

Review Memo - GSK Building - Rotarix

Date: March 21, 2008

To: Administrative File, STN 125265/0

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Subject: Review Memo- GSK Building ----/ Filling, Lyophilization of HRV Vaccine and ----
/Bulk Manufacture of HRV Vaccine: GlaxoSmithKline Biologics (License # 1617); STN
125265/0 - BLA for Rotavirus Vaccine, Live, Oral, Monovalent, Rixensart, Belgium.

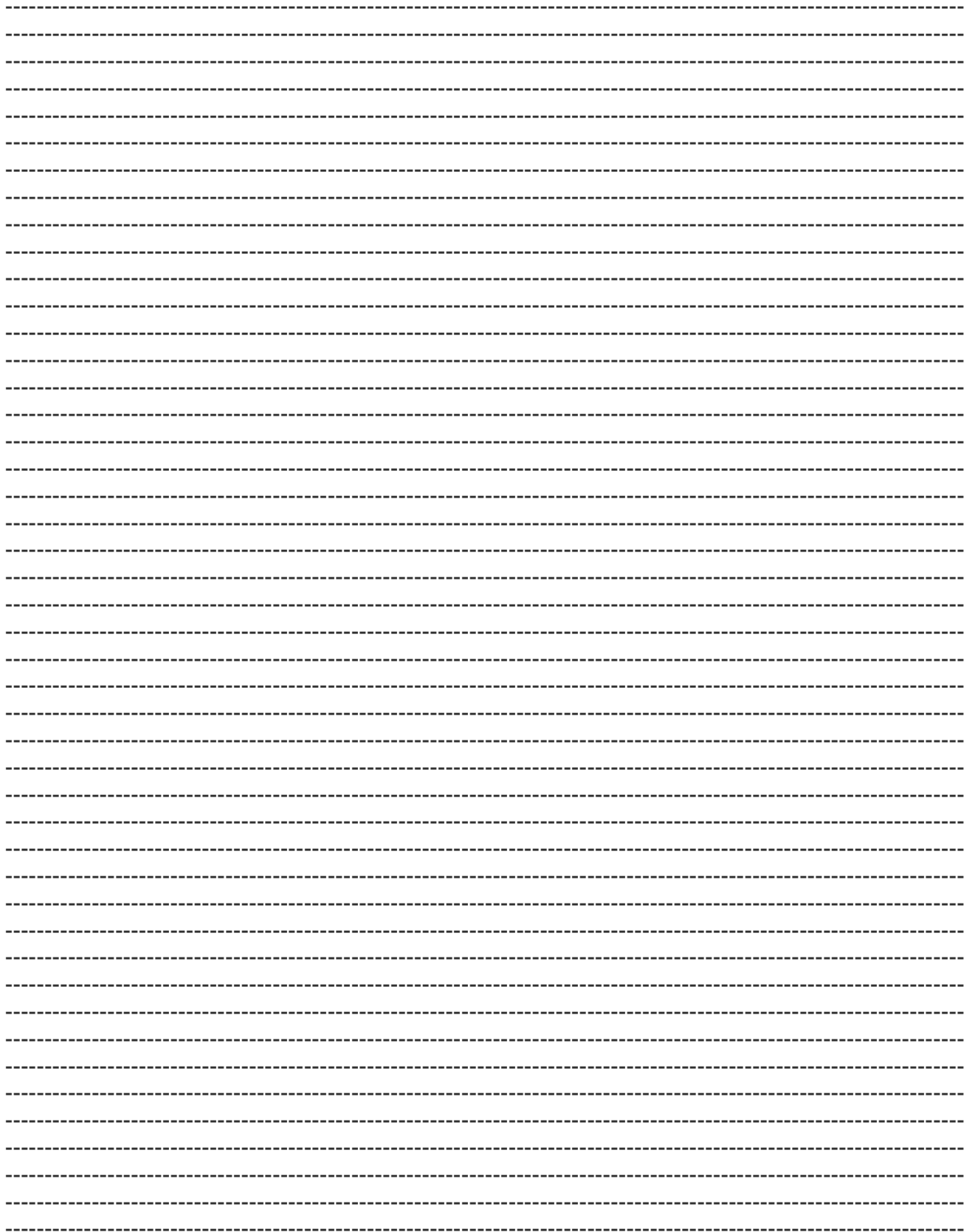
Action Recommended

The facility/equipment information related to vaccine manufacture in this BLA and corresponding amendments has been reviewed. Several review items were noted during the review process and were subsequently resolved. The BLA, as amended, is recommended for approval.

