DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
1401 Rockville Pike
Rockville, MD 20852-1448

Date: March 11, 2009

To: The File

From: Division of Vaccines and Related Products Applications
Office of Vaccines Research and Review
Point of Contact: LT Elizabeth J. Valenti, REHS
Regulatory Program Manager

Subject: Monthly Meeting, STN: 125300

Attendees

Al-Humadi	*Nabil*
Bash	*Margaret*
Blake	*Milan*
Burns	*Drusilla*
Campbell	*Karen*
deVore	*Nikki*
George	*Joe*
Gruber	*Marion*
Krasnicka	*Barbara*
Lee	*Martha*
Lee	*Robert*
Meysick	*Karen*
Roecklein	*Tina*
Trudell	*Nicole*
Sutkowski	*Elizabeth*
Sun	*Wellington*
Valenti	*Elizabeth*
Vann	*Willie*

eCTD

There have been reports of problems the eCTD files for this BLA. If anyone is having problems with the eCTD or accessing the BLA files please send an email to LTJG David Schwab and cc LT Valenti and Dr. Fiore.

Inspectional Issues and Moving Forward

There are ongoing submission quality, product quality, and process validation problems with the BLA data. Dr. Vann asked all reviewers to provide letter-ready comments regarding these and other problems. The inspection, which occurred February 18-27, 2009, also identified issues. April 1, 2009 is 90-days prior to the action due date. Amendments received after this date may be considered major amendments and extend the review clock by 90-days.

Major CMC/Inspectional Issue

Lot #-b(4)- failed --b(4)--- acceptance for MenW polysaccharide due to Novartis no longer assessing --b(4)-------- prior to completing the ---b(4)----------. This issue was recognized with all four strains. Novartis proposed revalidating the assay and process with a change from ---b(4)----------. Novartis proposed completing revalidation of the --b(4)---------- for MenW strain by March 31, 2009, and ----b(4)----------. See attached slides received from Novartis during inspection entitled, "MenW --b(4)----------: Proposed way forward," dated February 27, 2009.

Novartis's downstream steps were remarkably consistent, however MenW is not the -b(4)----- strain and the other three strains may be --b(4)----. Novartis failed to follow good cGMP and therefore has an invalidated process. They relied on subsequent testing results to determine consistency.

The review team concluded that Novartis does not have process, data, and monitoring properly controlled; the process must be revalidated for all four strain prior to approval. Process validation could not take place after approval or as a postmarketing commitment. A problem is that Novartis does not have any material from the other three strains available; therefore, they'll need to run additional campaigns to perform process re-validation.

Also, it was determined that one of the failed lots of monovalent material was used in one of the clinical trials. The review team will review whether the lot failure could cause or be associated with any inconsistencies in the clinical results. Dr. Vann has a trace back tree to determine if Lot #b(4), which was affected by this invalidated process, was used in clinical trials.

Dr. Gruber will discuss the review team's consensus with Dr. Baylor for concurrence. This will be a reason for a CR letter, but there will likely be other issues as well. Reviewers need to have reviews reasonably completed so all possible comments and requests can be included in the CR letter. Dr. Vann recommended reviewers send potential items for a CR letter to Cara and Betsy and copy him. LT Valenti also mentioned that the clinical review may need to go on the web if the BLA is issued a Complete Response.

LT Valenti will set up a telecon with Novartis to relay the need to validate the process for all four strains prior to approval.

Review of HPV Data in the BLA

A final clinical study report for concomitant administration of Menveo with Gardasil was submitted in Amendment 6 to the BLA (received February 24, 2009). The clinical statistician and clinical reviewer believe that it was agreed upon with Novartis that this data would not be included in the BLA. LT Valenti agreed to research the issue and communications and

determine whether the HPV data should be reviewed under the BLA or a future supplement, pending approval.

Action Items

1. Dr. Vann to determine if Lot #b(4) was used in clinical trials. *Completed March 13, 2009.*
2. LT Valenti to set up a telecon for the team to notify Novartis of the need to validate the process for all four strains prior to approval. *Completed March 19, 2009.*
3. LT Valenti to research communications with Novartis regarding submission of safety data from concomitant administration with Gardasil. *Documentation of pre-BLA meeting communications with Novartis was emailed to the review team on March 13, 2009 (see Attachment 1). It appears that with respect to the study results from protocol V59P18, the submissions received to date do not correspond with what was agreed upon in the preBLA meeting. If Amendment 2 is supposed to be the 6 month safety data it does not contain all of the data and it was not received within 3 months of the initial BLA submission. Also the final clinical study report in Amendment 6 was not agreed upon prior to the BLA.*
4. The review timeline and the due date for all review and review issues needs to be communicated to the review team.

