

Facility Review Memo, July 22, 2012 - Hyqvia

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Service

Public Health

Food and Drug Administration
Center for Biologics Evaluation and Research
1401 Rockville Pike
Rockville MD 20852-1448

Date: 04/19/2012, edited 07/22/2012

To: Administrative File, BL STN 125402/0

From: Pankaj (Pete) Amin, Senior Reviewer, OCBQ, DMPQ, MRB II, HFM-676

Through: Chiang Syin, Ph.D., Branch Chief, OCBQ, DMPQ, MRB II, HFM-676

Subject: Review Memo – BL STN 125402/0, Immune Globulin Infusion (Human), 10% with Recombinant Human Hyaluronidase: HYQVIA, a combination product including BLA 125105 (Immune Globulin Intravenous (Human), 10% Solution; Gammagard Liquid) and NDA 21-859 (Hyaluronidase Human Injection, Hylenex) Manufacturer: Baxter Healthcare Corporation

Action Due: 07/29/2012

Recommendation:

Based on my review, there is no complete response letter question for the facility related information submitted in the BLA. Only one information request question remain to be resolved.

Product Information

Baxter filed the BLA for the Immune Globulin Infusion (Human), 10% with Recombinant Human Hyaluronidase, which is a combination product of drug and biologic. The combination product consists of one vial of the Recombinant Human Hyaluronidase (rHuPH20) and one vial of Immune Globulin Infusion (Human), 10% (IGI, 10%) connected together in a dual vial unit with the vial stopper covered with a unified cap allowing access to both vials when the stoppers are removed. The IGI, 10% are identical to the currently approved GammaGard Liquid (STN BL 125105) with no changes in the manufacture of the final product. The rHuPH20 component is very similar to Hylenex Hyaluronidase human injection drug product (NDA 21-859, approved 2005), -----(b)(4)----- . The proposed final product is Immune Globulin Infusion (Human), 10% (IGI, 10%) with recombinant human Hyaluronidase (rHuPH20), intended for the treatment of patients with primary immunodeficiency (PI) with defects in humoral immunity.

Manufacturer

The following manufacturing facilities are involved in production of this combination product.

Component of Combination Product

Manufacturer site

Immune Globulin Infusion (Human), 10% (IGI, 10%)

Baxter
Boulevard Branquart 80,
7860 Lessines, Belgium

Note – Identical to Baxter's GAMMAGARD LIQUID Immune Globulin Intravenous (Human), 10% Solution (IGIV, 10%) product, which was approved by FDA on 27 April 2005 (STN BL 125105).

Note - Same facility and no change in manufacturing process

Baxter -----
------(b)(4)-----

Recombinant Human Hyaluronidase (rHuPH20)

*Note –
Bulk enzyme developer:
Halozyme Therapeutics, Inc.
11388 Sorreno Valley Road
San Diego, California 92121
Bulk enzyme manufactured under contract (NDA 21-859)
------(b)(4)-----
-----*

*Notes:
The bulk enzyme is further manufactured into the Recombinant Human Hyaluronidase (rHuPH20) at this facility. This is a new manufacturing location compare to approved NDA. Building (b)(4) – bulk enzyme further formulated and filled at this building. (Aseptic filling operation). Building (b)(4) – packaging and labeling operations.*

Baxter
Boulevard Branquart 80,
7860 Lessines, Belgium

Combination product - Immune Globulin Infusion (Human), 10% with Recombinant Human Hyaluronidase

*Note:
Only labeling and Packaging of combination products, no additional manufacturing of the combination product.*

Baxter ----(b)(4)----- Facility - Recombinant Human Hyaluronidase

Baxter

------(b)(4)-----
------. Building (b)(4) is a multi-product facility and includes separate areas for component preparation, formulation, and vial filling of rHuPH20. The ceiling, floors, and walls of the classified areas constructed of -----(b)(4)----- and select floors covered with -----
------(b)(4)-----

-----.

