



Food and Drug Administration
Office of Device Evaluation
White Oak Building 66
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Silver Spring, MD 20993

Intercenter Consult Memorandum

ICC1500057/BLA125574

Date: 12/17/2015

To: Pratibha Rana, M.S.
Regulatory Project Manager
OMPT/CBER/OBRR/PPMS

From: Ryan McGowan
Biomedical Engineer
CDRH/ODE/DAGRID/GHDB

Subject: Device Design Review
BLA125574 Antihemophilic Factor (Recombinant)

Recommendation: Approval for Considerations of Device Engineering Performance

I. Recommendation

The device consultant authoring this review memorandum has performed a design review of submission materials intended to support the safety and functionality of the of the device constituent parts of the subject combination product. This review covered evaluation of design documentation for the final finished device constituent parts of the combination product as provided in the BLA submission, master file documentation, and referenced 510(k) submissions. This review did not cover manufacturing of the device constituent parts, sterility or toxicity of the medication fluid path, or usability of the device constituent parts.

The review of submission documentation by CDRH/ODE found that the product components are of acceptable pedigree and that essential performance of the final fished device can be assured with a reasonable degree of certainty. Essential performance elements of the device system under review by the consultants were considered to be:

- Connection and compatibility of components
- Biocompatibility of non-primary closure components
- Functionality of the syringe
- Stability after exposure to aging and shipping conditions

Review of this information found that there are sufficient design control documentation and verification activities for the device constituent part of the combination product to recommend approval.

II. Consult Purpose

The Center for Biologics Evaluation and Research (CBER) requested a consult from CDRH/ODE for device constituent part design review of BLA125574, which is a combination product consisting of a reconstitution system that delivers Antihemophilic Factor (Recombinant). This NDA has been submitted by Bayer.

III. Combination Product Device/Biologic Container Closure Descriptions

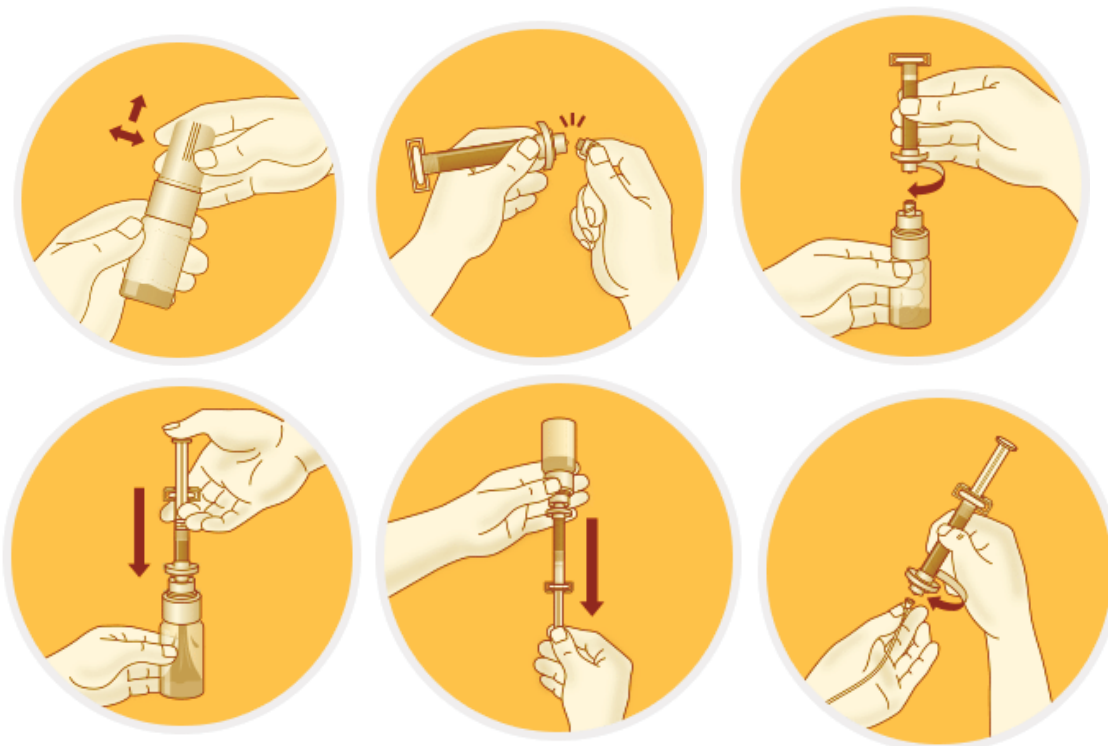
Section 3.2.P of the submission contains summary information on the design of the drug delivery system selected to administer the subject medication. The drug product is supplied in sterile glass vial either integrated with a cap BIO-SET, to form a container closure system and also allow transfer of diluent to facilitate reconstitution, or with aluminum over-seal together with a stand-alone vial adapter to facilitate reconstitution. The Drug Product is reconstituted with sterile water for injection contained in a prefilled syringe.