Excerpt from April 16, 2008, pre-BLA meeting minutes:

9. Novartis realizes that the Agency can only determine adequacy of a dataset after it has undergone full review. However, Novartis seeks concurrence with the Agency that the proposed clinical datasets from the pivotal studies will be adequate to support a complete review of the BLA:

   a. Full clinical data from protocol V59P13.

   b. Full safety data, without immunogenicity results from protocol V59P17.

   c. Full immunogenicity data (MenACWY and Boostrix® - alone, concomitant and sequential) and partial safety data (at least one-month post-vaccination with MenACWY, Boostrix, and the first dose of GARDASIL®) from protocol V59P18.

CBER Response:

a) CBER concurs with presenting all safety and immunogenicity data from protocol V59P13.

b) CBER concurs with presenting all safety data for persons 11-55 years old and SAE listings for persons 56-65 years old for protocol V59P17 without immunogenicity results. Other safety data for adults 56-65 years old and immunogenicity data can be submitted in a supplemental application if you intend to apply for an extended age indication in older adults.

c) CBER concurs with presenting immunogenicity data pertaining to MenACWY and Boostrix® concomitant vaccine evaluation and partial safety data (at least one-month post-vaccination with MenACWY, Boostrix, and the first dose of GARDASIL®) from protocol V59P18. We acknowledge, as stated on page 32 of the briefing document, your intent to provide 6 month safety follow-up data from this study during the BLA review. Please be advised that this safety update should be submitted as soon as possible but no later than 3 months from the initial BLA submission.

MenW [redacted] b(4)
Proposed way forward

February 27, 2009

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Topics to be addressed

- The established manufacturing process contains numerous steps that effectively [redacted] or eliminate N. meningitidis and the overall process has been shown to be valid and robust.
- Original process validation required [redacted] at the end of the formaldehyde treatment step. The MenW process does not consistently meet this criterion
- We will introduce additional controls for continued verification of process performance and will re-validate the [redacted] process with the new controls in place
- The definition of the [redacted] steps will be clarified in the BLA and validation data will be submitted as they become available

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Summary of current status

- Investigations revealed that the established formaldehyde treatment step [redacted] The initial process validation acceptance criteria for this step were set incorrectly. Also as a consequence of this mistake, respective statements in the BLA were incorrect.
- Detailed technical review confirms that the existing manufacturing process contains a number of steps that contribute to the effective inactivation or removal of microorganisms. No process changes are warranted.
- Test for [redacted] has been validated and was included in the process validation of N. meningitidis. All batches conformed at that step.
- The current product specification includes a test for [redacted] after [redacted]. Method validation at this step showed difficulties due to the highly bactericidal characteristics of the sample matrix.
- Further work is ongoing regarding the validation of the [redacted] test after the [redacted] step and the [redacted] test after formaldehyde treatment.

Assay validation

[redacted] *and* [redacted] *assays*

- Previously the tests performed on samples taken after the formaldehyde and [redacted] treatment steps were validated using [redacted] This is not relevant to the samples taken after [redacted]
- Attempts are currently being made to re-validate the established assays using the appropriate process matrices
- Re-validation of the [redacted] is challenging due to the highly bactericidal characteristics of this sample matrix. If necessary, attempts will be made to overcome this issue by modifying the method, i.e. [redacted]
- [redacted]

