

# Intercell BLA Review Memo - IXIARO

**To:** David Doleski., Acting Branch Chief, MRBII, DMPQ , OCBQ, CBER, HFM-676

**From:** Destry Sillivan , MRBII, DMPQ, OCBQ, CBER, HFM-676

**Subject:**

**Biologics License Application ( BLA)** Review Memorandum– Intercell AG (Intercell) Original Application for the manufacture of Japanese Encephalitis Virus (JEV) Vaccine, Inactivated, intended for active immunization against JEV (US License number 1790).

**STN:** BL STN 125280

CBER Receipt Date : December 20, 2007

Action Due Date : October 19, 2008 (Original Goal Date)

April 4, 2009 (Second cycle Goal Date)

**Action Recommended:** Approval

## **Summary:**

The BLA, submitted in eCTD format, consists of FDA form 356h and 3397, a cover letter, and all five CTD modules (Module 1: Regional Information, Module 2: CTD summary documents, Module 3: Quality, Module 4: Nonclinical Study reports, and Module 5: Clinical Study Reports).

JEV Vaccine, indicated for active immunization against JEV for persons aged eighteen years and older , is manufactured at Intercell Biomedical Ltd, located in Livingston, Scotland, United Kingdom. Final fill and formulation takes place at a contract filling facility: -----(b)(4)----- . The vaccine contains whole, inactivated virus with an Alum adjuvant, and is provided in a single dose, pre-filled syringe. Secondary packaging consists of a blister containing one pre-filled syringe with or without a separated needle. The blister is closed by a paper foil and placed into a box. This foil provides a tamper evident barrier.

Manufacturing begins with growth of an attenuated strain of JEV, strain SA14-14-2, on Vero cells, followed by viral harvest, vaccine purification steps, formalin inactivation, and aluminum hydroxide formulation. Intercell then ships Bulk drug product to -(b)(4)- ----- for filling into pre-filled syringes. Each unit dose of JEV Vaccine contains 6 mcg of the inactivated JEV, strain SA14-14-2 per 0.5 mL, and the vaccine does not contain any preservatives or antibiotics.

The bulk drug substance manufacturing facility is located at Intercell's Livingston, Scotland, UK site. Within the building, the firm included space for Manufacturing, Quality Assurance/Control, Document Control, Process Review and Control, Raw Material Quarantine, Testing and Release, Shipping and Receiving, Facilities Maintenance, and Administrative functions. Manufacturing processes performed include cell culture, viral infection/inoculation, viral harvest, ultrafiltration, ----(b)(4)--- and protein removal, sucrose gradient purification, viral inactivation, sterile filtration, and bulk filling. The facility is currently dedicated to the manufacture of JEV Vaccine.

The Pre-License Inspection (PLI) for this facility was conducted from May 8, 2008 through May 15, 2008. Upon completion of the PLI, nineteen observations were made on the FDA form 483 issued to the firm (see EIR associated with the inspection, as well as my 483 response review memo for a detailed review of FDA form 483 observations). Issues identified, but not limited to, included: failure to establish manufacturing step time

limits failure to incubate all media used in a media fill, failure to execute three successful cleaning validation runs for product contact equipment, failure to document equipment cleaning, implementation of a manufacturing process and/or testing procedures without supportive data, failure to follow Quality Unit and manufacturing SOPs, utilization of improper environmental monitoring practices, deficient stability sampling procedures, failure to conduct container closure studies for the bulk drug substance containers under extremes of pressure, failure to evaluate potential leachables and extractables from a product contact material, failure to store temperature sensitive materials in a manner that would assure correct temperature maintenance, failure to assure that Quality Unit released materials remain segregated from materials not yet so released, failure to properly qualify a facility utility, and allowance of a potential breach in integrity of the bulk drug product fill line downstream of the sterile filter.