The drug product is stored in a 10mL glass vial. The sponsor states that the device constituent part of the combination product is a pre-filled syringe and two options of reconstitution systems. Both reconstitution systems are presented for each dose:

1. 250, 500, 1000 IU/Vial Fill Sizes	
Container/Stopper:	Glass vial 10 mL colorless glass Type I (b) (4) Stopper bromobutyl gray (b) (4) for lyophilization
Seal/Adapter/Diluent:	
Option A:	Reconstitution cap / Diluent Prefilled Syringe: 2.5 mL Sterile Water for Injection in syringe
Option B:	Aluminum seal with plastic flip-off top/ Vial adapter Diluent Prefilled Syringe: 2.5 mL Sterile Water for Injection in syringe
2. 2000, 3000 IU/Vial Fill Sizes	
Container/Stopper:	Glass vial 10 mL colorless glass Type I (b) (4) Stopper bromobutyl gray (b) (4) for lyophilization
Seal/Adapter/Diluent:	
Option A:	Reconstitution cap / Diluent Prefilled Syringe: 5 mL Sterile Water for Injection in syringe
Option B:	Aluminum seal with plastic flip-off top/ Vial adapter Diluent Prefilled Syringe: 5 mL Sterile Water for Injection in syringe

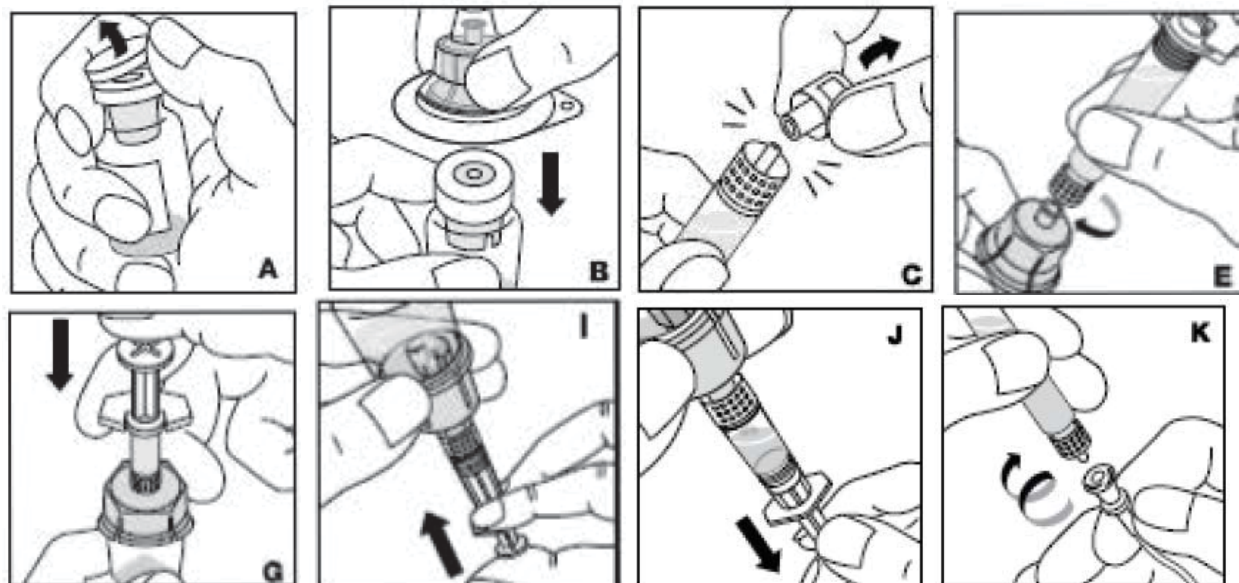
Reconstitution Option 1: Vial Integrated with Reconstitution System:

The sponsor describes reconstitution system option 1 as being a 10mL glass vial with a BIO-SET device. This presentation is stated to be identical to that used within the clinical study of the drug product and the same system used within the marketed product "Kogenate FS", which has been marketed in the United States by Bayer under BLA103332. Visual representation of the integrated reconstitution system is shown below:



