (b) (4) *certificates on* (b) (4) *samples from* (b) (4) *separate batches.*

Determination of sterility (b) (4) *according to* (b) (4) *is considered for each sampling point of accelerated and real time stability study proving a sterile devices over the claimed shelf life of* (b) (4)*, please refer to tables below:*

(b) (4)

Real time Stability Study for three batches Octajet Results on Sterility test (b) (4) for (b) (4)	
Sampling/expiration period [year]	(b) (4)
1	sterile

Supporting the claim of (b) (4) *shelf life the below mentioned tests are considered. The final updated reports on the* (b) (4) *stability study (*(b) (4)*) as well as for* (b) (4) *real time stability study are enclosed, will be provided until appr. April 20, 2017. Please refer also to response of question 1.*

(b) (4)

Reviewer Comment: Within Amendment #0048, the sponsor provided an accelerated aged stability study titled MA001992989S709-03-PVR. The testing provided is adequate to support the claimed (b) (4) shelf life. This deficiency is resolved. Please see a more detailed discussion of this testing in the preceding Reviewer Comment, above.

c) You stated that transportation and handling testing was conducted to demonstrate that the packaging remained in a satisfactory condition with no evidence of damage to the primary packaging, and you referenced the Packaging Transport Validation report, MA001992989S709-02-PVR. However, the Packaging Transport Validation that you provided does not indicate whether the validation was conducted on accelerated aged or real-time aged devices. Therefore, this information is not sufficient to support your claimed shelf life of (b) (4). Please clarify whether your transportation and handling testing was conducted on devices at the end of the (b) (4) shelf life. Please also provide justification that devices tested were representative of aged samples, addressing factors such as potential material deterioration or damage to packaging.

Sponsor Response: According to report Exhibit 13D, Packaging Transport validation report MA001992989S709- 02-PVR_B, transport and handling testing was performed by the supplier/manufacturer (b) (4) *with devices* (b) (4) *. Neither primary nor secondary packaging material showed any damages or deformation after several tests performed. Furthermore, visual and functional tests were performed successfully. Along with question 1 and 2 the below mentioned test are considered for accelerated and real time stability study to address also factors as potential material deterioration or damage to primary packaging.*

(b) (4)

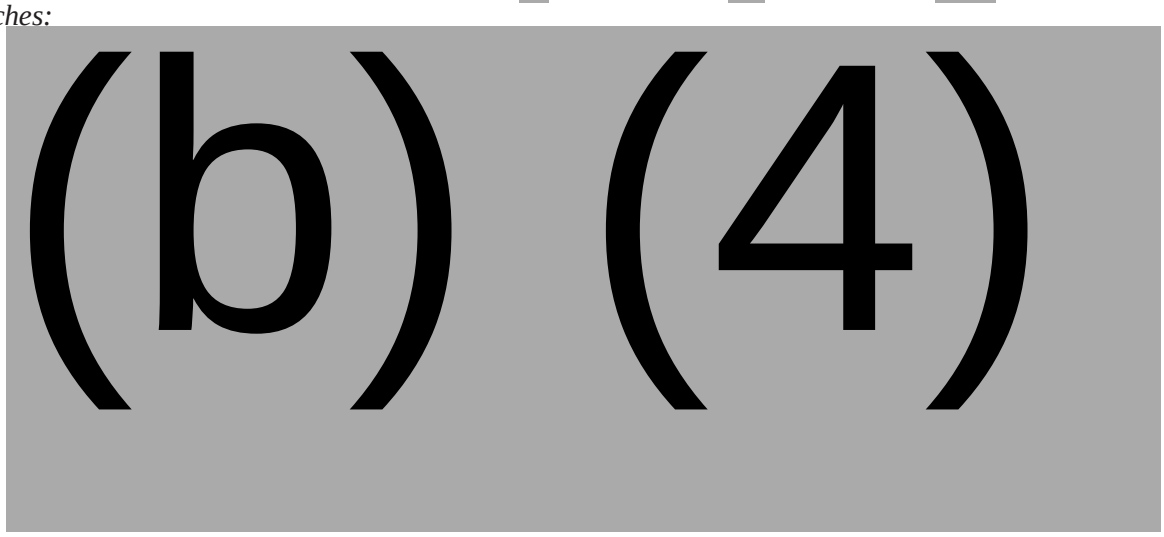
As agreed with the supplier/manufacturer (b) (4) *transfer device Octajet delivered to Octapharma has to have a remaining shelf life of* (b) (4). *Furthermore Octapharma is repackaging the Octajet as it will be marketed together with the product vial and the syringe filter as combination product. To support functionality of our combination product after shipping, we proposed a transport validation of the co-packaged product with the first commercial batch shipped to the US as a post approval commitment, refer to amendment #0041. Additionally we will package real time* (b) (4) *aged Octajets to address factors such as potential material deterioration or damage to packaging at the end of the shelf life.*