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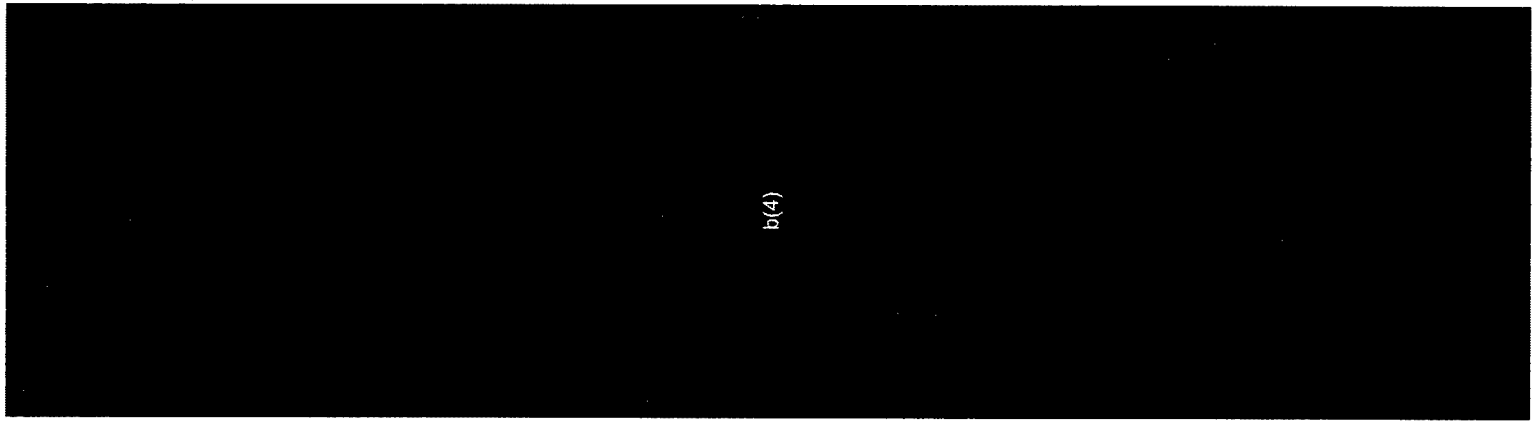
The way forward

Manufacturing process and controls

- The existing manufacturing process is valid and will remain unchanged
- Specification for [redacted] will be maintained. Validity of this method will be assessed in accordance with USP
- In accordance with recommendations in the draft FDA Guidance on Process Validation, continued monitoring and/or sampling will occur for the [redacted] steps) until sufficient data is available



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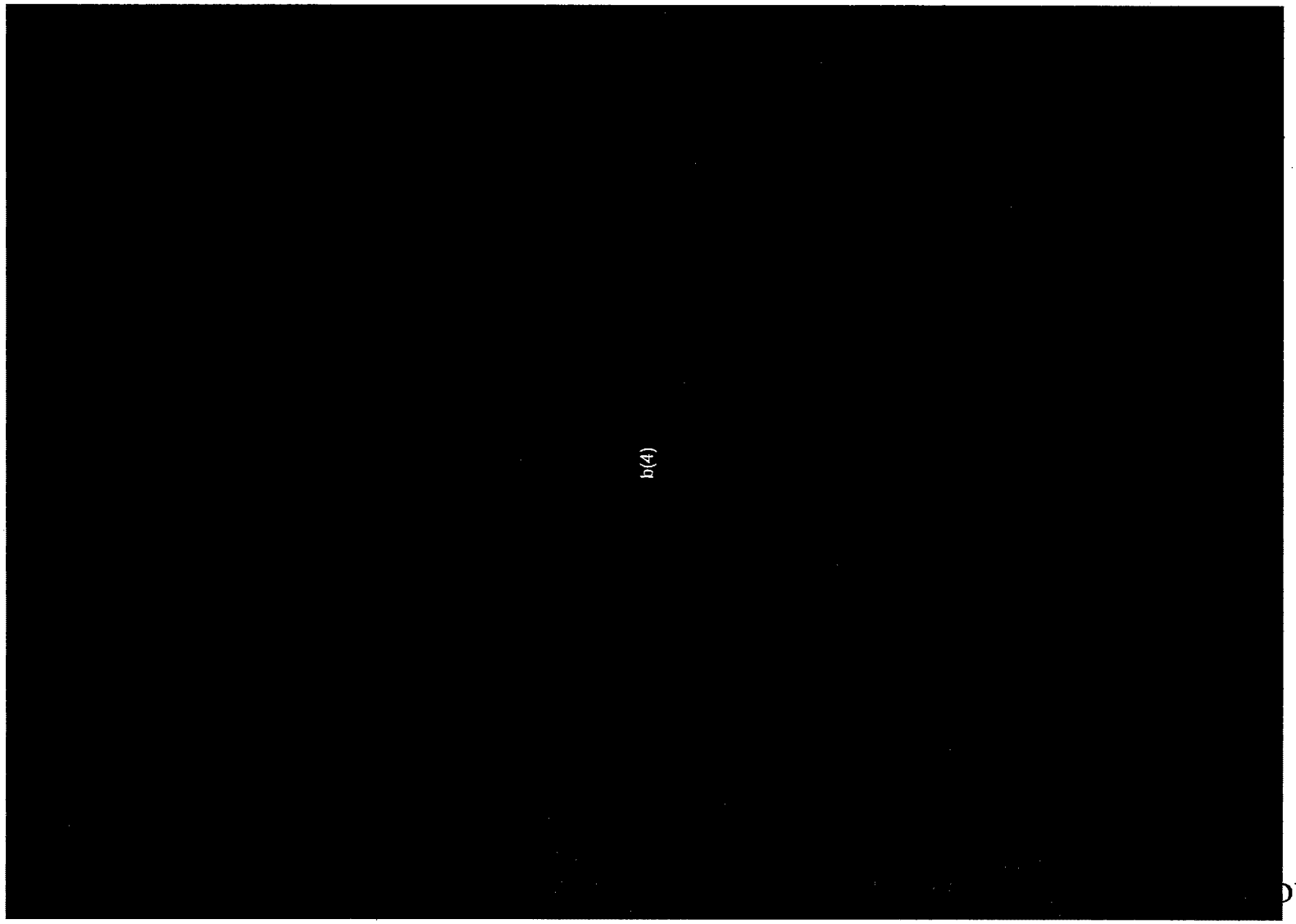
The way forward, cont.