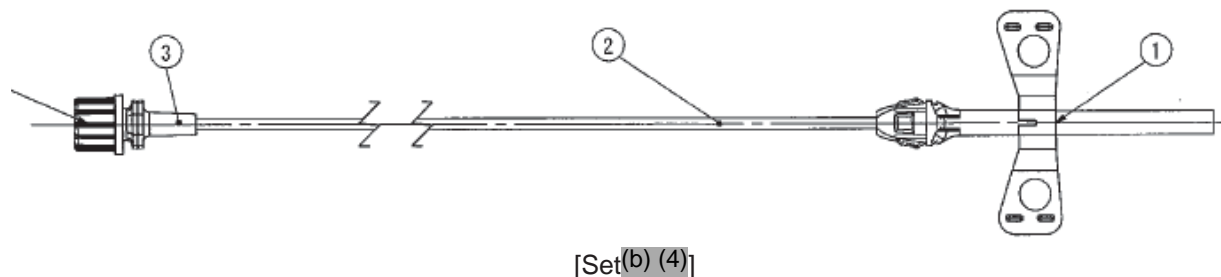
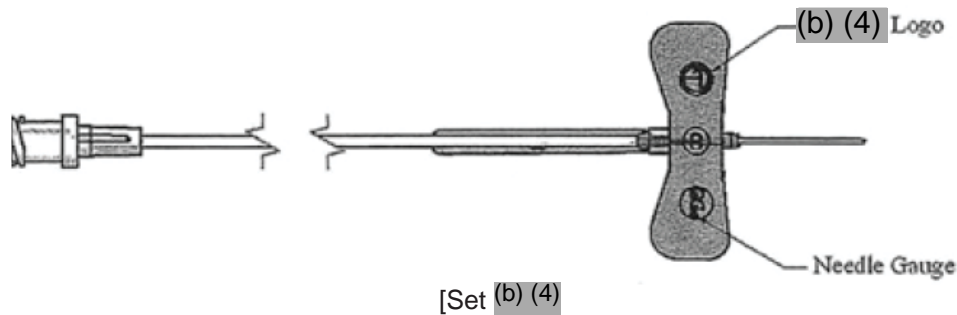
Reconstitution Option 2: Vial Provided with Separate Vial Adapter

The sponsor describes reconstitution system option 2 as being the 10mL glass vial with a vial adapter device. Visual representation of the integrated reconstitution system is shown below:



Infusion Devices

Regardless of the reconstitution approach, the sponsor provides a prefilled syringe, plunger rod, infusion set and infusion cannula, through which the reconstituted drug product is administered. Section 3.2R-45 through 3.2R-48 of the submission describes the infusion sets. The first set (ID (b) (4)) is manufactured by (b) (4) and the second, which contains a filter (set ID (b) (4)) is manufactured by (b) (4).



Section 3.2.P for the prefilled syringe describes the pre-filled syringe types (organized by size) and accompanying plunger rods. The syringes will be provided in 2.5 and 5mL sizes and the plunger rods will be provided disassembled from the syringe within the package.

IV. **Device Constituent Part – Design Review**

This review covers the following critical attributes related to functionality and safety of the device constituent parts of the combination product:

- 1) Statement of device inputs (system requirements and specifications), including:
 - a. Dimensional characteristics
 - b. Functional characteristics
- 2) Evidence of verification of device inputs (device testing/design output)
 - a. Dimensional characteristics
 - b. Functional characteristics
 - c. Connectivity of components
 - d. Sterility and biocompatibility
 - e. Stability and shipping