Reviewer Comment: The sponsor stated that for the packaging transport validation study, the primary and secondary packaging were tested (b) (4) **. They identified further testing of the primary packaging at the end of the claimed shelf life in the table above. This appears to be appropriate to support the package integrity over the shelf life. This deficiency is resolved.**

This sponsor response also references the transport validation testing of the co-packaged product to support the functionality of the combination product as a post approval commitment. Please note that evaluation of this planned testing is outside the scope of the sterility consult for the Octajet transfer device.

2. The document titled Amendment #0034 includes Bioburden Certificates for (b) (4) test samples in Exhibit 14B. However, within Section 14 – Sterilization and Shelf Life – (eCTD sequence #0028) you stated that bioburden testing was conducted on (b) (4) samples from (b) (4) separate batches. You also stated that the average bioburden from the (b) (4) batches was used to calculate the (b) (4) based on Table (b) (4) from (b) (4) . Please provide the bioburden test certificates for each of the (b) (4) samples from the other (b) (4) test batches to support your claim that (b) (4) is the minimum acceptable (b) (4) .

Sponsor Response: Please find enclosed in total (b) (4) certificates on (b) (4) samples from (b) (4) separate batches:



Reviewer Comment: The sponsor has provided the (b) (4) bioburden certificates that correspond to the bioburden data provided in the above table. The information provided appears to be adequate to support the minimum acceptable (b) (4) . This deficiency is resolved.

3. The document titled Amendment #0034 includes Endotoxin (b) (4) testing for the Octajet device in Exhibit 14E. However, Exhibit 14E does not clearly indicate how many device samples were tested for (b) (4) . Additionally, Exhibit 14E does not address whether you intend to conduct (b) (4) testing on every batch. Please note that the FDA Sterility Guidance document recommends that you provide confirmation that endotoxin testing will be conducted on every batch. Please clarify how many devices were tested for (b) (4) and provide a scientific justification that the sample size tested is sufficient to verify (b) (4) endotoxin limits are within the acceptable range for your subject device. Please also confirm whether you intend to conduct endotoxin (b) (4) testing on every batch, as recommended in the FDA Sterility Guidance Document. You may refer to the Submission and Review of Sterility Information in Premarket Notification (510(k)) Submissions for Devices Labeled as Sterile Guidance for Industry and Food and Drug Administration Staff for additional information.

Sponsor Response: As the FDA Sterility Guidance document recommends, (b) (4) testing is performed on (b) (4) and sample size is according to (b) (4) , please refer to table below:

Test Process	Sampling	Frequency	Limit
Endotoxin testing (b) (4)	(b) (4)		

For detailed information, please refer to the document, Working and Control Instruction No. LS-PKP.MA001992989S709 (item 140, production step Sampling and sample preparation) provided within amendment #0035 on February 23, 2017. During process validation (b) (4) *samples were analyzed see table below. In addition please find respective certificates enclosed:*

Test Process	Limit	(b) (4)
Endotoxin testing (b) (4)	(b) (4)	

Reviewer Comment: The sponsor has confirmed that (b) (4) **testing will be conducted on** (b) (4) **. The document labeled as Amendment #0044 also includes certificates of endotoxin limits for samples from** (b) (4) **separate batches. This complies with the sample size recommended in** (b) (4) **. This deficiency is resolved.**

Note: These deficiencies and responses were provided in the document titled Outstanding Response to FDA information request – Mar. 22 2017

1. In your response to the March 8, 2017 you provided Exhibit 13 C. Within Exhibit 13C, you have provided seal strength testing for the subject device. However, this information is not sufficient. We request that you please address the following concerns:

It is not clear whether you have performed seal strength testing on samples of the subject device (b) (4) . Please clearly state whether seal strength was evaluated for (b) (4) methods. Please be advised that package integrity testing should be performed on the subject device after it has been sterilized according to the validated sterilization methods described in your submission.

