



DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Center for Biologics Evaluation and Research
Office of Compliance and Biologics Quality
Division of Manufacturing and Product Quality

To: 125363/0
From: Sean Byrd, Dir. Reg. Rev. Ofc., CBER/OCBQ/DMPQ/BI, HFM-675
Through: Carolyn Renshaw, Chief, CBER/OCBQ/DMPQ/BI, HFM-675
Applicant: GlaxoSmithKline Biologicals, License #1617
Product: Meningococcal Groups C and Y and Haemophilus b Tetanus Toxoid Conjugate Vaccine [MenHibrix®]
Subject: Review Memo – Response to CR Letter for Meningococcal Groups C and Y and Haemophilus b Tetanus Toxoid Conjugate Vaccine.

BACKGROUND

GlaxoSmithKline Biologicals d/b/a GlaxoSmithKline (GSK), submitted their original Biologics License Application for MenHibrix® on 12 August 2009. The firm was issued a Complete Response letter on 11 June 2010 with four items under DMPQ purview.

The submission is in eCTD format.

Recommendations:

Response to item 86 is insufficient. It was a topic of an internal meeting in this Division which resulted in an Information Request sent to GSK on 23 June 2011. Please reference this T-con as found in the EDR for specific issues raised. The topic was then discussed in a T-con with GSK, DVRPA and DMPQ staff on 30 June 2011. Please reference this T-con in the EDR.

The other three items (85, 87, and 88) appear acceptable.

REVIEW

Facilities Items:

85. We acknowledge that you have submitted the method validation study for container/closure integrity testing for vials and syringes used for MenHibrix and its diluent ----(b)(4)----. Please provide the results of container/closure integrity testing for the lyophilized product and diluent manufactured at your Belgium facility. Please note that for the proposed -----(b)(4)-----

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[(b)(4)]

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[(b)(4)]

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The response is acceptable.

86. Regarding visual inspection of your diluent ---(b)(4)---- (filled at GSK), we acknowledge that you have provided validation for ----(b)(4)---- orientation, fill volume, and particulates. We also acknowledge that you have provided summary data for the (b)(4) most recent aseptic simulation runs for the ---(b)(4)----- with reject data. Please provide the validation of the 100% visual inspection with regards to container and closure defects. You should provide definitions of Critical, Major, and Minor defects with a rationale for how each type of defect was defined and the AQL/acceptance criteria for each type of defect. The validation should also cover inspector qualification and training. Finally, please provide the results of the 100% visual inspection for the diluent for the (b)(4) commercial lots of MenHibrix.

GSK Bio has made the commitment towards the FDA to perform a 100% manual inspection of US lots:

“Major and critical defects will be fully assessed for all of GSK Bio’s US licensed in both vials and –b(4)----- presentation.”

“The current 100% automated inspection program will be completed with an additional step of --b(4)----- to identify and remove defective containers prior to AQL inspection and release.”

- Visual inspection is performed according to the procedure '*Gestion et documentation de l'inspection visuelle manuelle*'.
- Personnel conducting the –b(4)----- must be trained against the procedures '*Gestion et documentation de l'inspection visuelle manuelle*' and '*Définition et classement des défauts seringues, flacons et tubes*'.
- Personnel conducting the –b(4)----- must be certified according to the procedure '*Certification d'un opérateur chargé de réaliser une activité d'inspection visuelle sur machine semi-automatique et/ou manuelle*'.

Validation of the –b(4)----- includes certification of the operators. Details of the applicable procedures are given in the following parts:

- **Part 1** - English summary of the French procedure '*Gestion et documentation de l'inspection visuelle manuelle*' (Description of the –b(4)----- inspection process)
- **Part 2** - English summary of the French procedure '*Définition et classement des défauts seringues, flacons et tubes*' (Type of defects to detected during the ---b(4)----- inspection)
- **Part 3** - English summary of the French procedure '*Certification d'un opérateur chargé de réaliser une activité d'inspection visuelle sur machine semiautomatique et/ou manuelle*' (Certification of the operators performing visual inspections).

GSK Bio proposes to submit the results of the –b(4)----- of the –(b)(4)-- filled with diluents for the –(b)(4)---- commercial *Menhibrix* lots as a post marketing commitment. The results will be submitted to FDA as they are performed on each of the (b)(4) diluents lots. As per today, a –b(4)----- of –(b)(4)-- filled with diluent as described hereafter has not been performed.

Procedure for --b(4)-----

Purpose:

This procedure outlines the actual –b(4)----- process and the documents generated to document this process.

Scope:

The procedure applies to a –b(4)----- of commercial and non-commercial vaccines and diluents, filled in –(b)(4)---- in vials. The procedure is applicable on the Belgian sites of GSK Bio.

Procedure:

When to conduct a visual inspection?

- In the context of an additional check of the diluents / vaccine manufacturing process.

- Following a non conformity found during the manufacturing
- In the context of an investigation linked to a complaint or deviation.

How to initiate a request for a ---b(4)-----

The --b(4)----- is conducted -----(b)(4)----- . The procedure defines responsibilities and references procedures to be followed during or after production.

What are the conditions of a ---b(4)-----

 -----(b)(4)-----
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Personnel conducting the inspection must be trained and certified against specific approved procedures.