Combination Product Design Inputs

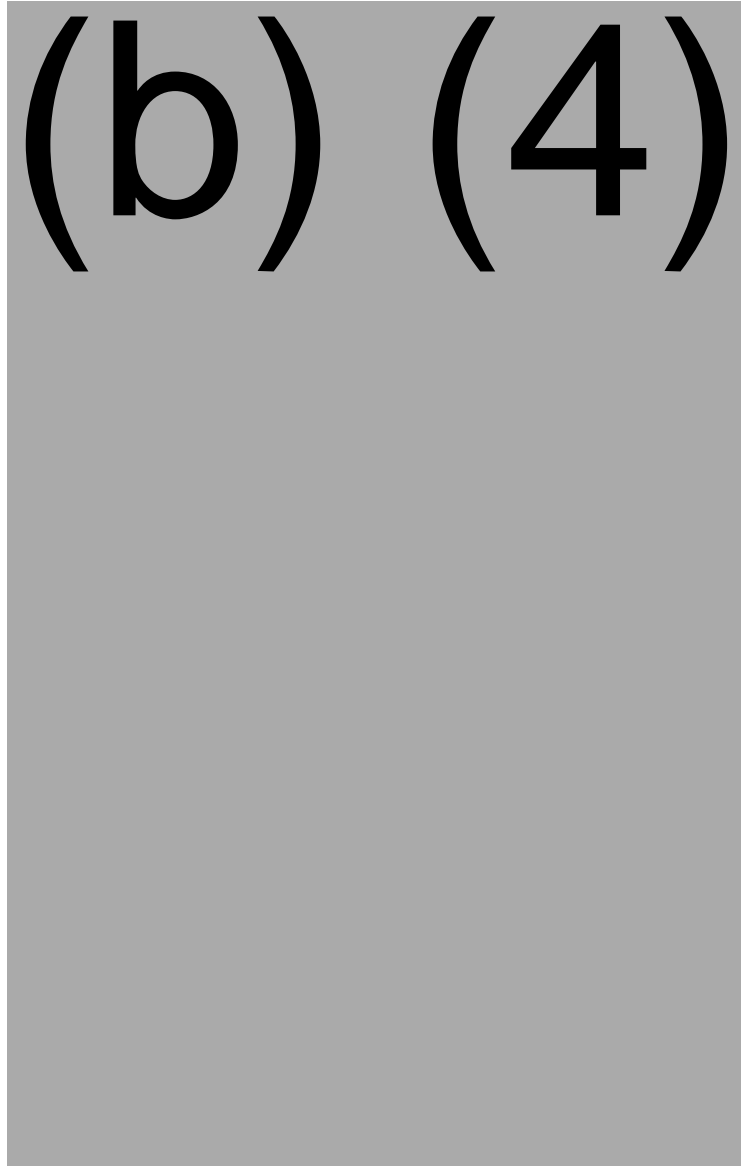
BIO-SET

The sponsor states that the BIO-SET reconstitution system is manufactured as a (b) (4) by Baxter LTD/Biodome. The sponsor describes the system as being comprised of a cap, a base and a needle/luer assembly. The cap and the base are constructed of (b) (4). The needle/luer assembly is constructed of a (b) (4). The reconstitution cap is attached to the base during the (b) (4). According to the sponsor, the device manufacturer pre-sterilizes the reconstitution cap by (b) (4) and sterilization dose was established and the sterilization process was developed, validated and controlled in accordance with ISO standards.

Section 3.P.P.7 for the powder closure contains the following specification list for the reconstitution cap:

Table 1-1. Specifications	
Test	Specification
Dimensional Inspection	All measurements are within specified tolerances
Certification Check	Must be present
Particulate Matter, (b) (4) Microns or Greater	(b) (4)
Particulate Matter, Microns or Greater	

The sponsor also included the following system drawings to define the product:



(b) (4)

Within the subject submission, the sponsor initially did not provide a detailed list of performance and functional specifications for the system, including attributes such as: resistance to removal of components, force required to activate the system, liquid removal rate, biocompatibility/leachable/extractable substances.

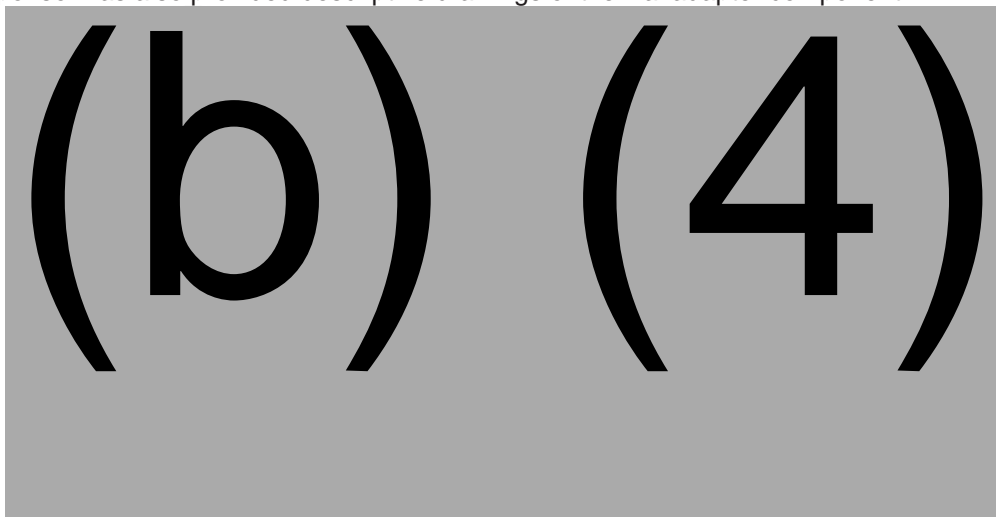
The sponsor also did not provide a master file or 510(k) clearance citation for the device; however they stated that this product is “identical” to the product used identical to the system used within the marketed product “Kogenate FS”, which has been marketed in the United States by Bayer under BLA103332. The sponsor provided a letter of reference to BLA103332 with the expectation that non-clinical information provided to support the device within BLA103332 is sufficient to support use of the subject product. In addition to this evidence, the sponsor has provided explicit device requirements for the system, including mechanical activation force required to access the vial, container closure integrity testing, and drug compatibility testing. These attributes are further described within the verification section, below. The reviewer finds this approach to demonstrating safety and performance of the BIO-SET acceptable.