Sponsor Response: Please note that a response was already provided on March 28, 2017 within amendment #041.

The following response was provided in Amendment #041: Seal strength testing was performed during aging study for (b) (4) *method.*

The package integrity was tested (b) (4) *validation according to* (b) (4) .

Reviewer Comment: The sponsor has confirmed that the seal strength testing was performed (b) (4) **methods. This deficiency is resolved.**

2. It appears that seal strength is the only barrier testing that was provided for your subject device. Seal strength testing alone is insufficient to demonstrate that the proposed packaging maintains a sterile barrier

throughout the claimed shelf life. Please provide additional testing such as ASTM F1929, Standard Test Method for Detecting Seal Leaks in Porous Package Materials by Dye Penetration, and ASTM F2096, Standard Test Method for Detecting Gross Leaks in Packaging by Internal Pressurization (Bubble Test) to demonstrate that the packaging presents an impermeable barrier. Please refer to ISO 11607-1:2006/(R)2010, Packaging for terminally sterilized medical devices – Part 1: Requirements for materials, sterile barrier systems, and packaging materials for more information related to appropriate package integrity testing.

Sponsor Response: Please note that a response was already provided on March 28, 2017 within amendment #041 except for the results of the dye penetration testing. A dye penetration test was performed in the course of real time stability studies (currently 1 year data available). Please refer to report MA001992989S709-03-PVR, page 11 and 16.

Reviewer Comment: In addition to the seal strength testing, the sponsor has also provided dye penetration testing in accordance with the FDA-recognized consensus standard, ASTM F1929, Standard Test Method for Detecting Seal Leaks in Porous Medical Packaging by Dye Penetration. Devices had been sterilized by (b) (4) prior to (b) (4) aging to represent the (b) (4) shelf life. The test report (Stability Report (b) (4)) indicates that the protocol was executed without deviations and the acceptance criteria were met. The sponsor also confirmed that real time testing is on-going for both the seal-strength and dye penetration testing. This deficiency is resolved.

Design Validation/Verification:

Performance testing was provided in the January 5, 2017 response to Information Request which included the following tests:

Testing of Attachment Force
Withdrawal of (b) (4) from vials via Luer Lock syringes

Testing of Attachment forces was completed with acceptance criteria of (b) (4) . The testing performed was in comparison to the (b) (4) device. It is noted that the sponsor did not perform tests to ensure what when used in combination with the drug vial.

It is also noted in the test report that results to test the attachment force of the water spike would not support any conclusions on the safety of the device in the field. The sponsor provided usability testing to show that the test uses could penetrate the seal and activate the device following the IFU.

Reviewer Comment:
IR to sponsor on February 6, 2017:
You have provided attachment force testing which compares the Octajet to the (b) (4) device and meets your acceptance criteria of an attachment force of (b) (4) . You have not performed this testing with your drug vial. We recommend that your performance testing is completed with all constituents of the combination product to ensure that your device performs as expected when used as a system. Please provide testing that supports that the attachment force when used with your drug vial still meets your criteria of (b) (4) .

Sponsor response:
The manufacturer/ supplier of the transfer device Octajet, (b) (4) , committed to perform additional performance testing. The following tests are going to be performed:

(b) (4)

Results of the above mentioned testing can be provided until latest March 20, 2017.

(b) (4)

Sponsor Response on March 22, 2017:

(b) (4)

(b) (4)

The sponsor submitted an updated draft protocol that testing will be in accordance to ISO 594. Review of the test report will be completed for adequacy.
IR to sponsor on February 6, 2017: **You have provided in your response to Question 1 received January 5, 2017 a test report in Annex 18A that states if all components of the Octajet are produced according to the specifications and assembly is done according to validated procedures, the device can properly connect to both vials. We expect that your combination product which includes information on your proposed device that is designed and manufactured per the requirements of 21 CFR 820 Quality Systems Regulations. Please provide a summary of the design controls of the device constituent.**

Sponsor Response:

The following design controls of the transfer device Octajet are in place considering the requirements of the combination product:

1) Material requirements:

Incoming components are purchased from qualified suppliers and inspected by (b) (4) according to the enclosed specifications as listed in the table below.

