DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

MEMORANDUM

Date: 19 March, 2015

From: Karen Campbell
Division of Biological Standards and Quality Control (DBSQC)
Office of Compliance and Biologics Quality (OCBQ)
Center for Biologics Evaluation and Research (CBER)
Food and Drug Administration (FDA)

To: **Biologics License Application Submission Tracking Number # 125525/0**

Subject: **Review of Lot Release Protocol Templates for Drug Substance and Drug Product of Biologics License Application for Diphtheria and Tetanus Toxoids and Acellular Pertussis Adsorbed and Inactivated Poliovirus Vaccine**

Through: William M. McCormick, Ph.D., Director, DBSQC/OCBQ/CBER/FDA

Cc: Juan C. Lacayo, Ph.D., Lead RPM, DVRPA/ OVRR
Matthew Steele, Ph.D., Chair, BLA Review Committee, DBPAP/OVRR

Applicant: Sanofi Pasteur Limited

Product: QUADRACEL – Diphtheria and Tetanus Toxoids and Acellular Pertussis Adsorbed and Inactivated Poliovirus Vaccine

1 General Information

1.1 CMC Review Identifiers and Dates

1.1.1 Biologics License Application (BLA) Submission Tracking Number (STN) #: 125525

1.1.2 Submission received by CBER: March 24, 2014

1.1.3 Review completed: March 18, 2015

1.1.4 Material Reviewed

Original BLA:

The following general module sections of the BLA were reviewed: M3 CMC, Quality

2 Executive Summary: The lot release protocol submitted in amendment 125525/0.8 on March 17, 2015 is acceptable for use. Sanofi has submitted a lot release protocol for Pentacel (STN 125145) for review and once approved it may be used for the release of product under STN 125525.

3 Review

3.1 Documents Reviewed

1. Lot release protocol templates in section 3.2.P.5.4 Batch Analyses
2. Multiple Module Information Amendment (section 1.11.4) regarding the lot release protocol template and the Proposed Lot Release Protocol DTaP-IPV/PRP-T (Pentacel) submitted in amendment 125525/0.3 on September 15, 2014. The Pentacel lot release protocol submitted in this amendment was not reviewed.
3. Multiple Module Information (section 1.11.4) regarding mycoplasma testing submitted in amendment 125525/0.5 on November 27, 2014
4. DTaP-IPV Lot Release Protocol submitted in amendment 125525/0.6 on February 3, 2015
5. Final DTaP-IPV Lot Release Protocol submitted in amendment 125525/0.8 on March 17, 2015

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3.2 Review

Comments on the Poliovirus (IPV) section of the lot release protocol were submitted to Sanofi on August 29, 2014, Sanofi responded in amendment 125525/0.3 on September 15, 2014. These comments and Sanofi's responses are addressed in the memo by Tahir Malik in the DVP Product Review Memo.

In addition to the comments sent on the IPV section CBER sent the following information request on the lot release protocol templates submitted in the original BLA, on September 12, 2014. Responses were received in amendment 125525/0.4 on November 13, 2014. CBER's comments are in bold, Sanofi's responses in italics.

Comment 2 - For all of the Poliovirus lot release templates (titled batch-analyses-2-6) all headers should read

cc: BL 125525/1726-B
Lot No.:
Licensed Name of Product: Diphtheria and Tetanus Toxoids and Acellular Pertussis Adsorbed and Inactivated Poliovirus

Sanofi Response
Headers for all poliovirus lot release templates are updated as suggested by the reviewer. As agreed with CBER during the 19 September 2014 Quadracel Mid-cycle Communication Teleconference, the final version will be submitted to STN: BL 125525 once approved under Pentacel STN: BL 125145.

Comment 3 - On page 2 of the Final Bulk template (titled batch-analyses-1), the cover page of lot release protocol, the Product License Number is not needed in the table, it will be in the header.

Sanofi Response
The cover page of the Final Bulk lot release protocol template has been updated as suggested by the reviewer. As agreed with CBER during the 19 September 2014 Quadracel Mid-cycle Communication Teleconference, the final version will be submitted to STN: BL 125525 once approved under Pentacel STN: BL 125145.

