

# Review of Responses Submitted by GlaxoSmithKline Biologicals to Issues on the Form FDA 483 - Rotarix

## Review Memorandum

**Date:** March 25, 2008

**To:** STN: BLA 125265\0

**From:** Jonathan McInnis, HFM-676;

Pete Amin, HFM-676;

**Subject:** Review of responses submitted by GlaxoSmithKline Biologicals to issues on the form FDA 483 issued at the conclusion of the December 2007 pre-approval inspection

**Manufacturer:** GlaxoSmithKline Biologicals

**Background:** Apre-approval inspection (PAI) of GlaxoSmithKline's (GSK) manufacturing facility at -----, Belgium was conducted from December 3-13, 2007 to support the Prior-approval supplement (PAS) STN BL 125265/0 for manufacture of rotavirus vaccine Rotarix. A form FDA 483 containing 3 items was issued at the conclusion of the inspection and the firm submitted responses in electronic format on January 15, 2008. These responses have been reviewed and review comments are provided below:

For ease of review, each 483 item is reproduced in bold print followed by CBER review comments on the response to the item. The inspection team consists of Jonathan McInnis and Pete Amin.

### Observation 1.

**Regarding ----- of stoppers used in the filling of the drug product, there is no documented valid statistical rationale for the sample size taken for ----- and other testing during validation. The batch size for stopper ----- is ----- stoppers. During validation, GSK tested -- stoppers per run for ----- stoppers for ----- and -- stoppers for ----- study. (Reference Protocol 20060546, Validation of the ----- of the -- container and of the ----- and ----- of the ----- stoppers using the ---- processor)**

The firm's response to revise the validation SOP #9000002685 *appears to be adequate*. GSK will document the rational for their sampling plan selected during validation. GSK considered the ----- process as a homogeneous and uniform ----- process. GSK stopper ----- is carried out through a -- minutes ----- of the stoppers via ----- in --- which subjects ----- stoppers to a robust ----- process. Stopper ----- process is performed using ----- injection after ----- steps to remove ----- the ----- phase. The ----- homogeneous condition was demonstrated via -----, GSK stated that stoppers are processed on a ----- basis which limits the applicability of a statistical approach to ----- subjected to the same process. GSK cited ----- which uses --- samples from ----- for either ----- or ----- testing as the load is uniform. GSK also cited --- FDA guidance for selecting -- samples for ----- test. This ----- section establishes that a sample size of -- units is relevant for sampling in a uniform lot.

### Observation 2.

**All information related to production is not included in the batch record. As examples:**

- Information regarding sample collection is not included in the batch record. A ----- sample is collected from the ----- following ----- and ----- . Upon review of the batch records for manufactured lots, there is no documentation of ----- sample collection.
- A cell count is performed ----- of Vero cells cultured for virus propagation. Information and calculations related to the cell count are not included in the batch record. The cell count information is reported to be for ----- and is ----- to determine if the cells for use in viral propagation are adequate in number (---- confluent). The cell count information is ----- if needed.

The firm's response to revise the batch record ***appears to be adequate***. GSK has revised the batch record as of December 12, 2007 to include the sampling instruction for collecting the ----- sample after ----- . Regarding cell count data, cell counts were performed for the ----- manufacturing campaign in ----- Vero cell ----- to assess ----- . Evaluation of ----- is ongoing and on its completion and approval of a addendum documenting ----- will ----- and perform a cell count ----- .

### Observation 3.

The ----- validation was not completed during -----  
----- . This ----- was reported in section 8.1.6 in the facilities section of the BLA for  
Rotarix. --- generates ----- based on approved ----- . These -----  
provide adequate ----- and ----- and ensure that the correct sequence of ----  
----- are given to operators. Operations are then ----- by operators. The  
capture of data is carried out ----- in the -----.

GSK has completed ----- qualification and firm's response ***appears to be adequate.*** -----

[illegible]