All materials used for the production of the components of the Octajet conform to USP Class VI for plastics. The used materials and the respective supplier specifications and/or safety data sheets (SDS) for these materials are attached in the enclosed Exhibits as listed in the table below:

(b) (4)

The packaging and labeling components for the finished device are listed in the table below. The specifications and/or material composition for the packaging materials are attached in the enclosed Exhibits that were provided by the supplier:

(b) (4)

(b) (4)

2) Manufacturing requirements, prove of functionality and release

The above mentioned components are (b) (4)

Once batch sterility is confirmed, a sterilization certificate is provided to (b) (4), who then releases the device for distribution.

For detailed information please refer to the enclosed document please, *Working and Control Instruction No. LS-PKP.MA001992989S709.*

Testing was provided to support the thread on the Octajet is in compliance to ISO 594, conical fittings with a (b) (4) luer taper. In the Test Report (20140523_LSEng-003) it is stated that the device should meet the standards. The sponsor will be asked to clarify the meaning of: should".

IR to sponsor on February 6, 2017:
In your test report in Annex 18B, you state that the thread on your device should meet ISO 594-1 and ISO 594-2 requirements. Please clarify the meaning of "should" We recommend that you perform testing as per ISO 594 and ensure that your device meets the requirements.

Sponsor Response received 2/24/2017:

(b) (4)

(b) (4)

(b) (4)

Reviewer comment:
The sponsor states that the testing will be provided by March 20, 2017. The sponsor will be reminded to provide the full test report for each test performed.

IR to Sponsor on February 6, 2017:
You have provided a leakage test report in Exhibit 18A, the method used to assess leakage testing is unclear within the submission. Please provide the test method used to assess for leakage and the rationale for use of the method. We recommend you perform air leakage testing to ensure there is no leakage between the vial, transfer device and syringe and the device performs as intended.

Sponsor response received February 24, 2017:
(b) (4)

Reviewer comment:
As stated above the sponsor will be asked to clarify testing to ISO 7886. This standard is for sterile syringes and is unclear how the proposed device shall conform to the standard.

IR to sponsor on February 6, 2017:
You stated in your January 5, 2017 response that additional testing is ongoing. Please provide a summary of additional tests that you are performing on your device. (b) (4) , and we expect your test reports to be submitted to the BLA. Please also note that we expect that the tests that you have performed to the specifications of your combination product.

Sponsor response on February 24, 2017:
The following additional tests are going to be performed:

1. Testing of attachment force and/or penetration force for both, Product and Water spike

2. Leakage testing (liquid and air) for, Product and Water spike as well as junction according to ISO 7886 and ISO 594

3. ISO 594 compliance verification testing of the female luer lock port as an integral part of the product spike including:

   a. Dimensional control acc. ISO 594-1 § 5.1 (calibrated test jig)
   b. Leakage assessment acc. ISO 594-2 – § 5.2 & §5.3 (water & air)
   c. Disconnection force acc. ISO 594-2 § 5.4
   d. Torque verification acc. ISO 594-2 § 5.5
   e. Screw connection verification acc. ISO 594-2 § 5.6
   f. Overriding force verification acc. ISO 594-2 § 5.7
   g. Stress cracking test acc ISO 594-2 § 5.8

(b) (4)

Reviewer comment:
The sponsor stated the test results will be provided by March 20, 2017. The tests proposed are identical to what was provided in the previous response.

The sponsor provided the full test reports for review on May 3, 2017.

125STD34x004_Functionality.pdf provided on May 3, 2017 includes the following test reports for the Octajet transfer Device.

Penetration force was measured for the spike and drug spike.

Table 5: Results of the penetration load test according to ISO 8536-6 (DIN 13097-4) for the Diluent Spike / WFI vial, for raw data please refer to Attachment 1

(b) (4)

Table 6: Results of the transferring time test, for raw data please refer to Attachment 2

(b) (4)

The transfer time of the WFI is within the acceptance criteria of (b) (4) **and the disconnection of the device was easily possible, thus test passed.**

Table 8: Results of the Air Leakage Tests, for raw data please refer to Attachment 4

(b) (4)

No air bubbles were observed, all samples are within the acceptance criteria, thus the air leakage test passed.