CBER response: This has been addressed adequately in the LRP submitted February 3, 2015

Comment 4 - On page 2 of the Final Bulk template, please remove the reference to the Electronic Filename until CBER has approved the use of electronic protocols for this STN.

Sanofi Response:
The cover page of the Final Bulk lot release protocol template has been updated as suggested by the reviewer. As agreed with CBER during the 19 September 2014 Quadracel Mid-cycle Communication Teleconference, the final version will be submitted to STN: BL 125525 once approved under Pentacel STN: BL 125145.

CBER response: This has not been removed from the lot release protocol template. CBER asked in the information request, as comment 2, dated February 26, 2015 that this be removed. It was adequately addressed in the LRP template submitted March 17, 2015.

Comment 5 - On page 13 of the Final Bulk template, please add (b) (4) test date

Sanofi Response

(b) (4) *On and off test dates for* (b) (4) *media types employed for sterility testing are included in the Final Bulk template, which correspond to the* (b) (4) *test dates. As agreed with CBER during the 19 September 2014 Quadracel Midcycle Communication Teleconference, the final version will be submitted to STN: BL 125525 once approved under Pentacel STN: BL 125145.*

CBER response: This was not adequately addressed. A further comment was sent on February 26, 2015. This has been adequately addressed with the addition of the Qualification/Requalification date to the sterility template on page 10 of 95 in the lot release protocol template submitted on March 17, 2015.

Comment 6 - On page 17 of the Final Bulk template, in the (b) (4) template, and other (b) (4) test results, on pages 11, 25, 31, 37, 43, 48 and 51 the units should be (b) (4) not (b) (4) since the CBER (b) (4) standard [measured in (b) (4) is no longer available.

Sanofi Response

The current reference standard for (b) (4) test ((b) (4) is a (b) (4) standard and can be expressed in both (b) (4)). The results will be updated in (b) (4) with the approved template. As agreed with CBER during the 19 September 2014 Quadracel Mid-cycle Communication Teleconference, the final version will be submitted to STN: BL 125525 once approved under Pentacel STN: BL 125145.

CBER comment, although both are correct Sanofi had agreed to change to (b) (4) however it was still (b) (4) in the LRP submitted on Feb 3, 2015. Sanofi may use either (b) (4) therefore this has been adequately addressed.

Comment 7 - On page 17, in the (b) (4) template, please add the specification.

Sanofi Response

The (b) (4) template has been updated to include the acceptance criteria and the method. As agreed with CBER during the 19 September 2014 Quadracel Mid-cycle Communication Teleconference, the final version will be submitted to STN: BL 125525 once approved under Pentacel STN: BL 125145.

CBER response: This is acceptable.

CBER sent the following comment on 04 November 2014

I just left you a voice mail regarding the mycoplasma testing used for the Quadracel lots. We are aware that a new method has been proposed, and possibly even used for the Quadracel lots to be released. We have a significant issue if the new, unapproved, mycoplasma testing has been used for the Quadracel lots. If the new unapproved method was used for Quadracel, we need you to quickly submit a CBE 30 supplement to the Pentacel file for approval. Be advised, if changes are deemed anything less than minor, we may change the supplement to a PAS. If it is submitted quickly, and approved, there may be not issued with the Quadracel lots or file. However, if there is an issue with the new mycoplasma testing, and it was used for the Quadracel lots, we will most definitely have an issue. If you can revert to the approved mycoplasma testing, any issues may be avoided.

Sanofi Response (submitted in the Multiple Module Information Amendment, Amendment 125525/0.5 on November 27, 2014)

The change in Mycoplasma Test analytical procedure was assessed by Sanofi Pasteur Limited as requiring an Annual Report and the change was implemented on 26 March 2014 to be filed with the 2015 Annual Report submission for Pentacel. To date, IPV (b) (4) *lots have been tested using the modified method, but these IPV* (b) (4) *lots have not yet been incorporated into any IPV* (b) (4) *lots; therefore the modified Mycoplasma test has not been used for any Quadracel or Pentacel lots.*

In order to avoid any misunderstanding, Sanofi Pasteur Limited would like to take this opportunity to explain the basis for our assessment of the reporting level for the modification of the Mycoplasma Test. According to CBER 1997 guidance "Changes to an Approved Application: Biological Products", section IV (6), modifications in analytical procedures may be reported in annual reports if there is no change in the basic test methodology or existing release specifications provided the change is supported by validation data. The acceptance criteria for the test are not affected by the change. The principal modifications are listed below

- (b) (4)

These changes are minor changes in analytical procedure and there are no changes in the principle or design of the test, so there has been no change in the basic test methodology. For comparison, the previous analytical procedure is illustrated in Figure 1 and the modified analytical procedure is illustrated in Figure 2.