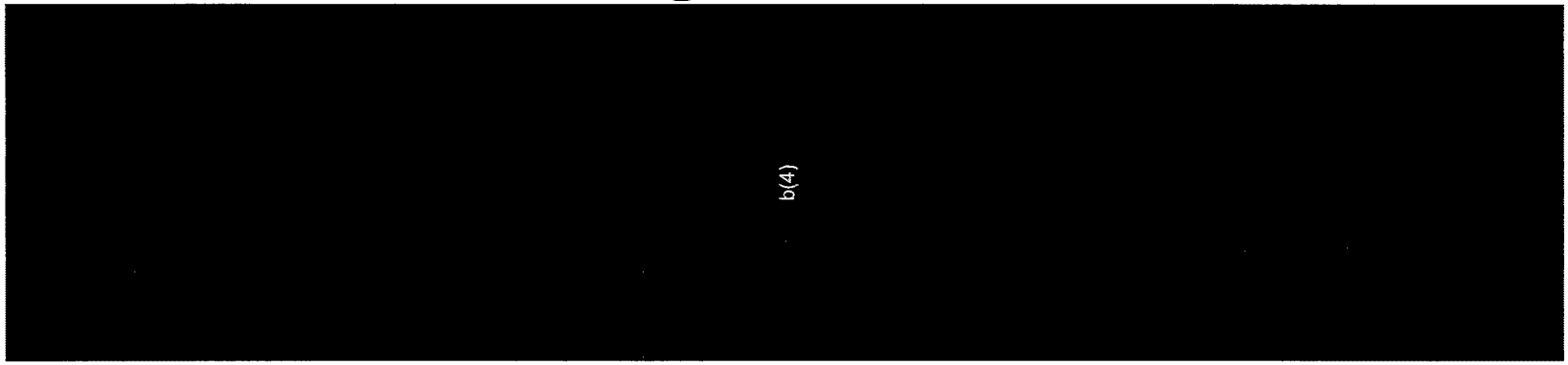
Process [redacted]



The way forward, cont.

Regulatory submissions

- During the ongoing BLA review, the following documents will be submitted as amendments before end of March 2009



