



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 –b(4)---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)-- tip-cap orientation, fill volume, and particulates. We also acknowledge that you have provided summary data for the –b(4)-- most recent –b(4)-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 b(4)/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 –b(4)----- 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)----- inspection 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)----- inspection 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 manual visual inspection 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 manual visual 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 manual visual 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)----- 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)----- with diluent as described hereafter has not been performed.

Procedure for Manual Visual Inspection of –b(4)----

Purpose:

This procedure outlines the actual manual visual inspection 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, ---b(4)----- or 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 manual visual inspection?

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

What are the conditions of a manual visual inspection?

The manual visual inspection area must be ---b(4)-----

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)----- ----- The operator inspects maximum: <ul style="list-style-type: none">• ---b(4)----- -----• ---b(4)----- -----
Method of ---b(4)-----	-----b(4)----- -----

Injectable –b(4)-----	
Criticality	Defect
Critical <u>AQL---b(4)-----</u>	<ul style="list-style-type: none"> • -----b(4)----- ----- • --b(4)----- • --b(4)----- • --b(4)----- ----- • -----b(4)----- -----
Major AQL--b(4)-----	<ul style="list-style-type: none"> • --b(4)----- • --b(4)----- • -----b(4)----- -----
Minor AQL-b(4)-----	<ul style="list-style-type: none"> • ---b(4)----- • ---b(4)----- • ---b(4)----- ----- • -----b(4)----- • --b(4)----- • ---b(4)----- • -----b(4)----- • --b(4)----- • -----b(4)----- ----- • -----b(4)----- -----

Procedure for the type of defects to be detected during manual visual inspection

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:

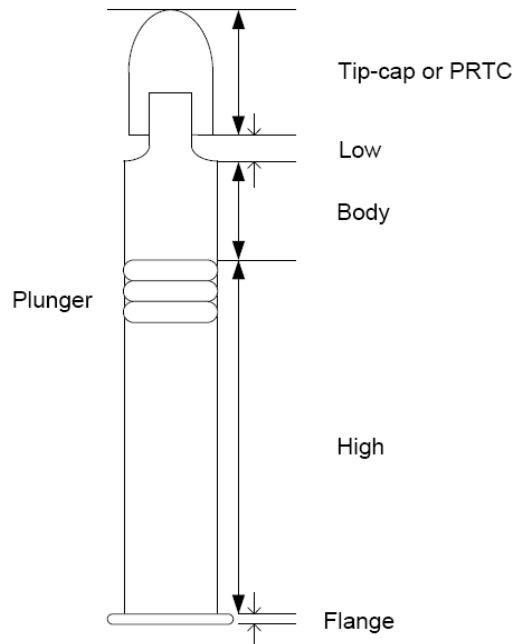
- The name of the defect;
- The criticality;
- The definition of the defect;
- Pictures representing the defect;
- Possible causes.

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 –b(4)---. 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)----- for luminosity and general status of the equipment.

The luminosity is also checked at the –b(4)----- day 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 determined to be not releasable: b(4)

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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 –b(4)--, vials and –b(4)--
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:

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

Details on the tests as part of the certification program are defined hereafter.

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

Acceptance criteria for the initial test are the following:

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

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COMMENT: On 23 June 2011 an Information Request covering eight topics was sent to GSK to discuss the visual inspection of the diluent --b(4)----. This IR was followed up with a teleconference with GSK representatives on 30 June 2011. During that telecon GSK agreed to respond to the IR with additional information. The response was received on 29 July 2011. A review of the responses follows below.

Review of the 29 July 2011 Response to the 23 June 2011 IR

1. *We do not agree with your proposal to submit the data on manually inspected lots of diluent as a Post Marketing Commitment. Please describe the procedure that will be used to perform the --b(4)----- of the diluent and show in detail how your*

---b(4)----- is related to the process. Also, please submit data for the first lot using the ---b(4)----- of filled lots of diluent as an amendment to the file.

GSK has agreed to perform a ----- b(4) ----- by the end of August 2011 and proposes to submit the data by the end of September. The response is acceptable.

2. *It is noted you use the AQL to either accept or reject a lot. The AQL is the “Manufacturer’s Risk” of rejecting a good lot; i.e. it is a business risk. Please define and submit your Reject Quality Level as the Lot Tolerance Percent Defect (LTPD) as it is the “consumer’s risk” of accepting a lot that is defective. Also, please submit the Operating Characteristic (OC) Curve; i.e. the plot of the percent defectives versus the corresponding probabilities of acceptance. In addition, please provide a justification for the current LTPD levels associated with critical and major defects.*

GSK generated the LTPD and the corresponding OC curves for the Critical and Major defects. The values are shown in the table below.

[
	b(4)
]	

GSK states this LTPD comparison shows that, whatever batch size considered, GSK Bio LTPD values are systematically more conservative compared to the rest of the industry average. The response is acceptable.

3. *Please provide your rationale for the AQL of Critical Defects as ---b(4)--- when it should be “accept on ---b(4)-----”*

The answer to this question was provided in response to question 2.

4. *We find the following statement confusing: “The current ---b(4)----- inspection program will be completed with an ---b(4)----- to identify and remove defective containers prior to AQL inspection and release.” Please clarify if defects rejected by the ---b(4)--- remain part of the follow-up ---b(4)-----*

GSK stated this will be answered at a later date.

5. *Please note that the b(4) is not considered a qualified piece of equipment and no decisions on lot disposition should be made based on information collected by the b(4). Once qualified, the data must be submitted as a CBE with data from product inspections and an indication that it will be used on diluent. However, if the b(4) is used only for the diluent and not reconstituted product, you may report your qualification as an annual report. Please comment.*

GSK stated this would be answered at a later date.

6. *Please provide your rationale for why liquid within the plunger stopper is considered a minor defect. Such fluid may be indicative of a container-closure integrity breach. Furthermore, if the diluent is ---b(4)-----, this liquid could be an indication of a problem in the sterilization parameters/conditions. Please note that during shipment these plunger stoppers do move, and may contaminate the sterile region of the barrel. Please comment.*

GSK states if the stopper lips are damaged, then liquid may be present between the flanges. Operators are trained and qualified to recognize critical stopper damage, and in this case, the defect is not classified as “liquid within the plunger stopper” but as “Defect of the plunger (integrity loss)” which is classified as critical defect.

In other words, the defect called “liquid within the plunger stopper” refers to the presence of liquid within the plunger stopper without any damage at the stopper lips.

This type of defect occurs during filling operations when a liquid droplet from the filling --b(4)- is left on the --b(4)--- internal side wall. Since the stopper is not damaged and is designed to maintain sterility during shipment, sterility is not compromised even if a liquid drop is present between the stopper flanges. Closure integrity of units with liquid in stopper has been demonstrated through passing media fills containing defective units (--b(4)--- within the stopper lips) and by additional ---b(4)----- . GSK provides data to this effect.

Regarding terminal sterilization risk, the cycle development and validation ensures the cycle is appropriate and avoids such an occurrence. Any process excursion would be captured during sterilization operation (alarm) or during review of conformity of sterilization parameters.

Overall, the response to this question is acceptable.

Please provide your rationale for why --b(4)----- particles visible to the naked eye are considered a minor defect. --- ---b(4)--- -----

1 page determined to be not releasable: b(4)

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

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---b(4)---

The response is acceptable.

---b(4)---

GSK states there is no sterile filtration of the Bulk.

As for all other filters 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.