According to Sanofi Pasteur Limited's US Pentacel license, the Mycoplasma Culture Method is per the current (b) (4) *method for the detection of Mycoplasma species (cultivable on artificial media). With the introduction of* (b) (4)

(b) (4) *, the current method was revised. Sanofi Pasteur Limited's modifications of our Mycoplasma Culture Method reflect the changes in the* (b) (4) *requirements.*

The modified procedure is compliant with the current version of the (b) (4) .

CBER response: CBER does not agree with this assessment and requests that the new testing procedure not be used until documentation had been submitted to STN 125145.

CBER's review the lot release protocol template submitted in amendment 125525/0.6 on February 3, 2015 found a number of deficiencies. The following comments were sent to Sanofi on February 26, 2015.

We have reviewed the lot release protocol template submitted on February 3, 2015 in amendment 125525/0.6. Although there was discussion of generating a new lot release protocol template with formatting changes, what was uses the currently approved format for the Pentacel (STN 125145) lot release protocol with the following items that need to be addressed before the lot release protocol can be used for product release.

Comment 1: In the header: The top line needs to read cc: 125525/1726-B and the Licensed Name of Product should be Diphtheria and Tetanus Toxoids and Acellular Pertussis Adsorbed and Inactivated Poliovirus Vaccine

Sanofi response: The header is updated as indicated:
cc: 125525/1726-B
Licensed Name of Product: Diphtheria and Tetanus Toxoids and Acellular Pertussis Adsorbed and Inactivated Poliovirus Vaccine

CBER response: This has been addressed adequately.

Comment 2: On page 1 of 87, please remove the reference to the electronic filename until CBER has approved the use of electronic protocols for this STN.

Sanofi response: Reference to the electronic filename is removed.

CBER response: This has been adequately addressed.

Comment 3: On page 9 of 87, Potency – Diphtheria and Potency – Tetanus were removed from the table. This is acceptable as long as the specifications are added to the Details for the tests on pages 12 – 14 for the tests.

Sanofi response: The enclosed Lot Release Protocol (LRP) template for Quadracel STN BL 125525 is aligned with the CBER-approved LRP format currently in use and on file with Pentacel™ STN BL 125145 which contains diphtheria and tetanus potency only reported in sections 2.4 and 2.5 (i.e., pages 12 to 14 of 47 of the enclosed LRP template). Modifications to

both the tests have been proposed with respect to the revised Pentacel LRP template currently under review with CBER. Once the revised Pentacel LRP template is approved, the same template will be implemented for the DTaPIPV components of Quadracel 5th Dose.

CBER response: CBER is satisfied with this response. This information will be included in the updated protocol template in the future.

Comment 4: On page 9 of 87, D-Antigen Content-ELISA, Limits need to be included.

Sanofi response: Limits for D-Antigen Content-ELISA are added as indicated (page 9 of 47 of the enclosed LRP template).

CBER response: This has been adequately addressed.

Comment 5: On page 10 of 87, in the sterility template for the Final Bulk we had requested that the (b) (4) test date be added, the (b) (4) date requested on the LRP should reflect the date the final bulk matrix was shown suitable for your sterility test method. In the future should the manufacturing process change and/or the test method be modified requiring the requalification of your sterility test method, then this (b) (4) date would be up-dated on the LRP. Please contact us if you have questions regarding the clarification of our expectations.

Sanofi response: This question was previously addressed and the following response below was provided relating to the revised Lot Release Protocol Template for Pentacel (STN 125145) currently under review with CBER.

Please note, once the revised template for Pentacel (STN 125145) is approved, the same template will be implemented for Quadracel 5th Dose (STN 125525) – given that the only difference between these LRPs is the license number in the LRP header.