Vial Adapter

The sponsor states that the reconstitution vial adapter (b) (4) is provided (b) (4) [REDACTED] The device is provided sterile and packaged to the sponsor by the device manufacturer. The drug sponsor has established the following specifications for the design of the vial adapter component:

Test	Specification
Visual inspection for cracks on the vial adapter body	The vial adapter must not have any cracks on the body
Visual inspection of the vial adapter to verify that there is no embedded matter greater than (b) (4) on the surface of the vial adapter	No embedded matter (b) (4)
Visual inspection for loose particles or matter	No loose particles (b) (4) No loose Matter (b) (4)
Visual Inspection of the vial adapter for damage that is not to the sterility barrier	No damage to the vial adapter other than the sterility barrier
Perform a fluid flow test with water to verify there is no blockage or engagement leak	The fluid pathway must not be obstructed
Blister integrity test	No leaks are detected

The sponsor has also provided descriptive drawings of the vial adapter component:



Component Description

- 1 Vial Adapter Body (b) (4)
- 2 Inline (b) (4) disc filter
- 3 Blister Pack
- 4 (b) (4) Lid

In addition to the independent specifications outlined above for the device, the sponsor has also provided a letter of reference with a 510(k) submission cleared by CDRH under (b) (4) . This submission was evaluated by the lead reviewer and it was found to contain the following relevant requirements:

- Sterile
- Non-pyrogenic
- Equipped with piercing spike
- Equipped with female luer connection

The consulting reviewer considered that the referenced 510(k) contains sufficient detail in terms of system functional specifications to support use within the subject submission and to conclude that the device is being used consistently within its original clearance, however within the sponsor's June 24, 2015 device information response, the sponsor stated that the vial adapter component had changed since the original 510(k) clearance. These changes were noted to not affect device specifications, which is acceptable for this section, however see additional detail about vial adapter changes within the verification section of this memorandum.

Pre-filled Syringe

The sponsor states that they will be providing two types of pre-filled syringes within BLA125574 kits, one syringe which is 2.5mL in volume and the other which is 5mL in volume. The sponsor provided syringe requirements within the original submission, included below:

From 3.2.P.1 – desc:

Name of Ingredient	Unit and/or Percentage Formula	Reference to Compendia
One syringe of diluent contains:		
Sterile Water for Injection	5.0 mL/syringe	(b) (4)
Overfill	(b) (4)	
Name of Ingredient	Unit and/or Percentage Formula	Reference to Compendia
One syringe of diluent contains		
Sterile Water for Injection	2.5 mL/syringe	(b) (4)
Overfill	(b) (4)	
Appearance	Clear Liquid	
Pharmaceutical Form	Liquid	
Container	Clear, colorless, (b) (4) glass, Type I, 5 mL syringe (b) (4)	
Plunger Stopper	Gray bromobutyl rubber (b) (4)	
Tip Cap	Gray bromobutyl rubber (b) (4)	

Appearance:	Clear Liquid
Pharmaceutical Form:	Liquid
Container:	Clear, colorless, (b) (4) glass, Type I, 3 mL syringe (b) (4)
Plunger Stopper:	Grey bromobutyl rubber (b) (4)
Tip Cap Stopper:	Grey bromobutyl rubber (b) (4)

The following additional specifications were provided within the pharmaceutical development section for the 2.5 and 5mL syringes:

- Type I glass barrel (b) (4)
- Bromobutyl stopper (plunger) and tipcap stopper

- (b) (4) tipcap housing with tamper-evidence feature
- Plunger rod (to be assembled by the patient to save space in the secondary packaging)
- Favorable mating characteristics of the inner surface of the glass syringe barrels

