DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

DISTRICT OFFICE ADDRESS AND PHONE NUMBER	DATE(S) OF INSPECTION
Director, Division of Inspections and Surveillance FDA / CBER / Office of Compliance and Biologics Quality 10903 New Hampshire Avenue (W071-5128) Silver Spring, MD 20993-0002 TEL: 240-402-9159 Industry Information: www.fda.gov/oc/industry	5/20-31/2019
	FEI NUMBER 3002806503

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT IS ISSUED

TO: Ms. Valerie De Schutter, Site Quality Head

FIRM NAME	STREET ADDRESS
Baxalta Belgium Manufacturing S.A.	Boulevard Rene Branquart 80
CITY, STATE AND ZIP CODE	TYPE OF ESTABLISHMENT INSPECTED
7860 Lessines, Belgium	Licensed Biological Manufacturer

THIS DOCUMENT LISTS OBSERVATIONS MADE BY THE FDA REPRESENTATIVE(S) DURING THE INSPECTION OF YOUR FACILITY. THEY ARE INSPECTIONAL OBSERVATIONS, AND DO NOT REPRESENT A FINAL AGENCY DETERMINATION REGARDING YOUR COMPLIANCE. IF YOU HAVE AN OBJECTION REGARDING AN OBSERVATION, OR HAVE IMPLEMENTED, OR PLAN TO IMPLEMENT CORRECTIVE ACTION IN RESPONSE TO AN OBSERVATION, YOU MAY DISCUSS THE OBJECTION OR ACTION WITH THE FDA REPRESENTATIVE(S) DURING THE INSPECTION OR SUBMIT THIS INFORMATION TO FDA AT THE ADDRESS ABOVE. IF YOU HAVE ANY QUESTIONS, PLEASE CONTACT FDA AT THE PHONE NUMBER AND ADDRESS ABOVE.

DURING AN INSPECTION OF YOUR FIRM (I) (WE) OBSERVED:

1. Input to and output from the computer or related system of formulas or other records or data shall be checked for accuracy. The degree of input/output verification was not sufficiently based on the complexity and reliability of the computer or related system. Specifically,

a) Process Change PR1314817, implemented on 10Aug2018, was initiated to secure the (b) (4) step, by limiting settings ((b) (4)). This change, PR1314817, was implemented to avoid sudden (b) (4) by limiting the increase of the (b) (4) and decreasing the (b) (4) (b) (4) (b) (4) , according to the (b) (4) of the system. As a result of an unexpected (b) (4) modification, this process change was unintentionally applied to the (b) (4) sequence of the (b) (4) of the (b) (4) which led to a deviation to the routine (b) (4) sequence, as the (b) (4) modulating (b) (4) remained (b) (4) during the (b) (4) sequence. This caused inappropriate (b) (4) from (b) (4) to the (b) (4) Tank. Since December 2018, a (b) (4) trend for endotoxins (LAL) for the (b) (4) sample ((b) (4) (b) (4)) and for the Final Container samples were observed. The (b) (4) trend for endotoxins was detected on (b) (4) Line (b) (4) used for the manufacture of Gammagard Liquid, HyQvia, and Cuvitru, and involved (b) (4) bulk lots. The root cause was determined on February 22, 2019 and a BPDR was submitted to FDA on April 4, 2019.

b) On June 10, 2018, a discrepancy was observed by an analyst between the limit recorded in the (b) (4) system and the SOP LE12QC2102/SOP-048719 for the microbial testing of the (b) (4) used for grade (b) (4) interventions and setup of the (b) (4) line by the aseptic (b) (4) operator. The introduction of the (b) (4) (b) (4) and (b) (4) testing positions, which corresponds to the (b) (4) and the (b) (4) respectively) took place in 2009. A retrospective review found that two results were not identified as being Out of Limit during the (b) (4) of Gammagard Liquid lot (b) (4) and (b) (4) sublot (b) (4) ((b) (4) ; and Gammagard Liquid lot (b) (4) ((b) (4)). Both test results were at (b) (4) (b) (4)). The Gammagard Liquid lot (b) (4) (expiration date June 24, 2020) and (b) (4) sublot (b) (4) (expiration date June 24, 2020) were distributed in the US market. A Biological Product Deviation Report was submitted to the FDA on July 20, 2018 (tracking number: 2018-058). The limit in the (b) (4) was

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	/S/	Prabhu P. Raju, Investigator Yonggang Wang, Ph.D. Biologist Mizanne E. Lewis, Investigator	5/31/2019

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corrected on June 29, 2018 (Deviation PR1308695).

