BLA Amendment Review Memo - Agriflu, November 28, 2009

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: File BL STN 125297/0/0006
From: Rebecca Olin, OCBQ/DMPQ/MRB2
Through: Chiang Syin, PhD, Chief, CBER/OCBQ/DMPQ/MRB2
Subject: Novartis Vaccines and Diagnostics (License #1750) BLA Amendment: For the addition of --b(4)-- Syringes to be filled on Filling Line ---------b(4)-------- located at the ----b(4)--- facility.
Action Due: November 28, 2009

Action Recommended
Recommend approval
Summary
Novartis submitted this amendment to the BLA in support of a new --b(4)---- syringe intended to be filled at the --b(4)---- filling facility (Building -b(4)-). This submission provided process validation, media fill, container closure integrity, automated visual inspection validation and stability data. Review of the data presented in this file was acceptable and covered all relevant issues. This container closure system was recently approved under STN 103837/5502 for the filling of Fluvirin on -b(4)- at the -b(4)- facility. I recommend approval of this file.
Review Narrative
This amendment also covers the following changes:

- Withdrawal of ----b(4)---------- as an alternate supplier of the staked needle syringes;
- Withdrawal of syringe filling line --b(4)--
- Container closure integrity data for the staked needle syringe
- Updated stability data in staked needle syringes for the 2007/2008 season (12 months real time) and 2008/2009 season (3 months real time).

Syringe
The new syringe is a ---------b(4)---------- glass syringe with a plastic rigid tip cap (PRTC) closed with a gray, latex free, ---b(4)---- plunger stopper. No needle is present on the syringe. The tip cap is a latex free ---b(4)----- tip cap (----------b(4)----------). The tip cap is lodged in a rigid plastic shell which is screwed onto the ----b(4)----. The syringe is closed with a gray, latex free, ---b(4)------- plunger stopper ----b(4)----------

The plunger stopper is the same as that used in the staked needle system. A full description can be found in my review memo for this BLA dated April 3, 2009.

The -b(4)--- syringe with PRTC and plunger stopper has been approved as the primary container closure system for Fluvirin also filled at the -b(4)- facility per STN 103837/5502.

Stability

Three lots of product from the 2008/2009 season filled into the -b(4)----- syringe system were put on stability at 2-8 °C, and one lot was held under accelerated conditions of ----b(4)---------- The syringes were held --b(4)--- to permit contact with the -b(4)---------- and stopper. Data up to the -b(4)- month test point was included in this submission. Data tables show conforming results for Haemagglutinin Content, Appearance, pH, Sterility and b(4)--- for the real time stability tests. Results for the accelerated testing for the -b(4)- week storage time at --b(4)-------- were within specification with the exception of one test conducted at -b(4)- weeks on a -b(4)- sample.

A leachable study is underway for the --b(4)- - syringe and focuses on the –b(4)-. The plunger stopper leachable profile was presented in the original submission.

The -b(4)- study consists of testing samples of Agrippal stored in -b(4)- syringes for volatile organic compounds using ---b(4)---------- with --b(4)---------- following ----------b(4)---------- of data were available at the time of submission and no volatile organic compounds were found above the reporting limit in the test sample or control. The study will be continued up to --b(4)-- and the Agency will be informed of any anomalous result during the study.

Container Closure Integrity

--b(4)---------- small scale media fill runs were performed using a single lot of -b(4)-. Each media fill used syringes of different lot numbers. After filling, the syringes were incubated at

---b(4)---------- followed by incubation at --b(4)-- for an additional --b(4)-------. The syringes were then tested for sterility by visual inspection and growth promotion. After -b(4)------of incubation no growth was seen in any syringe and the growth promotion tests were positive.

The integrity test protocol calls for media filled syringes to be ----------b(4)----------. This test is performed on

----------b(4)---------- syringes and the integrity tests are conducted at the following time points:

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

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

Time -b(4)- data were presented for the -b(4)- syringe sterility and integrity tests. After ---------b(4)---------- all syringes were negative for growth and the growth promotion tests were positive.

Process Validation

---b(4)--- batches of ---b(4)-- syringes each using the -b(4)- Filling Machine were manufactured for the purposes of verifying final product conformity, filling homogeneity and fill volume verification.

Filled product samples were tested for ------b(4)----------. Samples pulled at the -----b(4)---------- of filling were tested for --b(4)--. The low variability of the HA results for each batch run showed the fill resulted in a homogenous product. Data tables included in the submission showed all acceptance criteria were met for the above named tests for all --b(4)---- batches.

Media Fill Validation

A media fill history was presented for the staked needle container closure and included the original runs conducted in 2006 and included the following worst-case conditions:

- Filling speed set at 50% of routine production;
- The media fill operation covered the longest fill time with several machine stops ---b(4)----------
- There were 8 routine interventions, 2 maintenance interventions and 1 critical intervention made during the fills;
- Maximum personnel rotation (b(4));
- The filling area was not cleaned for -b(4)- days prior to the fills;
- Filling kits were ---b(4)---- at least -b(4)- days before the execution of each media fill;

Results of these fills showed each batch, consisting of over --b(4)-- syringes, contained only sterile units at the end of incubation.

An additional media fill was conducted specific for Fluvirin to increase the total working hours to b(4) hours. The results showed each batch, consisting of over -b(4)- syringes, contained only sterile units at the end of incubation

The media fill history from August 2006 to November 2008 was presented and showed passing results for all media runs.

-b(4)- lots of media were filled into the new --b(4)--- syringe to conduct container closure integrity testing. Each batch fill consisted of approximately -b(4)- syringes. Results showed no contaminated units. See the Container Closure Integrity section of this memo for more details of these studies.

Inspection System Validation for --b(4)-- Syringe

A Quality Risk Assessment was conducted to assess the staked needle syringe and --b(4)-- syringe for similarities and differences to determine if additional process validation

was required to introduce the -b(4)- syringe onto filling line ----b(4)---------- The study looked at the syringe dimensions and concluded the two syringes had the same barrel dimensions (barrel length, inner and outer diameter) and nominal volume of the syringe. Both syringes are received by the same supplier (--b(4)--------) in the same type of ---b(4)---------- system. Differences between the syringes include: ---------- b(4)----------

According to the Risk Assessment, the filling machine handles both syringes in the same manner and doesn't recognize a difference between them so that the flow of material, equipment, including the syringe ----b(4)----------, and personnel doesn't change from one type of syringe to the other. The plunger stoppers are identical and are thus handled in the same manner.

The one difference identified between the syringes is the fill volume. The target volume for the staked needle syringe is -b(4)- ml and the target volume for the -b(4)-------- syringe is --b(4)---. The difference is due to the presence of the needle on the --b(4)-- needle syringe. This was not considered to be a critical difference but fill volume was tested and results were within acceptance criteria.

The automated visual inspection was evaluated for each syringe. Each syringe undergoes a series of checks either by camera or optical measurement systems. The following defects are inspected by the inspection machine:

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

A review of the impact of the new syringe on the inspection stations was conducted.

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

Three differences were identified in the Inspection System evaluation, and they include:

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

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

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

A supplementary PQ was performed for defects of the -b(4)- and -b(4)- including broken -b(4)-, missing ----b(4)---------- of the --b(4)----------. Results showed that the inspection machine was able to detect these defects 100% of the time for the test sample.

History

Review Initiated: July 15, 2009
Review Completed: July 29, 2009
Telecon Date(s): None