

Microbiological Review Memo, December 19, 2013-Q-Pan

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

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To Administrative File for STN 125419

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Subject Original Biological License Application (BLA): Influenza A (H5N1) Virus
Monovalent Vaccine (Q-Pan H5N1): Review of Microbiological Test Methods.

Conclusion

Based on the review of the information submitted in support of this Biological License Application (BLA) for GlaxoSmithKline Biologicals' (GSK's) microbiological testing methods, to include amendments 125419.9, 125419.12 and 125419.14, I recommend approval of GSK's:

- -----(b)(4)----- bacterial endotoxin test method performed on their H5N1 Antigen final container (FC) product;
- -----(b)(4)----- bacterial endotoxin test method performed on their AS03 Adjuvant FC product;
- ----(b)(4)----- method performed as an in-process monitoring test on their AS03 Adjuvant;
- sterility by ----(b)(4)----- test method performed on both their H5N1 Antigen and AS03 Adjuvant FC products; and

- antimicrobial effectiveness test results performed on their combined (H5N1 Adjuvant/AS03 Antigen) product.

Background

On 22 February, 2012, GSK, submitted a BLA for their Influenza A (H5N1) Virus Monovalent Vaccine, with a trade name of Q-Pan H5N1. Q-Pan H5N1 is a non-infectious, 2-component monovalent, AS03-adjuvanted vaccine. The vaccine contains an inactivated, split-virion, A/H5N1 influenza antigen suspension component and an AS03 adjuvant system emulsion component. The H5N1 virus, grown in chicken eggs, is inactivated with ultraviolet light followed by formaldehyde, purified by centrifugation and disrupted with sodium deoxycholate. The AS03 adjuvant system is a homogenized, sterile, whitish emulsion composed of squalene, DL- α -tocopherol and polysorbate 80. Q-Pan H5N1 is supplied as two separate vials, a vial of H5N1 Antigen and a vial of AS03 Adjuvant. Once combined, the resulting volume provides 10 doses of a whitish emulsion, formulated to contain 3.75 μ g hemagglutinin (HA) of the A/Indonesia/05/2005 (H5N1) influenza virus strain and 5 μ g thimerosal per 0.5 mL dose. Q-Pan H5N1 should be administered as a 2-dose series by intramuscular injection, with the interval between the first and second dose being approximately 21 days.

The Q-Pan H5N1 Antigen is produced in the GSK's Quebec facility according to the FluLaval® seasonal influenza vaccine manufacturing process that is currently licensed in the United States, with the difference being Q-Pan's monovalent antigen bulk formulation (at 15 μ g HA/mL) contains thimerosal at 20 μ g/mL concentration, whereas the FluLaval® formulation includes three monovalent antigen bulks (each at 30 μ g HA/mL) with a thimerosal concentration of 100 μ g/mL. GSK stated in this BLA (i.e., in section: m1.2; 3: 'Information to determine need for pre-licensure inspection (m1.11.1)), 'Q-Pan is not being manufactured at this time and there are no plans to manufacture the vaccine until there is a declared need for the product. Given the current hiatus in the pandemic vaccine antigen manufacture and considering that 1) the antigen bulk manufacturing process of Q-Pan H5N1 vaccine has followed that for the seasonal FluLaval® bulk manufacturing process at the time of the manufacture and 2) GSK plans to supplement the BLA in the future with the relevant changes to the seasonal bulk manufacturing process...'; CBER can be assured that the GSK manufacturing process for Q-Pan H5N1 and FluLaval® should be considered identical - based off the aforementioned commitment by GSK – as only the final product formulations are different.

The AS03 Adjuvant packaged together with Q-Pan H5N1 Antigen for distribution in two different vials is made from squalene, DL- α -tocopherol and polysorbate 80. GSK procures their squalene from -----(b)(4)-----, as squalene is used primarily as a food supplement, a cosmetic additive and in pharmaceutical products and vaccines. Squalene is extracted from -----

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

----- . In humans, squalene is a key intermediate in liver cholesterol synthesis, a component of human blood and is part of the oily secretion of the sebaceous glands that act as a lubricant for hair and skin.

Since CBER's Division of Biological Standards and Quality Control (DBSQC) primarily reviews product test method qualification, validation and test specifications, this review will focus on assessing the validity and regulatory compliance of the following microbiological test methods:

- -----(b)(4)----- Bacterial Endotoxin Assay;
- -----(b)(4)----- Bacterial Endotoxin Assay;
- Bioburden Assay;
- Sterility Assay by -----(b)(4)----- ; and
- Antimicrobial Effectiveness Assay.

Review

Bacterial Endotoxin Assays

GSK performed two different bacterial endotoxin test (BET) methods, one for each FC component; that is they performed the ----(b)(4)----- Assay on the H5N1 Antigen FC and the ----(b)(4)----- Assay on the AS03 Adjuvant FC. Both these methods were performed and qualified in accordance with -----(b)(4)-----.

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

(b)(4)

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

(b)(4)

[illegible]

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

(b)(4)

(b)(4)

GSK performed a (b)(4) bioburden assay to quantify enumeration of mesophilic bacteria and fungi, which may grow under aerobic conditions in their (b)(4). To qualify the AS03 Adjuvant matrix for the bioburden assay, (b)(4) batches (i.e., (b)(4)) were used for Bacteriostasis and Fungistasis (B&F) testing.

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

(b)(4)

(b)(4)

GSK performed a membrane filtration sterility test on both Q-Pan H5N1 FC component products (i.e., the H5N1 Antigen and the AS03 Adjuvant) for the presence or absence of microbial contamination in accordance with --(b)(4)-- Sterility Tests and ---(b)(4)----- Sterility.

-(b)(4)

-(b)(4)

GSK performed a preservative efficacy evaluation on their combined (ready for administration) Q-Pan H5N1 product to demonstrate their thimerosal concentration is

- sterility test by -----(b)(4)----- is suitable for testing GSK's H5N1 Antigen and AS03 Adjuvant FC products; and the
- antimicrobial effectiveness test results indicate the 5 µg thimerosal per 0.5 mL dose of Q-Pan H5N1 vaccine is adequate to inhibit the growth of microorganisms that may be introduced inadvertently while repeatedly withdrawing individual doses from a 10 dose vial.