2. There is a failure to thoroughly review a batch or any of its components to meet any of its specifications whether or not the batch has been already distributed. Change Control PR1257198, opened on 6-Dec-2017 and closed on 21-Sep-2018, did not include a sufficient assessment on (b) (4) a critical material, used for manufacturing of Gammagard Liquid (GGL) and HyQvia. (b) (4) (item code (b) (4)) is used in the (b) (4) , (b) (4) , (b) (4) , (b) (4) , and (b) (4) (b) (4) steps. Specifically,

Change Control PR1252801 was opened on 17-Nov-2017 (closed on 23-Jan-2018) to remove the (b) (4) code from the Bulk Drug Substance (BDS) Bill of Materials (BOM) and for use of an alternative (b) (4) source of (b) (4) ((b) (4)). After implementation of this corrective action, final container lots were produced with (b) (4)) levels of rejects due to (b) (4)

Change Control Record PR1257198, closed on 21September 2018, documented a decision to use the (b) (4) (b) (4) , as a backup of the (b) (4) for the manufacture of Gammagard Liquid and HyQvia. Since early 2019, an increased level of visible (b) (4) was observed again during the (b) (4) visual inspection for Gammagard Liquid and HyQvia lots manufactured using (b) (4) from the (b) (4) . The (b) (4) were identified as (b) (4) A possible root cause was determined to be related to the implementation of the (b) (4) configuration. As a preventive action, the (b) (4) was replaced by the (b) (4) (b) (4) for manufacture of Gammagard Liquid and HyQvia on April 30, 2019. This investigation is ongoing.

3. Four non-medical broken vial US complaints for Gammagard Liquid were discovered in April, May 2017 and were not submitted as BPDRs until February13, 2018. Specifically,

a) PR1194575, dated 03April2017, reported 3 leaking damaged vials of Gammagard Liquid (10%, 10g, US).
b) PR1198237, dated 20April2017, reported customer received one Gammagard Liquid (10%, 10g, US) broken vial.
c) PR1205477, dated 24May2017, reported one Gammagard Liquid (10%, 30g, US) leaking/broken vial.

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d) PR1243345, dated 10Oct2017, reported one Gammagard Liquid (10%, 30g, US) broken vial.

These complaints were reported as one BPDR 2017-042, 049, 068, 142 on February 13, 2018, which exceeded the 45 Day Calendar limit.

4. The following Serious Unexpected Adverse Events were submitted in excess of 50 Calendar Days, which is > 15 Calendar Day post marketing reporting requirement. Specifically,

a) Gammagard S/D- 4 Serious Unexpected Adverse Events- Avg. Reporting Time- 224 Days
b) Cuvitru—8 Serious Unexpected Adverse Events-Avg. Reporting Time- 169 Days
c) HyQvia- 8 Serious Unexpected Adverse Events-Avg. Reporting Time-115 Days
d) Gammagard Liquid-11 Serious Unexpected Adverse Events-Avg. Reporting Time- 301 Days

5. Quality Investigations were not conducted per SOP-2024-Adverse Event Quality Investigations, dated March 23, 2018 for the following reported viral transmission and fungal infection events. The causality assessment in each case was assessed as possible by the company/manufacturer, and the lot numbers were known. Specifically,

a) Suspect Adverse Reaction Report, Case (b) (4) dated (b) (4) Gammagard Liquid Immunoglobulin, Lot (b) (4), reported fungal infection. The company comment assessed the event of Fungal infection as possibly related to Gammagard Liquid.

b) Suspect Adverse Reaction Report, Case (b) (4), dated (b) (4), Gammagard Liquid Immunoglobulin, Lot (b) (4), reported that patient contracted Hepatitis B from Gammagard Liquid (was negative 3 years ago). The company causality assessment assessed the event Hepatitis B as possibly related to Gammagard Liquid.

c) Suspect Adverse Reaction Report, Case (b) (4), dated (b) (4), Gammagard Liquid Immunoglobulin, reported Hepatitis C in a patient. Several Lots but not limited to: (b) (4), (b) (4) were used from 6Oct2016 to 25May2017. The company comment assessed the event Hepatitis C as possibly related to Gammagard Liquid.

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Minimal investigational activities specified in SOP-2024, Adverse Event Quality Investigations, 23Mar2018, included a review of the following: batch records, events during production, product release testing results (including sterility), environmental and bioburden testing results, pre and post filter integrity results, visual inspection of retention samples (where applicable), stability review, and NAT/PCR and/or serology testing.

6. The Room (b) (4) and Room (b) (4) is not of appropriate design for its intended use and for its cleaning and maintenance. Specifically,

a) The design of the (b) (4), (b) (4), Room (b) (4), has an unused portion of (b) (4) of almost (b) (4) in length, where (b) (4) is the (b) (4) of the (b) (4).

b) The design of the (b) (4) (b) (4), Room (b) (4) has an unused portion of (b) (4) of almost (b) (4) in length, where (b) (4) is the (b) (4) of the (b) (4).

These Points of Use are used for cleaning (b) (4) for Gammagard Liquid, Cuvitru, and HyQvia in the (b) (4) area.

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The observations of objectionable conditions and practices listed on the front of this form are reported:

1. Pursuant to Section 704(b) of the Federal Food, Drug and Cosmetic Act, or

2. To assist firms inspected in complying with the Acts and regulations enforced by the Food and Drug Administration.

Section 704(b) of the Federal Food, Drug, and Cosmetic Act (21 USC 374(b)) provides:

"Upon completion of any such inspection of a factory, warehouse, consulting laboratory, or other establishment, and prior to leaving the premises, the officer or employee making the inspection shall give to the owner, operator, or agent in charge a report in writing setting forth any conditions or practices observed by him which, in his judgement, indicate that any food, drug, device, or cosmetic in such establishment (1) consists in whole or in part of any filthy, putrid, or decomposed substance, or (2) has been prepared, packed, or held under insanitary conditions whereby it may have become contaminated with filth, or whereby it may have been rendered injurious to health. A copy of such report shall be sent promptly to the Secretary."