On September 26, 2008, Intercell was issued a Complete Response letter for the following outstanding inspectional issues and one outstanding review issue:

1. Outstanding inspectional issues identified on the FDA Form 483 dated May 15, 2008, issued at the conclusion of the pre-licensing inspection of your Livingston, Scotland location have yet to be resolved. You must satisfactorily resolve these issues prior to approval of the application.
  - a. Your response to observation number 1b is incomplete. In order to fully evaluate leachables/extractables studies for product contact materials, please submit the summary report of the -(b)(4)- in-house Performance Qualification (protocol number 06070701i) performed in July /August 2006.
  - b. Your response to observation number 1c is incomplete. Please provide data demonstrating any product inhibition/enhancement of the -----(b)(4)-----  
----- Assay observed during validation of the assay.
  - c. Your response to observation number 8b is incomplete. To fully evaluate your environmental monitoring program, please submit the complete revised SOP QC054. To date, only Appendices 4 – 19 of SOP QC054 have been provided. These Appendices are not adequate to determine if appropriate revisions have been made to SOP QC054.
3. As per our previous conversation earlier this month, the final report for -(b)(4)--sterilization via -----(b)(4)----- has not been submitted to your BLA. Please submit this final report for review.

In this Complete Response letter, the firm was also asked to provide the following information, apart from the Complete Response letter questions:

- The final report for cleaning validation for your contract filler, -(b)(4)-, (Validation Protocol document number 1750507-1, "Cleaning, Validation, Initial Validation, JEV") has not been submitted. Please submit this final report for review.

Intercell submitted their Complete Response on October 1, 2008. All review and inspectional issues associated with this PAS have been satisfactorily resolved. (see **Questions for Applicant** section, below and 483 response review memo for this file)

**Items Reviewed:**

My review includes an evaluation of the following sections submitted in Intercell's eCTD BLA: Module 2 sections 2.2 and 2.3, the entirety of Module 3, Quality, and all amendments to the BLA pertaining to relevant information requests.

**Review Narrative:**

**Manufacturing locations:**

*Manufacturer of the drug substance:*

Intercell Biomedical Limited

Oakbank Park Road

Livingston

Scotland , EH53 0TG, UK

*Manufacture of the Aluminum Hydroxide adjuvant:*

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

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*Testing of Aluminum Hydroxide:*

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

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*Aseptic filling of the Final Vaccine Lot:*

(b)(4) -----

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*Contract Assays are carried out by the following :*

[ ---- (b)(4) ---- ]

**Manufacturing Facility Overview:**

The Bulk Drug Substance manufacturing facility, as noted above, is located within a gated/fenced area in Livingston, Scotland, UK. The ---- (b)(4) ----- consists of -(b)(4)- manufacturing clean rooms, -(b)(4)- to -(b)(4)-, each accessed via --(b)(4)-- changing rooms. Entry to -(b)(4)- and -(b)(4)- changing areas are from the ---- (b)(4) ----. Access to the ---- (b)(4) ----- and to the ----- (b)(4) ----- changing areas is via the JEV clean corridor, which in turn is accessed via the JEV male and JEV female changing rooms. Materials and equipment enter the clean rooms via the JEV lobby/transfer area. The JEV returns corridor, ----- (b)(4) -----, is accessed via the exit change lobby. Offices, Development and QC labs, pre-commercial manufacturing suite, storage, and utilities areas occupy the remainder of the building.

Functions of manufacturing areas are as follows:

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

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# One (1) page determined to be not releasable: (b)(4)

----- (b)(4) -----  
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## **Final Container Filling Process:**

### *Shipment to Contract Filler:*

Post-manufacturing, Intercell processes the ----- (b)(4) ----- containing the Final Bulk Vaccine by ----- (b)(4) -----, followed by labeling and placement into a plastic container which is security sealed and stored at -(b)(4)-. Intercell then ships Final Bulk Vaccine from Intercell Biomedical, in Livingston, Scotland, to ----- (b)(4) -----, in ----- (b)(4) ----- in a temperature controlled container at -(b)(4)-.

### *Filling Facility and Equipment:*

As noted above, -(b)(4)- performs all operations where the product is exposed in laminar air flow areas. Filling is accomplished in Clean Room -(b)(4)-, in a ----- (b)(4) ----- system installed around the Grade -(b)(4)- (Class -(b)(4)-, ISO Class -(b)(4)-) ----- (b)(4) ----- area of the filling line. Filling line manipulations are only performed using (b)(4)

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Equipment which comes in contact with the product is ----- (b)(4) -----, and all production steps are performed in -(b)(4)- systems. The connection between the --(b)(4)-- which contains the FBV and the ----- (b)(4) ----- in an ISO Class -(b)(4)- background. Processes where product and sterilized components are exposed to the environment are performed under Grade ----- (b)(4) -----.