Table 7: Results of the Liquid Leakage Tests, for raw data please refer to Attachment 3

(b) (4)

Neither droplet was observed at the spikes nor at the junction, all samples within the acceptance criteria, thus the liquid leakage test passed.

5.4.1 Results of the Separation (Pull) Force Test

The separation forces are listed in the table below as minimum- maximum and mean values. In total (b) (4) samples were tested. For raw data please refer to Attachment 5.

Table 9: Results of the separation force test according to ISO 8536, for raw data please refer to Attachment 5

(b) (4)

The spikes and the rubber stoppers form a close and tight connection not too easy to separate and meet the expected results, thus the Separation (Pull) Force Test passed.

5.5 Tests of the female Luer Lock fitting of the Powder Spike

5.5.1.2 Results of the Ease to Assemble Test of the female Luer Lock

Requirement according to ISO 594-2, Chap. 4.5 b) semi-rigid fittings*:* (b) (4) ” In total (b) (4) samples were tested. For raw data please refer to Attachment 6.

Table 10: Results of the Ease to Assemble Test, for raw data please refer to Attachment 6

(b) (4)

(b) (4)

A satisfactory fit were achieved, all samples are within the acceptance criteria thus, the Ease to Assemble Test passed.

Table 11: Results of the Unscrewing Torque Test of the female Luer Lock, for raw data please refer to Attachment 7

(b) (4)

The fitting remained attached all samples are within the acceptance criteria, thus the Unscrewing Torque Test passed.

Requirement according to ISO 594-2, Chap. 4.2.1 – Liquid Leakage: (b) (4) " The connection was inspected during the tests for falling droplets additionally to the pressure monitored leakage tests. No droplets were observed. In total (b) (4) samples were tested. For raw data please refer to Attachment 8.

Table 12: Results of the Liquid Leakage Tests (female luer lock), for raw data please refer to Attachment 8

(b) (4)

No droplets were observed, all samples are within the acceptance criteria, thus the liquid leakage test for the female luer lock passed.

Results of the Air Leakage Test of the female Luer Lock

Requirement according to ISO 594-2, Chap. 4.2.2 – Air Leakage: "(b) (4) Additionally to the pressure monitored leakage test, the samples were inspected for running bubbles after 5 s visually. In total (b) (4) samples were tested. For raw data please refer to Attachment 9.

Table 13: Results of the Air Leakage Tests of the female luer lock, for raw data please refer to Attachment 9

(b) (4)

No air bubbles were observed, all samples are within the acceptance criteria, thus the air leakage test passed.

5.5.4.2 Results of the Overriding Torque Test for the female luer lock

Requirement according to ISO 594-2, Chap. 4.6: (b) (4) The diagrams will show a peak within the horizontal part of the curve when the reference fitting overrides (jump over) the thread of the testing sample. In total (b) (4) samples were tested. For raw data please refer to Attachment 10.

Table 14: Results of the Overriding Torque Test for the female luer lock, for raw data please refer to Attachment
10

(b) (4)

The reference fitting did not override the threads or lugs of the fitting, all samples are within the acceptance criteria, thus the Overriding Torque Test for the female luer lock passed.

5.5.5.2. Results of the Separation Force Test for the female luer lock

Requirement according to ISO 594-2, Chap. 4.3 : "(b) (4) " In total (b) (4) samples were tested. For raw data please refer to Attachment 11.

Table 15: Results of the Separation Force Test for the female luer lock, for raw data please refer to Attachment 11

(b) (4)

The fitting remained attached all samples are within the acceptance criteria, thus the Separation Force Test for the female luer lock passed.

(b) (4)

(b) (4)

Reviewer Comment: The sponsor has performed performance testing on the transfer device with the proposed glass vial. Testing completed is adequate.

IR to sponsor on February 6, 2017:
You also stated in that due to the specific design of you the device not all defined dimensions can be measured on the final device. We do not agree with your rationale as part of the Design Control requirements we expect that you address all design control issues through the initial design, planning and development, design input, design output, design review, design transfer, design verification, design validation that meets the proposed intended use of the final combination product.