Executive summary

GSK has successfully performed aseptic filling and lyophilization process for Rotavirus in the building ----. ----- filling lines ----- are currently operational and U.S. approved. The Building ---- includes ----- filling line (vial filling line ----) with ----- lyophilizers. The ----- vial filling line ----- filling area to the existing GSK Bio filling facility ----. The -----, which was completed in ---- and fully validated in 2006, is specifically designed for the manufacturing of ----- lyophilized vaccines in combination with ----- . ----- is similar ----- - to the US approved vial ----- filling line ----- . Following critical validations/qualifications were successfully completed:

- Formulation process (Bulk)-media fill
- Aseptic Filling (Media fill) for ----- filling line and Lyophilization
- process
- Lyophilization qualification
- Lyophilization process validation
- Lyophilization cleaning validation
- Lyophilization sterilization
- ----- qualification
- ----- Cleaning, sterilization and -----
- Container closure - cleaning/depyrogenation, sterilization, integrity
- Cleaning validation



- _____
- _____

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NOT RELEASABLE**

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Review Question (dated)

GSK Response (E-mail response Dated 3/10/09):

The ----- challenge test consists in:

- The following table gives the filters used in the process of lyophilized Rotarix:

Review comment:

Review Question:

Regarding Container closure information in BLA section 3.2.p.7

- I could not find (test results) information for the container closure (vials, stopper) compatibility, toxicity, biological tests. In addition could not find information on container closure integrity at proposed expiration date.
- Page 10 (section m3.2.P.7) describe the table with tests name and method of analysis. These methods reference -----, how these methods compare to --- methods. (Need justification).

GSK Response (E-mail response Dated 3/10/09):

The container closure system is in compliance with the requirements for liquid-based oral products as described in the FDA guidance for industry "Container Closure Systems for Packaging Human Drugs and Biologics," May 1999. The --- glass vial used in the oral Rotarix vaccine -----

The ----- stopper ----- vaccines -----
-----, Rotarix is GSK's first US licensed lyophilized vaccine.

----- has a --- for the ---- stopper on file with -----, A Letter of Authorization to allow FDA to reference this --- to support the licensure of Rotarix is provided. The stopper ----- conducted the extractable test data and -----
----- stopper.

In terms of container closure integrity, testing was performed at expiration for the three phase III clinical consistency lots (RVC018A42, RVC019A43, and RVC021A44), i.e. after storage at +2°C/+8°C for -- months. The three lots conformed in terms of closure integrity at the proposed ----month expiration date. Additionally, the three commercial ----- lots -----
-----, and ----- were tested at release and results were acceptable. These lots are currently on stability and will be tested again at expiration. A description of the Container Closure Test Method 9000001067 and Container closure test results for the three commercial ----- lots (indicating which lots are on stability) are provided.

The container closure integrity test consists of several ----- and ----- steps applied to the samples -----, The integrity is confirmed -----
-----, GSK provided results from the three proposed lots as follow

Container closure Integrity Test Results:

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The GSK monograph references ----- which is the ----- monograph entitled: -----

-----." This monograph is considered more stringent than --- because it requires testing in addition to those described in ----- namely, -----
-----, Furthermore, the --- monograph does not specify specifications for the different tests performed, whereas there are specifications described in -----, GSK's position is that the methods described in the -- monograph are appropriate for use for GSK Rotarix Oral Vaccine.

Review comment

GSK response appears to be adequate to address testing of stopper for compliance with ---- test and container closure study. The extractable study reported the analytical test methods used and test result obtained but no conclusion. The ----- test met the requirement of ----- The stopper considered -----.

Review Question

GSK Response (E-mail response Dated 3/10/09):

Stated below is further clarification of the cleaning and ----- rationale and validation of the lyophilizers as described in the Rotarix BLA and documents reviewed at the PAI in December are as follows:

- The maintenance of the ----- of the ----- freeze dryers is ensured during at ----- days after -----, based on the following rationale:

- The validation approach for the lyophilizers and the rationale stated above were previously submitted and discussed during the Type C meetings held on April 27, 2005 and December 19, 2006, and are also described in the Rotarix BLA document (Module 3.2.A.1 in section 10.3.3.1.4 of the narrative) submitted in June 1st, 2007.

GSK response appears to be adequate. GSK response clarified that lyophilizers' each -----
- followed by the ----- cycle.

GlaxoSmithKline Biologicals (hereafter GSK) has submitted a Biologics License Application (BLA) for Human Rotavirus Vaccine Live Oral. The proposed proprietary name is Rotarix®. The candidate vaccine has been investigated under BB-IND ----, initially submitted to CBER on July 31, 2000 and in several non-IND studies conducted outside of the United States. The non-IND studies are being submitted pursuant to 21CFR §312.120 as pivotal for claims of safety and efficacy. GSK's candidate Human Rotavirus Vaccine, *Rotarix*, is an oral vaccine available as a vial of lyophilized vaccine to be reconstituted with liquid diluent provided in a prefilled oral applicator. Each 1-mL dose contains at least 10^{6.0} median Cell Culture Infective Dose (CCID₅₀) of live, attenuated human rotavirus (HRV) strain after reconstitution. *Rotarix* vaccine is intended for the prevention of rotavirus gastroenteritis

caused by G1 and non-G1 types (including G2, G3, G4, and G9) when administered as a 2-dose series to infants 6 to 24 weeks of age.

The bulk vaccine is manufactured at the ----- facility in buildings ----- . The --- buildings use ----- processes and equipment. ----- manufactured in building --- is intended for the US market. Filling is performed in building ---. Diluent is manufactured and filled at the Rixensart site in building --.

This review covers bulk operations performed in ---- at the ----- site.

Review

Manufacturing process of the Rotavirus vaccine bulk

The following flow diagram illustrates the manufacturing process.

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