Major equipment utilized for filling are a ----(b)(4)--- to ensure ----(b)(4)---, a --- (b)(4) ----- autoclave for sterilization of equipment, and a --- (b)(4) --- filling and stoppering machine. Intercell states that the equipment has been qualified, and that all initial qualifications were performed no earlier than 2005, and that scheduled requalifications have all been performed. Intercell states that equipment is cleaned either manually or in an equipment washing machine according to defined procedures, and that a product specific cleaning validation was performed for -(b)(4)- filling

equipment. However, no protocols or results from the cleaning validation were provided. (see **Questions for Applicant** section, Filing letter questions, Number 4).

*Room/Line Clearance:*

-(b)(4)- performs room cleaning and line clearance after completion of each production run, and performs line cleaning after each production step using line specific check lists to ensure that the production area is free of materials from the previous production campaign. Line cleaning also includes cleaning procedures for production equipment and premises. Prior to use in production, the identity and cleanliness status of equipment used in filling is verified and documented. Prior to filling, the identity of the container/closure system components is verified and documented. Other products filled in clean room -(b)(4)- are -----(b)(4)----- and -----(b)(4)-----, and they fill or otherwise handle -----(b)(4)-----.

*Filling procedure:*

------(b)(4)-----  
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-(b)(4)- employs the following methods/assays to ensure product quality;

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

Additionally, Intercell has specified the following final container specifications/ release tests:

- Appearance
- -(b)(4)-
- -(b)(4)-----
- Sterility
- -(b)(4)-----
- Potency
- Aluminum
- -(b)(4)-----
- General Safety Test

**Process Validation-Bulk (Intercell):**

Intercell executed three conformance lots in support of their BLA. -(b)(4)- additional lots were also process to final material in support of their Phase III clinical trials. Bulk lot numbers were -----(b)(4)-----, Dates of manufacture of these lots were -----(b)(4)-----, and batch sizes were -----(b)(4)-----, respectively.

Final Bulk Vaccine specifications and results are as follows (derived from Table 3.2.S.4.4-2 –Batch Analysis results):

Test	Specification	Results (by lot)		
		----(b)(4)-----	----(b)(4)-----	----(b)(4)-----
-(b)(4)-----	-(b)(4)----- ----- ----- -----	-(b)(4)----	-(b)(4)----	-(b)(4)----
<b>Sterility</b>	-(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)---	-(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)--

Additionally, Intercell manufactured -(b)(4)- batches in support of their phase II and III clinical trials. Three of these batches were compared against the consistency lots, above. No significant differences were observed between these three batches and the consistency batches with the exception of an out of specification for -----(b)(4)----- for Run A, (----- (b)(4)-----) manufactured for use as Phase III clinical trial material. Material for this batch was used in the pivotal non-inferiority trial IC51-301. Clinical trial results demonstrated that material from this batch was non-inferior to the currently licensed product, JE-VAX. The limit for -----(b)(4)----- was changed from --- (b)(4)- - ----- to --- (b)(4)----- for the consistency batches.

#### **Process Validation-Fill/Finish ( -(b)(4)-):**

Initial Process Validation at -(b)(4)- validated --- (b)(4)--- of filled material and a qualification of the batch volume range. -(b)(4)- placebo fills were successfully performed. The bulk placebo volumes were manufactured at Intercell, by incorporating -  
----- (b)(4)-----

----. Due to the potential variation in yield of Drug Substance, and hence Final Bulk Vaccine, a range of placebo weights was utilized. Following manufacture, the placebo lots ----- (b)(4)---, overwrapped and shipped to the -(b)(4)- under temperature-controlled conditions at -(b)(4)-.

Filling line parameters were adapted from ----- (b)(4)----- and from -(b)(4)-, where necessary, to optimize the filling process. --- (b)(4)-- demonstrated a consistent filling process and the parameters were utilized in Placebo -(b)(4)--. Placebo -(b)(4)- was filled with a target fill of -(b)(4)- mL; -- (b)(4)--- were filled with a target fill of -(b)(4)- mL. Measurement of the ----- (b)(4)----- showed that the fills achieved the



specification of mean value  $\pm 15\%$ . These placebo lots provided a bracketing approach to validate a maximum batch size range of approximately (b)(4)-.