The sponsor also cited and provided cross-reference to a Type-III master file (b) (4) for the syringes. This document contains dimensional and material specifications for the referenced syringes, including:

1. Dimensions and bill of materials for the syringe, plunger, and tip-cap
2. Performance requirements for the tip-cap and tip-cap removal
3. Performance requirements for the luer-lock component
4. Biocompatibility certificates and information for the tissue contacting portion of the syringe system:
 - Acute systemic Toxicity
 - Intracutaneous Toxicity
 - Muscle Implantation
 - Cytotoxicity
 - Hemolysis
 - Physiochemical Tests
 - Heavy Metal Analysis
 - Pyrogen Study
 - Mutagenicity

The consulting reviewer finds the above information acceptable to support basic safety and function of the pre-filled saline syringes, however the reviewer considers that complete evaluation of the syringes in the context of the intended use will be assessed by the in-use reconstitution and leachable studies to be conducted by the sponsor and assessed by the CMC reviewer.

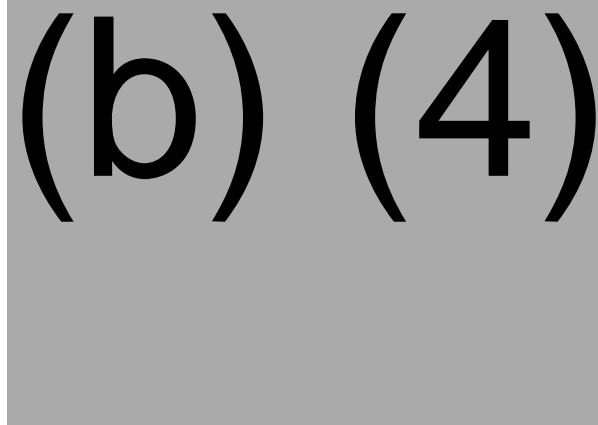
Administration Set

The sponsor references two IV administration sets, each with cannula component to accomplish IV administration. The sponsor has included descriptive information regarding the “winged infusion set with filter (b) (4) by (b) (4) within section 3.2.R:

Component	Composition
Needle cap	(b) (4)
Cannula	
Wing hub	
Needle hub	
Needle protector	
Tube	
Luer Connector	
Filter (23 µm)	
Luer Cap	
Lubricant	
Adhesive	

The sponsor has provided the following specification information for the “administration set” (b) (4) device under 3.2.R:

Components:
 Wing hub
 Tube
 Cannulae
 Lubricant
 Adhesive
 Protector
 Adapter cap
 Safety protector
 Safety hinge
 Luer adapter



Test	Specification
Visual inspection	The infusion set must have manufacturer lot number and expiration date. Other defects are calculated according to respective AQL levels.
Perform a fluid flow test with water to verify there is no blockage or engagement leak	The fluid pathway must not be obstructed
Blister integrity test	No leaks are detected
Dimensional inspection	Must meet required tubing and cannula lengths

The sponsor did not provide sufficient descriptive elements for each infusion set used within the combination product within the original application. Specifically, the sponsor did not provide dimensional, mechanical, functional, sterility, or biocompatibility information for these sets. This was requested of the sponsor and responded to within a June 24, 2015 correspondence.

In response, the sponsor provided letters of authorization for two 510(k) clearances covering both infusion set products (510(k) clearance (b) (4) for the (b) (4) infusion set and 510(k) clearance (b) (4) for the (b) (4) infusion set.)

(b) (4) for the (b) (4) Infusion Set

The consulting reviewer inspected the 510(k) provided for the (b) (4) infusion set and found the following specification information.

- Intended for intravascular administration of medication
- Provided sterile
- Provided pyrogen free
- Equipped with a luer lock component
- Constructed with biocompatible components
- Constructed with bonds that retain components and prevent leakage

(b) (4) for the (b) (4) Infusion Set

The consulting reviewer inspected the 510(k) provided for the (b) (4) infusion set and found the following specification information.

- Intended for intravascular administration of medication
- Provided sterile
- Provided pyrogen free
- Equipped with a luer lock component
- Constructed with biocompatible components

- Constructed with bonds that retain components and prevent leakage

Based on the above information located within each 510(k), the consulting reviewer believes the referenced infusion sets are appropriately specified for the intended use prescribed under the subject submission.

