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

From: Rebecca Olin, OCBQ/DMPQ/MRB2

Through: Chiang Syin, PhD, Chief, CBER/OCBQ/DMPQ/MRB2

Subject: Novartis Vaccines & Diagnostics, Inc. (License # 1751) BLA: For the active immunization of persons 18 years of age and older against influenza disease.

Action Due: May 11, 2009

Action Recommended

A Complete Response Letter will be issued.

Product

Influenza Virus Trivalent Subunit Vaccine, Inactivated (proposed trade name Agrippal®)

Questions for CR Letter

1. According to the Quality Risk Analysis of Antigen Filtration for Flu in Building b(4) there are --b(4)---------- filters available for use at the -b(4)- filtration step; the ----b(4)---------- filters. This document states that the -b(4)- filters are identical but no information is provided in support of this claim. Please provide your evaluation of the filters and the data used to conclude that the filters are identical.

2. In the Quality Risk Assessment, the Batch Record, and the Validation Report for the ---b(4)-- Filtration Process the specific type of filter is not identified; however the vendor validation of the --b(4)--- filters provided in your submission related to specific filters such as the -----b(4)----------. Please provide the specific models of ---b(4)--------- filters that you are using for -b(4)- filtration and indicate if the filters are being used ---b(4)----------. If so, please provide your justification in light of the vendors' use of specific strains in their validation reports.

3. There is no data in the submission regarding b(4) testing for extractables and leachables for the --b(4)-------- filters. Please provide data for these studies.

4. The vendor reports for the ---b(4)---------- filters are not consistent as to the types of tests or in some cases the depth of testing conducted (see the --b(4)----- extractables testing compared to that of ---b(4)------). Please provide your testing protocol including information as to what specific validation tests were required, what worst case testing was required, the acceptance criteria and your evaluation of the study results.

5. According to Validation Report for the Syringe Filling Process for Filling Machine -b(4)----------, reference is made to a dosage verification study conducted on samples taken every --b(4)-----. There was no information regarding the purpose of the study and no data was presented to indicate the outcome of the study. Please provide information regarding the study, the test results and study conclusions.

6. In your submission there was no information or data submitted for the b(4) chamber used to --b(4)--- the stopper bags or the -b(4)---- machine used to unpack syringes. Please provide the validation protocol and final reports for these pieces of equipment.

7. The new filling machine referred to in the submission and that has been subsequently withdrawn includes an --b(4)----------. There is no reference to a --b(4)-- step for the syringe -b(4)- for filling line --------b(4). Are the syringe b(4) for this line -b(4)- before they enter the Class b(4) filling room? If so, please provide the validation of this step. If not, please explain how you control potential contamination from syringe b(4) from entering the filling room.

8. Regarding Inspection Machine -b(4)-. The validation information provided was insufficient to conduct a complete review. Please provide your validation protocol and final report which should include:

    a. A complete description of the inspection machine;
    b. A description of what --b(4)---------- results mean;
    c. A description of how the validation tests were conducted including a description of test sets, number of runs, acceptance criteria and a discussion of the results and conclusion;
    d. Please provide data to support how the False Reject Rate was calculated and provide data for the False Accept Rate.
    e. Provide your procedure for the performance test runs conducted before and after each batch is inspected including.

9. Please provide media fill data to support the assurance of sterility ----------b(4)-filtration, through formulation, storage and aseptic filling of the final product.

10. The documents referred to as containing extractable and leachable data (3.2.P.2.3) for the container closure qualification did not contain this information. Please submit all

extractable and leachable studies and data including those conducted according to b(4)-requirements.

Summary

Novartis submitted this BLA in support of the manufacture of Influenza Virus Vaccine (IVV) at the Siena and --b(4)----- manufacturing facilities. Agrippal is a thimerisol-free vaccine containing the purified outer membrane proteins, Haemagglutinin (HA) and neuraminidase (NA) from each of the three annually recommended influenza virus strains. This BLA is submitted for the approval of Agrippal for the immunization of adults 18 years and older.

The Drug Substance (Monovalent Pooled Harvest) from each of the three selected virus strains is combined to produce the trivalent final Drug Product. The final product is provided in single-use, pre-filled syringes.

Manufacture from egg inoculation to the --b(4)----- stage is conducted in Building b(4) of the Siena site. --b(4)---------, formulation, and filling are conducted in Building b(4) at the b(4) site.

Agrippal is filled in -b(4)- on the --------b(4) filling line -b(4)-; however, during the review of this BLA, I noted the inclusion of Filling Line -b(4)- (---------b(4)). No data was included to support the use of this filling line in routine manufacturing. Discussions with the firm during the PLI resulted in the firm promising to remove this filling line from the BLA because sufficient stability data could not be provided within the review cycle. Amendment 6 to the BLA was submitted on February 26, 2009 and included the withdrawal of syringe filling line -b(4)-.

The Pre-License inspection, dated February 5-13, 2009, resulted in the issuance of an FDA-483.

Review Narrative

Manufacturers

The following manufacturers are involved in the Monovalent Pool Harvests (Drug Substance)

Site	Responsibility
Novartis Vaccines & Diagnostics S.r.l. Via Fiorentina 1 53100 Siena Italy	• -----b(4)---------- • --b(4)---------- • ---b(4)----------
--b(4)---------- --b(4)---------- -----b(4)---------- -b(4)-	• ---b(4)---------- • -----b(4)----------
-----b(4)---------- ---b(4)------- -b(4)- ----b(4)---------- -b(4)-	• ------b(4)----------
---b(4)---------- --b(4)---------- ---b(4)---------- -b(4)----------	• -----b(4)----------

Drug Substance

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

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

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

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

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

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16 Pages determined to be not releasable:
b(4)

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

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

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

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

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

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

There was no data submitted to indicate that extractable and leachable studies were conducted according to b(4) test requirements. **See CR Question #10.**

Container Closure Integrity

The integrity of the pre-filled syringe was evaluated by conducting media fills and microbial ingress studies.

