BLA Review Memo, April 22, 2014 - GARDASIL 9

22 April, 2014
CBER REGULATORY REVIEW
To Administrative File: STN 125508/0
From Dr. Claire H. Wernly,
Laboratory of Microbiology, *In-vivo* Testing and Standards
DBSQC/OCBQ/CBER/FDA
Through Dr. James L. Kenney, Chief
Laboratory of Microbiology, *In-vivo* Testing and Standards
DBSQC/OCBQ/CBER/FDA
Dr. William M. McCormick, Director
DBSQC/OCBQ/CBER/FDA
Subject BLA: Review of Sterility and ---(b)(4)--- Endotoxin Test Qualifications for GARDASIL®9 [9-Valent Human Papillomavirus (HPV) Vaccine, Recombinant].

Recommendation
Based on the scope of this review, I recommend approval of this Biologics License Application (BLA).
Conclusion
After a thorough review of this BLA, and the response to CBER's Information Request (IR) (Amendments 125508/0.4 – received on 14 March, 2014), this reviewer finds the sterility and ----------(b)(4)---------- methods were qualified in accordance with ----------(b)(4)----------, respectively, by demonstrating that the product matrix for GARDASIL®9, manufactured by Merck Sharp & Dohme, Corp (MERCK) is suitable for these intended test methods.
Background
On December 10, 2013, Merck Sharp & Dohme, Corp (MERCK) submitted a BLA for GARDASIL®9 (9-Valent HPV Vaccine, Recombinant). GARDASIL®9 targets HPV Types 6, 11, 16, and 18 also targeted by the currently licensed quadrivalent HPV vaccine (GARDASIL®) as well as additional HPV Types 31, 33, 45, 52, and 58. HPV Types 16 and 18 are responsible for approximately 70% of cases of cervical cancer. An additional 20% of cases are due to HPV Types 31, 33, 45, 52, and 58. Therefore, the addition of five more HPV Types to the GARDASIL®9 vaccine has the potential to prevent up to 90% of cervical cancers.
GARDASIL®9 is a recombinant vaccine prepared from purified virus-like particles (VLPs) of the major capsid (L1) protein of the Human Papillomavirus (HPV) Types 6, 11, 16, 18, 31, 33, 45, 52, and 58. The respective L1 proteins are produced by separate fermentations using recombinant *Saccharomyces cerevisiae* and self-assemble into VLPs similar in conformation to native virions. Following purification, the respective VLPs are adsorbed onto amorphous aluminum hydroxyphosphate sulfate (adjuvant)

creating nine HPV ----------(b)(4)---------- which are then combined to form the final nonavalent (9vHPV) drug product. The final product is a sterile 0.5 mL suspension for intramuscular injection presented as either a single-dose vial or a prefilled syringe, to be administered as a three dose regimen. Each presentation is formulated to contain 30/40/60/40/20/20/20/20/20 µg of HPV 6/11/16/18/31/33/45/52/58 ----------(b)(4)-------. Other ingredients include: sodium chloride (-----(b)(4)-----), L-histidine and sodium borate (---(b)(4)---), polysorbate 80, (----------(b)(4)----------) and water for injection (solvent). GARDASIL®9 is indicated in girls and women (9 through 26 years) and boys (9 through 15 years) for the prevention of diseases caused by the HPV types included in the vaccine.

The DBSQC reviews BLAs and Supplements to ensure analytical methods are appropriate, properly validated and the product matrix is suitable for the intended test method. DBSQC also reviews release specifications for microbial and endotoxin testing and sterility to ensure they reflect process capability and meet regulatory compliance. These review activities support DBSQC's lot-release mission, which is the confirmatory testing of submitted product samples and review of manufacturers' lot-release protocols to ensure biological products are released according to licensed test methods and product specifications. Therefore, this review will focus on the qualification reports for the sterility and -(b)(4)- test methods to determine if the GARDASIL®9 product matrix is suitable for these intended test methods.

Review

Sterility Test Qualification

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

----------:

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

----------.

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

Endotoxin Test Qualification

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

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

Summary

After a thorough review of the information submitted in this BLA, this reviewer finds MERCK's GARDASIL®9 sample matrix is suitable for testing using their sterility and -(b)(4)- methods; these tests were qualified and performed in accordance with ----------(b)(4)----------, respectively. Therefore, this reviewer finds these methods acceptable for their intended purpose and recommends their approval.