The three consistency lots utilizing the Final Bulk Vaccine manufactured at Intercell were filled at (b)(4)- in July and August of 2007. The following table provides lot information:

<b>Lot</b>	(b)(4)-----	(b)(4)-----	(b)(4)-----
<b>Date of Final Bulk Vaccine manufacture</b>	(b)(4)-----	(b)(4)-----	(b)(4)-----
<b>Size</b>	(b)(4)-	(b)(4)-	(b)(4)-
<b>Date of Filling</b>	(b)(4)-----	(b)(4)-----	(b)(4)-----
<b>Number of Syringes</b>	(b)(4)-	(b)(4)-	(b)(4)-
<b>(b)(4)- lot number</b>	(b)(4)-----	(b)(4)-----	(b)(4)-----

Final Container Test results are as follows:

<b>Test</b>	<b>Specification</b>	<b>Results (by lot)</b>		
<b>Lot</b>		(b)(4)-----	(b)(4)-----	(b)(4)-----
<b>Appearance</b>	(b)(4)----- ----- ----- ----- -----	(b)(4)-	(b)(4)-	(b)(4)-
<b>Sterility</b>	(b)(4)----- -----	(b)(4)-	(b)(4)-	(b)(4)-
<b>(b)(4)-</b>	(b)(4)---	(b)(4)-	(b)(4)-	(b)(4)-
<b>(b)(4)---</b>	(b)(4)-----	(b)(4)-----	(b)(4)-----	(b)(4)-----
<b>Rabbit Pyrogen Test</b>	(b)(4)-----	(b)(4)-----	(b)(4)-----	(b)(4)-----
<b>Potency</b>	(b)(4)-	(b)(4)-	(b)(4)-	(b)(4)-
<b>Aluminum</b>	(b)(4)-----	(b)(4)-----	(b)(4)-----	(b)(4)-----
<b>(b)(4)-----</b>	(b)(4)-	(b)(4)-	(b)(4)-	(b)(4)-
<b>(b)(4)-----</b>				
<b>(b)(4)-----</b>				
<b>(b)(4)-----</b>	(b)(4)---	(b)(4)-	(b)(4)-	(b)(4)-

#### Media fills:

##### *Intercel-Bulk fill:*

Intercell states that three media transfer runs simulating aseptic filtration from (b)(4)-- -- through (b)(4)- sterilizing filters -----(b)(4)-----, and further aseptic formulation with aluminum hydroxide in (b)(4)- were successfully performed

All standard interventions which relate to potential asepsis were identified and carried out. Each media fill event was recorded by video.

Results observed for all testing yielded no growth in any filled --(b)(4)-- after incubation at (b)(4)- for --- (b)(4)---- and --(b)(4)-- for -----(b)(4)----- . At this point a sample of

media was taken and immediately examined under -----(b)(4)----- for signs of microbial growth. Media taken from successful media filled containers was tested at the end of the incubation period of each individual media fill for growth promotion testing. Environmental Monitoring (EM) was performed in rooms -----(b)(4)----- during each media fill. Results for all testing passed acceptance criteria, and one deviation was reported an out of specification for non-viable particulates in room -(b)(4)-. Intercell attributed this deviation to -----(b)(4)----- near the particle counter. Media fills also simulated worst case conditions, to include maximum batch size, non-routine interventions, and maximum number of operators present.

During review of the protocol for media fills during the PLI, procedures for the media fill were observed to be inadequate in that only --(b)(4)-- of the sterile-filtered media was incubated and observed for growth. Therefore, Intercell amended their procedures to allow for incubation of the entire filled lot, and repeated the media fill from June 20-23, 2008, incubating all of the filtered media. Media fill lots were -----(b)(4)----- -----(b)(4)-----. Intercell simulated the fill for the both the -----(b)(4)----- Final Bulk Vaccine. Results indicated no growth for any of the three lots filled, incubated in either Final Drug Substance or Final Bulk Vaccine formulation steps.