Sponsor Response:
Please find enclosed the document *Working and Control Instruction No. LS-PKP.MA001992989S709* describing all design controls performed during manufacturing (including release) of the Octajet device.

Reviewer Comment:
The sponsor provided a work and inspection procedure document. The sponsor has provided the design requirements of the device and the design controls in place. The sponsor also provided engineering drawings of each component with device specifications. The sponsor's response is Adequate. Design validation has been conducted as well as certificates of conformity will be provided to ensure the device will meet the design specifications.

IR to sponsor on February 6, 2017:
You have provided in your response received by the Agency on January 23, 2017 that batch analysis for the syringe filter and Octajet. We believe there is a misunderstanding. We expect that you provide lot release documentation to ensure that future devices are verified to meet specifications prior to distributions. Please provide a lot release protocol which will be utilized to verify new devices are manufactured per your specifications. The lot release data should be justified as statistically acceptable.

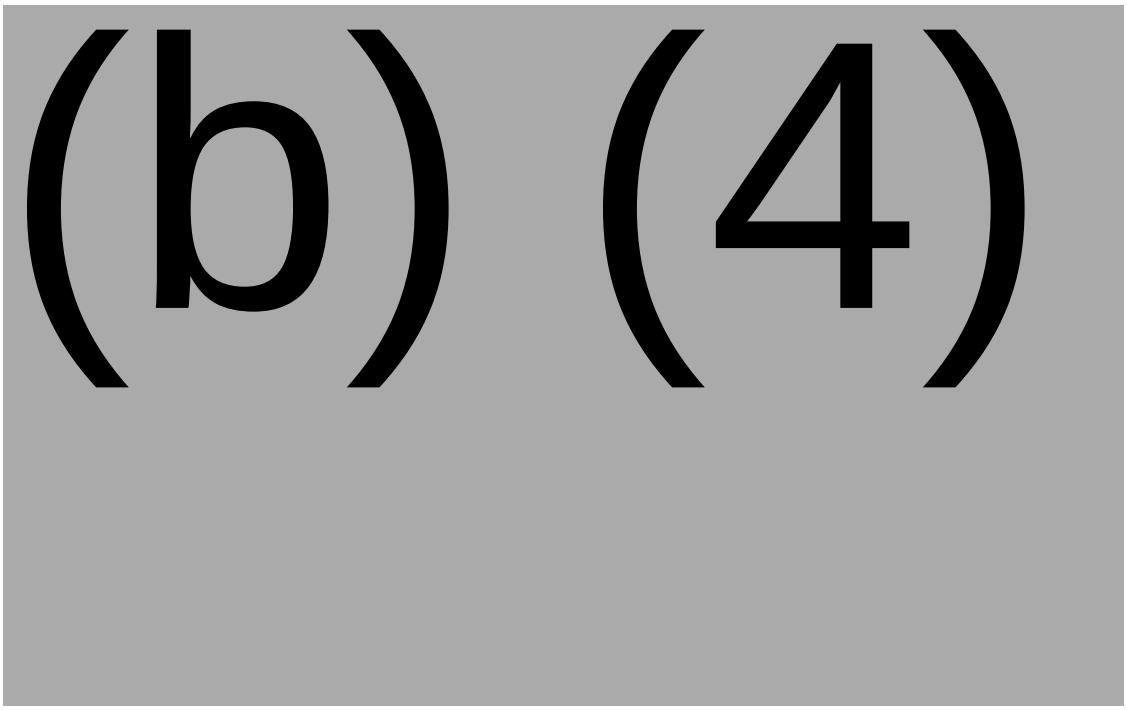
Sponsor Response received 2/24/2017:

TransferDeviceOctajet:

Please find enclosed a template and a respective example of a lot release protocol of the transfer device Octajet, *CoC_MA001992989S709* provided by the manufacturer/ supplier, (b) (4) . This lot-wise received Certificate of Conformity certifies the following:

1. Manufacturing of the Octajet is in accordance with the mutual agreed specification MA001992989S709 in-between Octapharma and (b) (4)
2. That the used polymer materials meet USP class VI and are TSE/BSE free
3. That the assembling and packaging is performed in clean room class (b) (4) to ISO 14644-1 (Class (b) (4)) and the packaged device has been sterilized

The table below gives a brief overview on testing parameters, sampling and frequency of in process controls and release performed by the manufacturer/ supplier, (b) (4) . For more detailed information, especially on in-process controls, please refer to the document, *Working and Control Instruction No. LS-PKP.MA001992989S709*. Please note that this document is an internal, confidential document from the supplier (b) (4) and is not provided to Octapharma with delivered lots.