Process Flow

(b)(4) provided a general flow chart and an overview of the manufacturing. The Recombinant Human Hyaluronidase formulated on the ------(b)(4)-----

- ---(b)(4)-----

HVAC system

The Production HVAC system, ---(b)(4)---, consists of a makeup system with air drying and humidification supplying conditioned makeup air, a supply and return system with --(b)(4)----- units including cooling and heating (only cooling coil: -----(b)(4)-----; cooling and heating coil: ---(b)(4)-----, a 100% fresh air mechanical room air handler, and an exhaust air system. Each fill room of the controlled environment -----(b)(4)----- the zone of an air-handling unit to maintain working room static pressures, temperatures, relative humidity, and air changes and flows specific to that area. (b)(4) stated that air pressure differentials, relative humidity, and temperature monitored and recorded routinely. There are ----(b)(4)----- systems in each filling suite. (b)(4) is also checking all critical freezers, coolers, and incubators (b)(4). All critical systems equipped with emergency power generators.

Area classification

(b)(4) has qualified the Class ----(b)(4)----- and Class ----(b)(4)----- areas. (b)(4) stated that the results of this PQ were used to assist in determining sampling sites, which were incorporated into the routine environmental monitoring (EM) program. (b)(4) approved SOP No. 07-04-029 “Environmental Monitoring Master Plan”, SOP No. 07-08-001 “Environmental Monitoring

2 pages determined to be not releaseable

 -----(b)(4)-----

Cross contamination

(b)(4) interpreted risk of cross contamination by taking several precautions against contamination or cross contamination during production activities. (b)(4) claimed that changeover procedures are implemented according to standard operating procedures. Only dedicated or single-use contact-to-product equipment is used for products. (b)(4) acknowledges their ---(b)(4)----- facility as multi-products faculties. (b)(4) provided a list of precautions against cross contaminations follow:

- ---(b)(4)----- filled at a time per filling suite.
- Filling suites regularly sanitized per Standard Operating Procedures.
- ---(b)(4)----- formulated at a time per formulation room.
- Formulation rooms routinely sanitized per Standard Operating Procedures.

- Exterior of raw material containers wiped down with -----(b)(4)-----
-----.
- The only sterile product introduced into the -----(b)(4)----- areas. Biologic products utilize single-use or dedicated product-contact equipment.
- Identification and separation of clean versus dirty equipment, as well as sanitized versus sterilized equipment.
- Equipment and materials wiped down with an approved sanitizing agent prior to placement in the -----(b)(4)-----.
- Only approved containers or product contact surfaces used: type -----
----- (b)(4) -----.
- Equipment properly maintained through a preventive maintenance program.
- Validated cycles used for washing, and sterilizing product contact equipment.
- Increasingly restricted access to controlled manufacturing areas and aseptic filling areas. (Accessed by key card to -----(b)(4)-----).

In addition, (b)(4) claimed that the products and intermediates are clearly labeled and identified by batch number, material name and only QC released material is allowed to be handled in the production area. Products of different release status (i.e. quarantine status according to validation activities) is clearly identified and stored separately. Validated cleaning procedures are established to clean and, where applicable, sterilize equipment between each production run. Equipment is properly labeled according to its cleaning status. The production area is cleaned and sanitized according to cleaning/sanitization schedules defined in writing procedures. Shared non-product contact production equipment that is unable to be sterilized is -----
----- (b)(4) -----.

----- Manufacturing equipment in the production area is cleaned before and after use. I noted that (b)(4) claimed that all the product contact equipment used in the rHuPH20 process are dedicated or single use, so there is less concern for cleaning validation.

The qualified sanitizing agents currently in use at (b)(4) are -----(b)(4)----- ensures that -----(b)(4)----- aseptic formulation and filling areas are -----(b)(4)----- or validation exercise or a minimum of ---(b)(4)----- Other -----(b)(4)----- areas are fully sanitized (b)(4) during routine production or a minimum of ---(b)(4)----- with ---(b)(4)--- cooling zones sanitized (b)(4).

It appears that (b)(4) has taken adequate precautions against cross contamination that is aligned with the industry standards. This is an FDA licensed facility and inspected several times in the past (last inspection was VAI). There is no new major modification to the facility or equipment due to the introduction of the rHuPH20 product into this facility.