The inspection method is as follows:

Equipment Used	-----b(4)-----
Type of defects to be deleted	See table below
Number of units simultaneously inspected	--(b)(4)-- --(b)(4)---
Inspection pace	-----b(4)----- ----- -----b(4)-----: <ul style="list-style-type: none"> • -----b(4)----- -----; • -----b(4)----- -----.
Method of ----b(4)-----	-----b(4)----- -----

-----(b)(4)-----	
Criticality	Defect
Critical ----(b)(4)---	<ul style="list-style-type: none"> • -----(b)(4)----- -----; • -----; • -----; • -----(b)(4)----- -----; • -----(b)(4)----- -----.
Major ----(b)(4)---	<ul style="list-style-type: none"> • -----; • ----- • -----(b)(4)----- -----
Minor --(b)(4)---	<ul style="list-style-type: none"> • -----; • -----; • -----(b)(4)----- -----; • -----(b)(4)----- --; • -----; • -----; • -----(b)(4)-----; • -----; • ----- • -----(b)(4)----- -----.

Procedure for the type of defects to be detected during ---b(4)-----

This procedure provides information on the type and criticality for each type of defect that is likely to occur in -b(4)----- and vials filled with vaccines or diluents in filling buildings of Rixensart and (b)(4). The procedure applies to commercial and non-commercial lots filled in b(4)---, vials and -b(4)-----. The procedure is applicable in the departments “QA”, “Filling”, “Packaging” and “QC Physico chimie”.

This procedure provides the following information for each type of defect that is likely to occur in -b(4)----- and vials filled with vaccines or diluents:

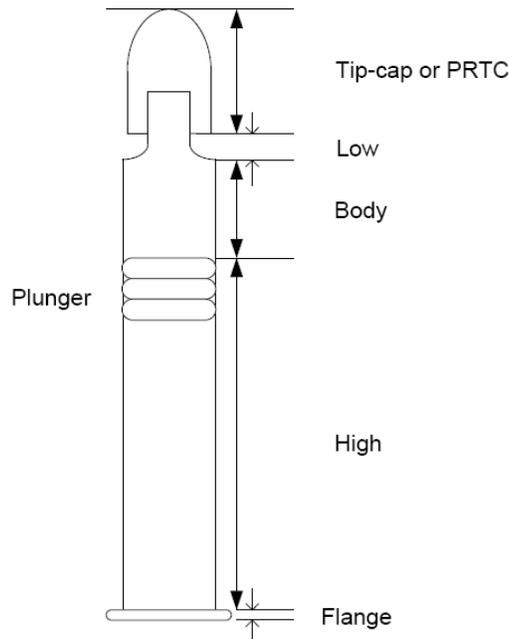
- The name of the defect;
- The criticality;
- The definition of the defect;
- Pictures representing the defect;
- Possible causes.

The typical defects are categorized into three criticality levels in function of the impact on the patient, of the use of the product and of the risk of patient complaints.

- **Critical** defects are defects that have a direct impact on the product identity, purity and quality and that may have a risk for patient safety.

- **Major** defects do not include a patient risk but may have a significant impact on the product use.
- **Minor** defects have no impact on patient safety neither on use of the product. They risk negatively impacting the GSK or product's image.

Certain defects are classified according to their position on the syringe. The terminology used is shown in the following graphical representation:



For oral vaccines, the ---(b)(4)--- is only conducted for defects that are related to a loss of integrity.

The duration of an inspection period is ---(b)(4)---.

After each period, there is a break of ---(b)(4)--- in the inspection room, or a break in the rest room.

The maximum duration of the ---(b)(4)--- per shift and per person should not ---(b)(4)--- of the duration of that shift.

The light intensity must be minimum ---(b)(4)--- at the inspection point.

Each unit must be controlled ---(b)(4)--- and general status of the equipment.

The ---(b)(4)--- is also checked at the ---(b)(4)--- using a ---(b)(4)---, to assure that the value exceeds the minimum of ---(b)(4)--- at the inspection point. This check is documented in a production check list or in a logbook.

How to manage the boxes containing the vials / ---(b)(4)--- to be inspected?

1 page redacted to (b)(4)

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

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Comment: There is no description of what the test kit contains.

Certification of the operators performing visual inspections

Purpose:
This procedure provides information on the certification of an operator who performs manual and automated visual inspections.

Scope:

The procedure applies to commercial and non-commercial lots filled in syringes, vials and tubes. The procedure is applicable in the departments “QA GMP”, “QA release”, “QA Systems”.

Procedure:

The procedure outlines the process of (b)(4) types of operator certification. The selection of the appropriate type results from the output of the decision tree documented in a specific procedure. The difference is related to the impact of the product, and the regulatory impact of the activity. Certification of (b)(4) includes an additional step compared to the certification of (b)(4).

The different steps in the certification process can be summarized as follows:

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- -----(b)(4)-----
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The operator is authorized to conduct ----(b)(4)----- “Kit to be inspected / inspection method to be used”.

Acceptance criteria for the initial test are the following:

1 page redacted due to (b)(4)

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

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

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

The response is acceptable.

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

GSK states there is no ----(b)(4)----- of the Bulk.

As for all other (b)(4) used covering Hib-TT, (b)(4), Bulk MenC-TT, Bulk MenY-TT, sucrose, and Tris solution, GSK provides validation summaries covering chemical compatibility, extractables studies, and bacterial challenge studies.

A review of the validation studies provided appear to indicate each (b)(4) at the steps which they are used have been appropriately qualified.

The response is acceptable.