Syringe filter:

Please find enclosed a respective example of a lot certificate of the syringe filter *CoQ_6644185* provided by the manufacturer/ supplier, (b) (4) . This lot-wise received Certificate of Quality certifies the following:

1. that the materials of construction have been evaluated in accordance with the United States Pharmacopoeia (USP) Biological Reactivity Test, *In Vivo* <*88*> (USP Class VI-121°C Plastics Test).

2. that the criteria for filtration area, operating pressure and operation temperature are met

3. that the product underwent a sterilization by gamma irradiation in the specified dosage range

(b) (4) Octapharma to be submitted as part of BLA STN 125612.

Please refer to the enclosed statement by (b) (4) , the, (b) (4) .

Additionally, please refer to response to question 7 for a description of the in house testing performed by Octapharma to ensure that the device meets the specification.

Reviewer comments:
The sponsor states that the device manufacturers will be providing lot release testing for the devices incoming to Octapharma. They sponsor also states that Certificates of Conformity will be received for the devices during incoming control. The sponsor states that quality control will be performed on the incoming filter lots by the applicant. The response is adequate.

Labeling:
The sponsor has provided Instructions for Use for the proposed drug product which includes use of the copackaged devices.

FIBRYNA package contains:
- 1 single-use vial of FIBRYNA concentrate
- 1 transfer device (Octajet)
- 1 particle filter

FIBRYNA should be reconstituted with 50 mL of Water for Injection (not provided).
Do not use FIBRYNA beyond the expiration date. FIBRYNA contains no preservative. Use aseptic technique when preparing and reconstituting FIBRYNA.
The procedures below are provided as general guidelines for preparation and reconstitution of FIBRYNA.

Reviewer comments:
The sponsor has provided labeling which includes directions for use with the proposed devices. In the sponsor's January 5, 2017 response, labeling for the Octajet was included. The sponsor was asked to clarify if the additional labeling will be included in the combination product.

IR to sponsor on February 6, 2017:
You have provided labeling for the Octajet device in your January 5, 2017 response. It is unclear if the labeling will be included in your combination product. Please clarify if you intend to include the Octajet device labeling with your combination product.

Sponsor Response:
The Octajet device labeling will be part of the combination product.

Reviewer Comment:
The Sponsor's response is Adequate.

Stability Data

The sponsor has provided sterility information to include shelf life of the Octajet device and information regarding the shelf life of the filter was provided in the 510k.

Reviewer Comment:
The sponsor has not provided stability or shipping validation studies of the copackaged combination product. The sponsor is expected to perform assessments on the device constituents over time to assess the functionality of the device through the drug expiration.

IR to sponsor on February 6, 2017:
We are unable to locate stability or shipping validation studies of your copackaged combination product. We expect that you perform assessments of the device constituent over time to assess the system functionality of your device through the drug product expiration. We also expect that to support

functionality of your combination product after shipping, that you provide evidence that your system is capable of withstanding the effects associated with shipping which may include temperature excursions, withstanding vibrational and atmospheric effects.

Sponsor response received on 2/24/2017:

The combination product consists of the drug product, the transfer device Octajet and the syringe filter. Each constituent has a confirmed shelf life of at least (b) (4).