Material Control

----- (b)(4) -----

----- (b)(4) -----
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- ----- (b)(4) -----
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[(b)(4)]

Container Closure

The container closure system chosen for rHuPH20 2 ml, 13 mm vial size consists of a -- (b)(4) ----- glass vial and a ----- (b)(4) ----- rubber with an aluminum/ plastic flip-off seal. The same type of vial was chosen for the 5 ml and 20 ml product presentations and a rubber stopper that is --- (b)(4) ----- . The aluminum/plastic flip-off seal is the same for all product configurations except that the 2 ml product uses a 13 mm seal while the 5 ml and 20 ml use a 20 mm seal. Drawings are provided in the Container Closure System section (3.2.P.7). All vials (2-mL 13 mm, 5-mL 20 mm, and 20-ml 20 mm) are ----- (b)(4) ----- 13 mm stoppers are ----- (b)(4) ----- . The 20 mm stoppers are received at ----- (b)(4) ----- .

----- (b)(4) -----

----- (b)(4) -----

----- (b)(4) -----

11 pages determined to be not releaseable

----- (b)(4) -----

----- (b)(4) -----

----- (b)(4) -----

Water System

The water for injection system used in the process is already qualified system and no major change made to the system since the last cGMP inspection. The WFI system is a closed, re-circulating system with the main distribution loop maintained at a temperature of (b)(4) and with --(b)(4)-- cool loops providing (b)(4) water to specific use points. The Water for Injection (WFI) produced at (b)(4) in Building (b)(4) is used but not limited to the preparation of drug product, -----(b)(4)----- of production equipment. The incoming city water is monitored for -----(b)(4)--content -(b)(4)- and endotoxin and -----(b)(4)----- performed -----(b)(4)----- The -----(b)(4)----- Systems -----(b)(4)----- are monitored -(b)(4)- for -----(b)(4)-----; endotoxin analysis is performed --- (b)(4) --. Full testing is performed on the affected system following maintenance/repair activities. Following the (b)(4) system shutdown all ports within the affected -----(b)(4)---- system are sampled and tested for microbial, -----(b)(4)----- --(b)(4), endotoxin and --- (b)(4) ----- from each WFI system is collected --- (b)(4) -----

and tested for (b)(4). (b)(4) from each WFI system is collected and tested (b)(4) for the presence of

(b)(4). The (b)(4) purified water system is sampled and tested for microbial and TOC and conductivity analysis at least (b)(4), or following preventative maintenance or filter change. (b)(4) provided a summary of the WFI system monitoring data and test results indicated that the WFI system under control.

Bulk Packaging

(b)(4) provided information on rHuPH20 bulk labeling and packaging operation in the Building (b)(4). Building (b)(4) is a multi-product facility and includes separate areas for manual inspection and

(b)(4)

(b)(4) explained the product flow as follow: The bulk products from the Building (b)(4) manufacturing facility or (b)(4) are transferred to Building (b)(4) and are received in receiving area

(b)(4)

Dual Vial Unit Device

The combination product is supplied as an integrated package with the Immune Globulin Infusion (Human), 10% (IGI, 10%) component and the Recombinant Human Hyaluronidase (rHuPH20) component connected together by a collar/stand and with the vial stoppers covered with a unified cap allowing access to both vial stoppers when removed. The packaging design creates a barrier against using rHuPH20 separately from the associated IGI, 10%.

Combination Product

The bulk enzyme is further manufactured into the Recombinant Human Hyaluronidas (rHuPH20) product, which is one of the two components of the combination product, by Baxter (b)(4) facility. The rHuPH20 product is shipped to the Baxter's Lessines facility for labeling and packaging. Baxter provided the following information on their labeling and packaging operation for the combination product at Baxter Lessines, Belgium.

Baxter utilized the semi-automated line is to package the combination product. To avoid mix-up, Baxter handles (b)(4) occurs in a packaging room at any given time. Line clearances are performed before and after the packaging of each lot. Printed material reconciliation is performed at the end of the operation. Prior to labeling and packaging, capped vials (b)(4)

Baxter provides brief labeling and packaging process description. The vials are placed onto the

vials, ability to wash and handle vials at maximum vial washer speed, and ----(b)(4)----- particle removal.

----- (b)(4) -----

- validation report for the most recent (b)(4) requalification of the 20mm stopper washing. The (b)(4)- requalification demonstrated a --(b)(4)-- reduction of endotoxin, particulate removal ----- (b)(4)-----.