- Post-marketing approval commitment to submit as CBE-30s

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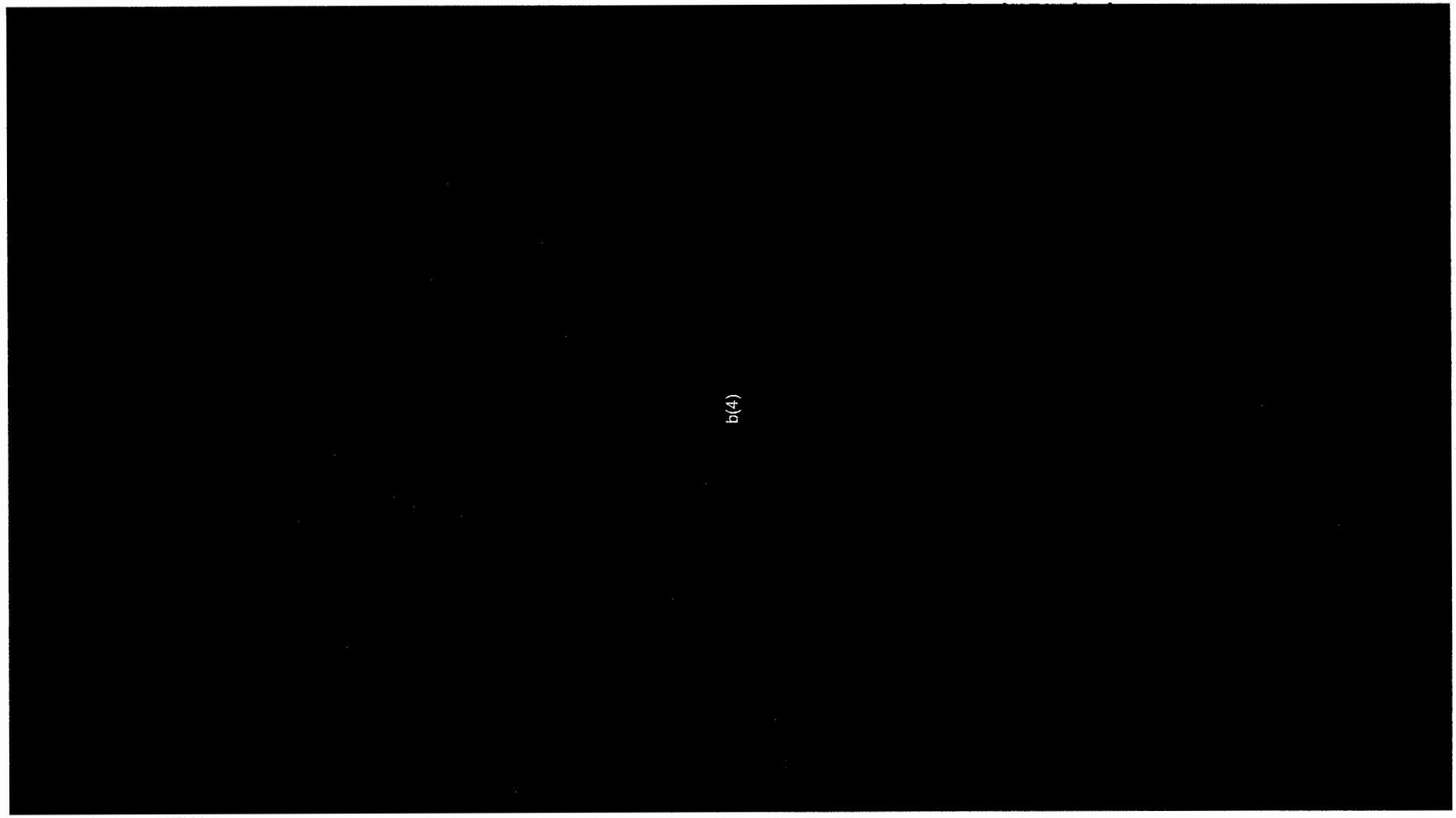
Clarifications in the BLA

Description of [redacted] *step in section 3.2.S.2.2 of BLA*



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Back-up

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Documents affected in the BLA

Module 3

- Section 3.2.S.2.2 (polysaccharides)
  - Update of process description and controls. No change in process - only re-introduction of b(4) b(4) controls performed during original process validation at: b(4) b(4)
- Section 3.2.S.2.4 (polysaccharides)
  - Update of control of critical steps and intermediates (re-introduction of b(4) control at steps mentioned above)
- Section 3.2.S.2.5 (polysaccharides)
  - Update process validation summaries of the b(4) steps (no process change, but controls of b(4) with modified acceptance criteria) in section 3.2.S.2.5.2 Qualification/Evaluation of Post Process-Validation Changes, including relevant process validation protocols, reports and technical reports
- Section 3.2.A.2
  - Update of Adventitious Agents safety evaluation to reflect new description of b(4) step

Module 2

- Sections 2. 3.S.2 (polysaccharides) and 2.3.A.2, to reflect Module 3 modifications