Regarding the transfer device Octajet, it was stated in document Annex 4 "*Section 14 – Sterilization and Shelf Life" provided in amendment #0027 (eCTD sequence #0028) submitted on January 5, 2017, that* the initial submitted shelf life of (b) (4) has been assigned to the Octajet based on the results of the accelerated aging stability study. In the meanwhile, additional obtained data prove a shelf for up to (b) (4). The stability test plan and report (*MA0019929879S709-03-PVP* and *MA0019929879S709-03-PVR,* respectively) are enclosed. Furthermore transportation and handling testing was conducted demonstrating that the packaging remained in a satisfactory condition with no evidence of damage to the primary packaging. Please find enclosed the Packaging Transport Validation report, *MA001992989S709-02-PVR.*

To support functionality of our combination product after shipping, we propose a transport validation of the co-packaged product with the first commercial batch shipped to the US as a post approval commitment. Please find the proposed protocol *150VPR1708* enclosed.

Reviewer Comments:

Review of the updated test plan which includes an updated (b) (4) shelf life of the Octajet will be reviewed. The sponsor has provided the proposed protocol to support functionality of the combination product, and stated that the combination product will be tested accordance to 130SOP006 "Visual inspection of freeze-dried products, substance and (b) (4) and WFI used for reconstitution and verification of solubility of freeze-dried products". This does not appear to include functional requirement testing of the combination product which will be testing after shipping.

IR to the Sponsor:

You have stated that to support functionality of the combination product testing will be performed in accordance to ISO 130SOP006, however we are unable to locate essential performance testing of the combination product after shipping in the transport validation protocol.

Please note that in Lieu of a post market commitment for the essential performance testing of the device constituent of the combination product, stability data to support the essential performance requirements of the device constituent would be considered for review.

Sponsor Response on March 22, 2017:

Please find below the list of tests to be performed in course of the transport validation of the combination product.

The transport validation protocol 150VPR1708 has been updated accordingly.

In regards to stability data, please be informed that the testing at the (b) (4) month time point during the currently ongoing stability studies 14P012 and 14P013 will be performed with constituents (product, Octajet, syringe filter) that have all been stored for (b) (4) month. The corresponding stability protocols have been updated to clearly state this requirement. Please find protocol 14P012

and 14P013 enclosed in section 3.2.P.8.2. Results of the (b) (4) months' time point will be available in Q2 2018.

Reviewer comment:
The sponsor has provided performance testing on the transfer device when used with a surrogate drug vial which is similar in specifications to that of the proposed vial. The testing that is provided is adequate. A post market commitment is not necessary.

HF Usability study:
The sponsor had provided a HF usability study which CBER had requested review of by CDRH. The device is considered a low risk device to be used by health care professionals, therefore CDRH believes a HF study is not necessary. However recommendations were made to the labeling based on the findings of the study and the potential leaking that occurs with use of the Octajet. The sponsor had initially stated that the addition of the filter was to mitigate the leaking that occurred by health care professionals when the vial is inverted.

IR to sponsor:
In your Human Factor Study, you stated to mitigate the risk of a leaking product vial after reconstitution a syringe filter was implemented. It is unclear if the product vial was leaking after reconstitution when attached to a syringe or if the user was inverting the product vial upside down after reconstitution. We recommend you assess the cause of the leakage with the product vial attached. We believe that the Octajet is an open luer connector which is expected to leak when inverted and connected to a drug vial. We believe that the leakage can be mitigated by providing clear instructions to the user to connect a syringe prior to inverting the vial to withdraw the fluid. Please review your instructions for use and consider revising them to provide clarity. We are unclear of the purpose of the syringe filter if the syringe is attached prior to inverting the vial.

Sponsor Response on February 16, 2017:
We agree that the Octajet is an open luer connector, which is expected to leak when inverted and connected to a drug vial. Please find below the revised instruction for use with changes written in **bold.** Step 8 points out to not invert the product vial upside down and step 9 to connect a syringe filter and syringe prior inverting the vial to withdraw the fluid.
The purpose of the syringe filter is to remove potential particles from the reconstituted product prior intravenous application.

Reviewer Comment:
The sponsor has provided updated instructions for Use with the recommendations which are adequate.

Summary:

The sponsor has a provided in this BLA submission device specifications for the copackaged Octajet transfer device and filter to be supplied with the proposed Fibryna vial. The information provided in this submission including the performance requirements (design verification/validation), compatibility and lot release of the Octajet transfer device and the (b) (4) filter (cleared under (b) (4)) is considered acceptable and all outstanding deficiencies have been addressed in this submission.

Recommendation:

Approval of the device constituents (Octajet and (b) (4) filter) of this combination product.