IR question 3

Please provide the most recent (b)(4) vial depyrogenation validation protocol and report including a discussion and resolution of any deviations observed during validation (2 mL, 5 ml and 20 ml vials).

Baxter Response

Baxter performed (b)(4) vial depyrogenation validation. The routine confirmations of the ----- (b)(4) ----- for the 5mL 20mm was conducted as per SOP No. 04-07-037. The most recent validation (#VL1001019) was successfully completed and meets all acceptance criteria. Following acceptance criteria were met during (b)(4) requalification:

- The minimum number of containers challenged during the run with sufficient quantities to ----- (b)(4) -----.
- A minimum of ---(b)(4)----- was achieved for each temperature monitoring device at the completion of the depyrogenation cycle.
- All (b)(4) endotoxin challenges vials attain at least a ---(b)(4)----- of bacterial endotoxin.
- All temperature monitoring devices were calibrated within (b)(4) of the reference temperature.

IR Question 4

Please provide your most recent stopper (b)(4) sterilization requalification protocol and summary report including deviation, investigation and corrective action taken (each of -- (b)(4) --- 13 mm, 20 mm stopper and 20 mm ready-to-sterilize stoppers).

Baxter Response

Baxter conducted stopper performance qualifications based upon ---(b)(4)---, focusing on the stopper ----- (b)(4) -----
-----.

----- (b)(4) -----

----- All cycle meets validation acceptance criteria and demonstrated ----(b)(4)-----.

Following are list of acceptance criteria that were met during (b)(4) stopper requalification.

- Each temperature sensor calibrated within ----(b)(4)---- of the ----- (b)(4)-----.
- Each temperature sensor reached a minimum (b)(4) during the -----
----- (b)(4)----- temperature has been reached.

- All temperature sensors read a minimum of -----(b)(4)-----.
- A minimum of -----(b)(4)-----.

- All BI's and the negative control exhibited no growth after -----(b)(4)-----.

Baxter provided a summary of validation for the most current validation confirmations. The validation # VL1011003, #VL1011004, VL1011005, VL1011006, VL1011007, VL1011008, VL1106015, VL1106035, and VL1107009 meet all validation requirements and the (b)(4) requalification of the different size stoppers was successful.

Question 5

Please provide the maximum worst-case durable load configuration ---(b)(4)----- sterilization confirmation protocol and report summary including discussion and resolution of any deviations observed during validation.

Baxter Response

Baxter stated that Performance Qualifications for filling equipment are performed according to SOP No. 04-05-001, Performance Qualification of the Production Autoclaves, and are based on maximum and minimum worst-case durable load configurations. The worst-case durable load includes the most difficult pieces of equipment to sterilize, which are based upon past validations for different load configurations yielding consistent cold spots. The PQ consists of a minimum of Three-loaded chamber heat distribution and penetration studies for both the minimum and maximum worst-case load configurations. Loads falling between the minimum and maximum worst-case configurations are considered validated following a one-time confirmation of the specific load.

The maximum worst-case durable load configuration requires a validation confirmation - --- (b)(4) per autoclave. These ---(b)(4)----- validation confirmations are performed according to SOP No. 04-07-007, Validation Confirmation of the Production Autoclaves. Baxter provided a validation report for the VL1106025, VL1106026, and VL1106027. Following acceptance criteria were met and validation was successful:

- A minimum of -----(b)(4)-----.
- All BI's and the negative control exhibited no growth after -----(b)(4)-----.
- Each temperature sensor calibrated within -----(b)(4)-----.
- Each temperature sensor reached a minimum -----(b)(4)-----.
- All temperature sensors read a minimum of -----(b)(4)----- of exposure.

IR question 6. Media Fill:

Please provide the most recent media fill --- (b)(4) -- requalification ----- (b)(4) ----- protocols and the report including a detail discussion and resolution of any deviations observed.

------(b)(4)-----

---. Baxter provided three successful performance qualification runs, these runs demonstrated that the cleaning procedures effectively removed the residual product and cleaning agent from the product contact manufacturing equipment.

CBER Question

Please provide your classified areas OQ/PQ validation summary (protocol and summary reports).