System Integration

The sponsor has not outlined explicit system specifications in terms of the ability of the system components to interface appropriately. However, the reviewer considered that the following design characteristics as well as verification evidence, as presented within the section below, is sufficient to satisfy the concerns of system integration:

- 1) Use of standardized luer connector components on the infusion sets, syringes, and vial access devices
- 2) Use of standardized vial neck sizes at the vial-vial access device interface
- 3) Verification testing (non-clinical) which assessed drug quality and sterility attributes
- 4) Validation testing (clinical) which challenged use of the device in the form of human factors and clinical studies

Combination Product Verification Activities

BIO-SET

The sponsor posits that the usability, safety and effectiveness of the platform primary container closure system and the reconstitution cap have been successfully demonstrated with the drug product and study population during clinical studies and with prior cleared use under other BLA submissions, however they have also performed a number of verification activities with the system.

(b) (4) Testing (both after manufacturer and to expiry):

Section P.2.4.02 of the submission contains container closure integrity information for the BIO-SET pre-attached to the vial. The sponsor states that this testing, in combination with the stability testing which assesses the closure integrity shows that this requirement is satisfied. Review of these materials are deferred to CBER.

Compatibility with Biologic Product:

Section P.2.4.05 of the submission contains biologic-device compatibility information for the BIO-SET pre-attached to the vial. Review of this information is deferred to CBER, however the reviewer notes that testing provided (32p2-pharm-dev 12) does not appear to contain information which assures that the dose volume was recovered from the vial/cap assembly. This was communicated to the CMC reviewer for the subject submission, and the reviewer agreed to pursue information response questions for this test and to provide evaluation of results within her memorandum.

System Extraction Studies:

Section P.2.4.06 of the submission contains information on the extraction of the glass vial and stopper components of the container closure system. Review of this information is deferred to CBER, however this section (32p2-pharm-dev 14) does not appear to contain information on the extractable compounds from the device fluid path of the BIO-SET. This was communicated to the CMC reviewer for the subject submission, and the reviewer agreed to pursue information response questions for this test and to provide evaluation of results within her memorandum.

The need for the above testing, and the need for CMC to evaluate the results of such testing was communicated to the regulatory project manager at the mid-cycle review meeting. In response, the regulatory project manager contacted La’Nissa Brown and ensured that she would be covering these aspects of the review. On June 22, 2015 the CMC reviewer issued information requests related to system extraction and recovery studies. Review of responses to these information requests is considered as deferred to the CMC reviewer.

Mechanical Testing:

Pharmaceutical Development section 11 describes mechanical testing conducted to determine the force required to puncture the vial using the reconstitution system with the BIO-SET. This evaluation found that across three lots, the force to activate the system and open the vial was never reported to be more than (b) (4). This is considered acceptable; however no information was presented within the submission which challenges the mechanical attributes of the system after aging and shipping. This information was requested of the sponsor on June 9, 2015. In response, the manufacturer stated that shipping studies were performed on the biologic kits and assessed the ability of the vial adapter components to retain essential attributes of sealing and integrity after shipping and aging. This was verified by inspection of sections 3.2.P.8 and 3.2.R.39.

The sponsor deferred shipping and aging of all other components to the individual 510(k)s submitted for each device. Each 510(k) was examined for evidence of shipping and aging studies:

Aging/shipping/sterilization for the (b) (4) Infusion Set

510(k) (b) (4) was referenced to support the shipping, aging, and sterility of the (b) (4) infusion set for use with the subject biologic product kits. As part of the 510(k) submission, the sponsor provided information which validated the shelf life of the set packaging to be (b) (4) years. This evaluation involved artificial aging the device to a period equal to (b) (4) years and re-challenging all essential performance attributes. The sponsor also claimed conformance to (b) (4), a recognized shipping standard, and provided performance information supporting that the product could be safely shipped according to that method. The sponsor provided information supporting that sterilization methods used for the infusion set would achieve appropriate limits for intravenous use. This is considered acceptable.

Aging/shipping/sterilization for the (b) (4) Infusion Set

510(k) (b) (4) was referenced to support the shipping, aging, and sterility of the (b) (4) infusion set for use with the subject biologic product kits. As part of the 510(k) submission, the sponsor provided information which validated the shelf life of the set packaging to be (b) (4) years. This evaluation involved artificial aging the device to a period equal to (b) (4) years and re-challenging all essential performance attributes. The sponsor did not provide information supporting that the device could be shipped to the customer without damage. The sponsor provided information supporting that sterilization methods used for the infusion set would achieve appropriate limits for intravenous use. This is not considered acceptable as the 510(k) does not provide shipping information. The sponsor has agreed to conduct shipping testing of the entire biological kit, which will resolve this outstanding concern (see system shipping test, below)

Aging/shipping/sterilization for the (b) (4) Vial Adapter

510(k) (b) (4) was referenced to support the shipping, aging, and sterility of the (b) (4) Vial Adapter for use with the subject biologic product kits. The 510(k) contained information supporting that sterilization methods used for the infusion set would achieve appropriate limits for intravenous use, however no information related to shelf life or

shipping could be located within the submission. Within an information request response on September 11, 2015, the sponsor provided record of shipping and aging tests conducted on the (b) (4) Vial Adapter by the 510(k) holder. This is considered acceptable.