-(b)(4)- *Final container:*

The aseptic filling process in -----(b)(4)----- is re-validated ----(b)(4)----- ----- by process simulation trials (PSTs) carried out according to an SOP, using a -(b)(4)- approach. All operators are involved in ----(b)(4)--- PST in any 12-month period. The fill volume is -(b)(4)- mL into a -(b)(4)- ml syringe. The minimum number of units filled during the media fill is -(b)(4)-. The following limits are set:

- Alert limit: -----(b)(4)----- (an investigation will result and --(b)(4)-- -----, -----).
- Action limit: -----(b)(4)----- (re-validation is required; ----(b)(4)----- -----, -----).

Intercell provided the results of the most recent media fills performed by -(b)(4)- for this filling line, as follows:

	June 2006			April/May 2007		
Date						
Batch #	-(b)(4)-----	-(b)(4)-----	-(b)(4)-----	-(b)(4)-----	-(b)(4)-----	-(b)(4)-----
Filling	1 st	2 nd	3 rd	1 st	2 nd	3 rd
# filled/incubated	-(b)(4)-	-(b)(4)-	-(b)(4)-	-(b)(4)-	-(b)(4)-	-(b)(4)-
Total contaminated	0	0	0	0	0	0

(see **Questions for Applicant**, July 24, 2008 section, question 8)

#### Method Validation:

*Total Viable Count (---(b)(4)---):*

Intercell provided Validation Protocol VAL/ASSAY/122-P, but did not provide data from the executed protocol (see **Questions for Applicant**, Filing Letter Questions section, question #2). Intercell stated that qualifications will be carried out for each product to be tested as per PhEur 2.6.12, USP <61> (Suitability of the Counting Method in the Presence of the Product) and USP <1227> (Validation of Microbial Recovery from

Pharmacopoeial Articles). Intercell provided the Final Report for the protocol; the protocol's completion date was March 19, 2008. Testing was performed by filtration of --

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

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

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. Test samples and reference tests were performed ----- (b)(4) -----

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----- . Review of the data indicates that Intercell has successfully validated their Total Viable Count assay, and no deviations were observed during validation of the method.

*Sterility:*

Intercell performs sterility tests via the --- (b)(4) - method (----- (b)(4) -----) using the --- (b)(4) ----- method due to presence of aluminum hydroxide adjuvant. -- (b)(4) -----

-----

----- and the other with ----- (b)(4) -----.

----- (b)(4) ----- is added. The -----

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

----- . Units are visually examined for growth -- (b)(4) ---- during the - (b)(4) - incubation period. Intercell states that they perform the method according to USP <71> ----- (b)(4) ----- requirements.

Validation has been performed to exclude a bactericidal or fungicidal effect of the Final Vaccine during sterility testing (inhibition test). The media used for sterility testing must promote the growth of selected microorganisms, independent of whether the medium was in contact with the product or not. Test organisms used were appropriate.

The sterility test media ----- (b)(4) -----

cultures of the above organisms at -- (b)(4) --. The sterility media - (b)(4) - were - (b)(4) - at - (b)(4) -----.

Intercell states that all test organisms showed evident and comparable growth characteristics in ----- (b)(4) ----- during a - (b)(4) - testing of each medium with a - (b)(4) ---- -----, independent of whether the media had contact with the product or not.

*Bacterial Endotoxins:*

Intercell assays for endotoxin content by using a ----- (b)(4) ----- assay. The - (b)(4) -- ----- method is a ----- (b)(4) ----- for the detection of gram-negative bacterial endotoxin. - (b)(4) - of standard, sample and positive product control (for interfering/ enhancing factors) ----- (b)(4) -----

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----- is

monitored ----- (b)(4) ----- . The time required for the -----

----- (b)(4) ----- the amount of endotoxin present. Intercell states that the method complies with -- (b)(4) ----- USP <85>.