Please provide laminar flow hood qualification summary (protocol and summary reports).

HEPA filter certification plan and most recent certification summary

Baxter Response:

Baxter provided validation summary reports for the fill room (b)(4) (report # 43311), fill machine (b)(4) media fill validation (VL1105027 and VL1112018) and HVAC validation (VL0512039). All validations successfully completed and met acceptance criteria.

Baxter provided the laminar flow hood qualification summary (VL0811026). All acceptance criteria were met.

Baxter stated that Routine certification is performed at -(b)(4)-- intervals for all critical and -----(b)(4)----- intervals for all remaining classified area filters. -----

------(b)(4)-----

----- . Certification indicates the classified areas are capable of providing an aseptic environment.

CBER Question

Procedures for routine environmental monitoring program (frequency, alert, action limits, test locations).

Baxter response

Baxter provided their environmental monitoring program procedures including SOP # 07-04-029 "Environmental Master plan", SOP # 07-04-001 " Viable surface monitoring", SOP # 07-04-003, "fingertip and fallout monitoring", SOP # 07-04-020 "Monitoring total count", and SOP # 07-04-021 "Quantitative monitoring of the air in classified areas".

Baxter provided a summary of last three month environmental monitoring report and the report indicated that no negative trend was identified and environments in classified areas was under control.

CBER Question

Please describe your plan to verify the container closure integrity over the shelf life of the product including sensitivity of the container closure test method.

Baxter Response

Baxter stated that they will verify container closure integrity over the shelf life of the product using a validated -----(b)(4)----- method with known sensitivity.

Baxter informed that testing will be performed using components that represent final product container/closure configuration, and that have been exposed to storage conditions that are deemed "worse case" (e.g., time, temperature, relative humidity) with respect to sterility maintenance. Baxter did not provide any additional specific

on existing validated equipment. On these existing labeling machines, a pre-printed barcode is checked on each label in order to be sure that the right label is used. The expiry date, lot number and manufacturing date are printed in human readable characters in a data matrix. These on-line printed characters are automatically checked with a validated ---(b)(4)-- system. After an automated inspection, the two labeled vials are conveyed to the semi-automated line for combining into an inseparable, dual-vial unit. Baxter provided the labeling machine validation report (Report # -----(b)(4)----- and IOQ of the semi-automatic assembly line validation report # -----(b)(4)-----). During the semi-automatic assembly qualification, -(b)(4)-- for each of the five dosage configurations of the combination product were assembled and 100% visually inspected (manually). The validation was successful and met all acceptance criteria.

CBER Question

Please provide acceptance criteria for packaging and labeling operations.

Baxter Response

Baxter stated that the packaging and labeling operations acceptance criteria are detailed in SOP LE20QC03070 titled "Description of the Inspection Process during Packing Operations". -----(b)(4)-----
-----). In addition, Baxter provided a specific acceptance -----(b)(4)-----.

CBER Question

Please describe any changes (change control) to the packing and labeling process or equipment after the confirmation lots (combination product).

Baxter Response

Baxter stated that there have been no changes to the packing and labeling process of the combination product.

CBER Question

Please describe your label storage procedure.

Baxter Response

Baxter provided a procedure # LE20QC03151 "Label Room QA management" which describes the label storage procedure.

CBER Question

Please describe how unlabeled filled containers are controlled to prevent a mix-up.

Baxter Response

Baxter stated that SOP LE16SG02062 titled "Description of Component Preparation and Back to Stock after Production" describes the control of the unlabeled filled containers.

CBER Question

Please provide the facility diagram which traces through the combination labeling and packaging process.

Baxter Response

Baxter provided the facility diagram that outlines the sequences of combination labeling and packaging process.

Based on the information provided and additional Baxter responses to IR questions, I recommend approval of this BLA.

Outstanding Information request that need to be resolved:

- (b)(4) submitted a comparative protocol for the introduction of a new product into the licensed production areas. This comparative protocol should be submitted as stand-alone (PAS).
- The buffer used in the rHuPH20 process required information on the -----(b)(4)----- control need current update.
- (b)(4) needs to provide the Dual unit manufacturer/supplier information.
- The container closure study over product shelf life (stability) needs updated information.