Whole System Shipping Assessment

In response to an Agency information request, the sponsor completed and submitted system-level shipping information for the diluent syringe, infusion sets, and vial adapter components of combination product within BLA amendment 039. This assessment exposed each of these components to simulated shipping conditions and then assessed the secondary and primary packaging components, as well as the functionality of the device components. Each device lot (n=60) passed the assessments and testing. This is considered acceptable.

Vial Adapter

The submission provided limited verification information for the vial adapter, with the exception of biologic-device compatibility. The sponsor has deferred verification of the vial adapter to cleared 510(k) (b) (4) was found to have sufficient information to verify independent (device only) requirements, but the submission was found to not contain sufficient detail to verify the biologic sponsor's own requirements as included within section "Vial adapter (b) (4) medical device STED.2.2.02-01 Product Specification and Test Procedure" of the submission. Additionally, the consulting reviewer was not certain if the device cleared within the referenced (b) (4) 510(k) was representative of the product sold by (b) (4) presently. The Agency posed these questions to the sponsor, and within June 11, 2015 and September 11, 2015 responses to Agency questions, the sponsor provided:

1. Test reports demonstrating that all essential performance characteristics of the vial adapter device were satisfied. These reports were examined and found to be acceptable.
2. A detailed report from (b) (4), the supplier of the vial adapter, describing changes made to the device since the original clearance and methods used to verify and validate those changes. This information was found to be acceptable.

The consulting reviewer has no residual concerns regarding the vial adapter component.

Pre-filled Syringe

Verification information for the pre-filled syringe is located within master file (b) (4)

In addition to information provided within the master file, the sponsor also conducted assessments of syringe functional characteristics such as container closure integrity tests and break-loose and glide-forces within 3.2.P.8 of the submission. The performance of the syringe is considered acceptable from a device attribute perspective. Evaluation of container closure attributes for the pre-filled syringe are deferred to the CMC reviewer.

Administration Sets

The sponsor has not provided any verification information for the stand-alone administration sets. The sponsor has evaluated these sets for their effect on biologic compatibility; however this alone is not sufficient. Within a June 9, 2015 information request, the sponsor was asked to provide information supporting functionality of the administration sets for use within the biologic kits. The sponsor provided reference to the cross-referenced 510(k) clearances for these devices. The consulting reviewer examined each 510(k), (b) (4) for the (b) (4) Infusion Set and (b) (4) for the (b) (4) Infusion Set and found that appropriate verification of functional and physical attributes had been conducted to support the intended use of each product, and that the cleared intended uses under the 510(k)s were substantially identical to

the intended use of the sets within the subject biologic submission. This approach is considered acceptable, however final verification of infusion set function is considered as represented by the system integration tests described within the section below.

System Integration

Section P.2.6.01-01 P.2.6.01-02 of the submission includes assessments of biologic-device interaction with each vial access and administration set configuration. These assessments are deferred to CBER; however the reviewer noted that no volume recovery is specified within these tests. This concern was provided to the review division as part of the mid-cycle meeting for the submission. Requests and evaluations of data to support dose accuracy and recovery of the system are considered as “master tests” for system function and the review of these tests are deferred to the CMC reviewer.

The reviewer also notes that the submission does not appear to contain an assessment of leachable or extractable compounds from the BIO-SET, vial adapter, or either administration set. This concern was provided to the review division as part of the mid-cycle meeting for the submission. Requests and evaluations of data to support safety of compounds leaching from the device components are deferred to the CMC reviewer.

V. Recommendation

The consulting reviewer recommends approval of the BLA in the context of device constituent parts for the combination product. The reviewer notes that the review of a number of system attributes, including the container closure assembly and in-use studies have been deferred to the CMC reviewer.

VI. Concurrence Table

Digital Signature Concurrence Table		
Reviewer Sign-Off	Ryan J. Mcgowan -S	Ryan J. Mcgowan -S 2015.12.19 12:49:33 -05'00'
Branch Sign-Off		Richard C. Chapman -S 2015.12.17 17:14:46 -05'00'