The media fill studies were conducted in August/September 2006 in which -b(4)- syringes containing --b(4)---------- from three media fill runs were incubated at --b(4)---------- for -b(4)- days followed by an -b(4)---------- day incubation at -b(4)------. Visual examination at the end of each incubation period showed no growth.

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

Consistency Lots

Drug Substance: ----------

---b(4)---

---:

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

Drug Product: Three full-scale lots (----b(4)----------) and 1 batch at ----b(4)----------) were manufactured in support of process consistency at the formulation stage and the same full-scale lots were used in the validation of the filling line with each lot producing approximately -b(4)- syringes each.

Bioburden and Endotoxin Reduction

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

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

[b(4)]

2 Pages determined to be not releasable:
b(4)

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

Facilities and Equipment

The following sites and buildings are used for the manufacture of Agrippal:

Siena

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

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

No equipment validation information was submitted in the BLA and was covered during the Pre-license inspection in February 2009. No deficiencies were included for equipment validation on the FDA-483 issued at the conclusion of the inspection.

Major or Critical equipment list for the Siena site includes:

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

Major or Critical equipment list for the -b(4)- site includes:

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

HVAC – Siena and -b(4)-

Building b(4) (Siena)

The HVAC system for Buildingb(4) has a single air handling unit (AHU) that provides 100% ----b(4) pass air to the operations areas. There are terminal HEPA filters in Class b(4) and b(4) manufacturing areas and Biological Safety Cabinets (BSC) and Laminar Flow Units (LFU) that provide Class b(4) air to areas in which open aseptic operations occur.

Room temperature, relative humidity and pressure differentials are monitored and are on automatic alarms.

Room conditions are maintained by a computer regulated system----------b(4)----------

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

Building b(4) (Siena)

The HVAC System for Building b(4)hasb(4)AHUs,b(4)of which provide -b(4)- pass air and one provides b(4) recirculated air. A-b(4)--- system is used to monitor and control room temperature, relative humidity and pressure differentials.

The control system for the HVAC system consists of three main units: a ----b(4)---------- -----

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Each terminal HEPA filter housing is equipped with a differential pressure entry port. Several of the terminal filters are equipped with -b(4)----- magnehelic gauges to indicate filter clogging. In the AHU and filter banks there are ----------b(4)----- across the filter to indicate filter clogging to the control system.

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

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

----b(4)------- ---------- ---------- ---------- ---------- ---------- ----------
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Water – Siena

Building b(4)

Building b(4) has clean steam system.

Clean Steam: The clean steam system was originally installed in the 1990s and expanded over the years to accommodate the expansion in production needs. The latest modifications were conducted in 2006. Steam is generated by a -b(4)-- generator for use in ---b(4)---------- ---------- The generator is fed by an-b(4)----- system. The feed and distribution system are constructed of --b(4)----------

----b(4)--- ---------- ---------- ---------- ---------- ----------
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No data was presented; however the validation data and routine monitoring data were covered during the PAI and presented no significant deficiencies

Building b(4)

Water: Building -----b(4)---------- WFI systems that supply WFI to the viral vaccine manufacturing areas. Each system has its own controls, WFI still, storage tanks and circulating loops.

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

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

Change Over

SOP 248698 covers the changeover between the production campaign with seasonal strains and the production campaign with pandemic strains. Also included are the activities that are performed with changing strains during seasonal production. The SOP prevents the simultaneous presence of pandemic and seasonal strains.

Changeover activities include room cleaning, room fumigation, decontamination timeframes, process equipment cleaning and timeframes, parts replacement and materials elimination.

Cleaning is performed -b(4)- in the live virus areas during pandemic production and -b(4)- for seasonal. Cleaning includes the room and the equipment such as incubators and hoods.

---b(4)---

Cleaning methods and timeframes were provided for production equipment including disinfectants, detergents and sanitizers used.

---b(4)---

Cleaning Validation

Building b(4)

There are no equipment surfaces that are in direct contact with the product. Cleaning validation is not applicable for this building.

Building b(4)

Cleaning validation was conducted concurrently with the 2007 Influenza production campaign.

The type of soil present on product contact surfaces was identified. When more than one type of soil is present an assessment was performed to identify which was the most difficult to clean and this soil was used during the validation. Soils were identified for product equipment and included -----b(4)----------

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

Cleaning efficacy was determined using ----b(4)----------. At the end of each cleaning procedure samples were taken to establish cleaning effectiveness as well as dirty and clean hold time.

A matrix approach was used in cases where similar or identical pieces of equipment are used. Matrixing is based on equipment materials of ---b(4)--- ----------equipment used in the manufacture of the same or similar production that are cleaned by the same or similar cleaning process.

No data specific to individual pieces of equipment were presented but were reviewed on inspection. One 483 item regarding cleaning of the egg inoculator was included on the FDA-483 issued at the conclusion of the inspection.

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

Building b(4)

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

Environmental Assessment or Waiver

Novartis is applying for an exclusion under 21 CFR 25.31(c) since Agrippal is a biologic. Novartis attests that the drug substance and drug product are manufactured following current local environmental requirements.

History

Review Initiated: November 17, 2008
Review Completed: April 3, 2009
Telecon Date(s): None