On page 16 of 46 of the Final Bulk template, please add the (b) (4) test date.

Response: The objective of Sterility Testing is to demonstrate the absence of viable contaminating microorganisms (bacteria and fungi) in the samples. The principle of the test is based on the premise that of a test sample, any bacteria present in the sample would be retained on the (b) (4). Any viable bacteria present on the (b) (4) could then be cultured upon incubation at an appropriate temperature and using the appropriate growth media. If no growth is observed, the sample is considered sterile.

The (b) (4) parameters were included in the test method validation (per Protocol # 3VAL-009-02 "Sterility Testing Using The (b) (4) Procedure By (b) (4) Technique). The method validation demonstrated that the method could detect and support the growth of bacteria and fungi, if present, and that the samples do not exhibit any (b) (4) effects.

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

The "On test" and "Off test" dates for the (b) (4) *media and incubation temperatures are provided in the template on page 16 of 46*

CBER response: This has been adequately addressed with the addition of the Qualification/Requalification date to the sterility template on page 10 of 95 in the lot release protocol template submitted on March 17, 2015.

Comment 6: On pages 44, 55, and 66 of 87, for the virus titer and Identity please include the poliomyelitis virus type in the specification.

Sanofi response: Poliomyelitis virus type for the virus titer and Identity is now included. (Pages.5 of 11 for each poliovirus type 1, 2 and 3).

CBER response: This has been adequately addressed.

Comment 7: On pages 36 and 37 there are Diphtheria Toxoid Adsorbed and Tetanus Toxoid Adsorbed test results; please add the test results, including the specific toxicity tests that were in the Pentacel version of the lot release protocol template submitted 11/27/2014.

Sanofi response: (b) (4) *test results with specific toxicity tests are added to align with the CBER approved LRP format currently in use and on file with STN BL 125145 for Pentacel (pages 41, 42, 44 and 45 of 47 of the enclosed LRP).*

CBER response: This has been adequately addressed.

Comment 8: Between pages 26 and 27 under section 3.0 Component Pertussis Test Summary please add back the section for the Filamentous Haemagglutinin (FHA) lot release tests.

Sanofi response: The section for Filamentous Haemagglutinin (FHA) is added as indicated (pages 27 to 30 of 47).

CBER response: This has been adequately addressed.

Comment 9: CBER is aware that the specification for Fimbriae Types 2 and 3 for (b) (4) has changed from (b) (4). Please use the new specification (b) (4) on the lot release protocol, adding a note indicating when this specification changed to accommodate the acceptance of lots formulated with batches of FIM released when the previous specification (b) (4) was in place.

Sanofi response: The new specification of (b) (4) is now indicated in the LRP. A note will be added at the time of actual LRP submission to accommodate the acceptance of lots formulated with batches of FIM released with the previous specification of (b) (4).

CBER response: This has been adequately addressed.

Comment 10: In Sanofi's response to Comment 6 dated 12 September 2014, Sanofi indicated that they would change the (b) (4) reference unit from (b) (4). Although both can be used CBER would prefer the use of (b) (4) in the (b) (4) templates.

Sanofi response: This question was previously addressed and the following response below was provided with respect to the revised Lot Release Protocol Template for Pentacel (STN 125145) currently under review with CBER.

Per (b) (4), the units should be (b) (4), because the CBER (b) (4) standard measured in (b) (4) is no longer available. Please request to use the International Standard, which is measured in (b) (4)

Response: The current reference standard for (b) (4) is a (b) (4) standard and can be expressed in both (b) (4) Results will be reported in (b) (4) with the approved template.

CBER response: This has been adequately addressed.

On February 3, 2015 an email addressed to Joseph Quander from Samuel Shek of Sanofi requested approval of changes to the lot release protocol Pentacel (STN 125145), this protocol is currently under review, once approved this same protocol can be used for 125525.

3.3 Conclusions

The lot release protocol submitted on March 17, 2015 in amendment 125525/0.8 is acceptable for use. In addition, when the lot release protocol for Pentacel (STN 125145) submitted to CBER has been approved, this protocol with the appropriate changes to the STN and licensed name can be used for the lot release of STN 125525.