However, during the PAI it was observed (FDA form 483, number 1c) that the data from validation studies performed to validate the Assay was incomplete. Intercell supplied the

data on August 22, 2008, when responding to FDA form 483 observations. One deviation was described, as follows:

Insufficient endotoxin recovery was observed during the testing at process stage -(b)(4)- batch --- (b)(4) --. An investigation into potential sources of error was performed to determine possible reasons for the insufficient endotoxin recovery; no demonstrable root cause could be assigned. Due to the inconsistency of this result when compared to previous results (from the validation and routine in-process testing), the test was repeated in accordance with facility SOP using the same sample as used in the original test. The repeated test results of minimum inhibitory dilution -(b)(4)- were consistent with previous batch and with previous JEV commercial batches. Subsequently a third batch, --- (b)(4) ---, was tested and the expected endotoxin recovery achieved giving a minimum inhibitory dilution of -(b)(4)-. An addendum to the protocol VAL/ASSAY/126-P was executed with two further confirmatory batches (----- (b)(4) -----). Intercell stated that endotoxin recovery for both batches was consistent with previous results, both giving minimum inhibitory dilution of -- (b)(4) -. Intercell provided the full discrepancy report.

Review of the data from the validation study and the attached discrepancy report indicate that Intercell has adequately validated use of the chosen ----- (b)(4) ----- method.

*Sterile Filtration Validation:*

-(b)(4)- contracted -(b)(4)-, the manufacturer of the sterilizing grade filter utilized in the JEV Vaccine manufacturing process, to conduct a microbial retention validation study. The study was performed at -(b)(4)- using ----- (b)(4) ----- on the September 2, 2005. Described study methodology appears to be consistent with that outlined in ----- (b)(4) -----.

-(b)(4)- reported that previous pre-requisite qualification activities demonstrated that the test organism, (b)(4) ----- was viable in the product for a ----- (b)(4) ----- utilized ----- (b)(4) -----, each from a different batch, including one filter with a minimum quantitative bubble point specification. Each test filter was subject to a bacterial challenge of ----- (b)(4) ----- -- at a concentration ----- (b)(4) ----- of filter membrane, suspended in product under simulated process conditions. Acceptance criteria were as follows:

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

Filters tested were approximately -(b)(4)-fold smaller than manufacturing size utilized (-- (b)(4) -----). Experimental flow rate was ----- (b)(4) -----, as compared to the manufacturing sterile filtration flow rate of ----- (b)(4) -----, representing a -(b)(4)- fold difference. Comparing the difference in flow ----- (b)(4) ----- (b)(4) ----- filter. Therefore, the challenge represents a worst case regarding overall flow through the filter.

Testing results passed all acceptance criteria.

**Container Closure/Closure Integrity:**

*Bulk Container/Bulk Container Closure:*

The final bulk container is a -----(b)(4)-----, supplied sterile (---(b)(4)---- -----  
---) to Intercell. Intercell provided the technical product master file for the -----  
------(b)(4)-----

----- has completed an extensive list of biocompatibility tests for --(b)(4)--, to include tests demonstrating compliance with USP <87>, USP <88>, and ISO 10993-3, -4, and -11. -(b)(4)- also performed a bank of material interaction studies, to include chemical resistance studies, WFI storage stability, and extractables/leachables. Results of studies indicate product compatibility with Final Bulk Vaccine.

Intercell claims the ----(b)(4)----- meet the requirements of USP Plastic -----(b)(4)-----, and are in compliance with ISO 10993-1 for devices with external communicating devices with blood path, indirect. They meet also the requirements of USP Plastic -----(b)(4)----- and accelerated ageing corresponding to two years of natural ageing.

Intercell did not submit container closure integrity testing protocols and/or final reports for studies performed by Intercell for the -----(b)(4)----- used to Final Bulk Vaccine (see Filing Letter Questions, **Questions for Applicant** section, question #1). Lack of container closure integrity testing for the -----(b)(4)----- was also noted on FDA form 483, presented to Intercell at the close of the PAI.

Intercell addressed this apparent deficiency during the PAI and subsequent submissions. Intercell contracted the supplier, -(b)(4)-, to conduct container closure integrity test studies using -(b)(4)- filled at Intercell (filled with -----(b)(4)----- -- -----, per normal manufacturing procedures). -(b)(4)- were then evaluated via -----(b)(4)-----.

All filled -(b)(4)- passed acceptance criteria.

*Final Container/Final Container Closure:*

The vaccine is supplied as a pre-filled ----(b)(4)---- syringe containing a 0.5-mL single dose. The syringe system is comprised of an empty glass syringe barrel assembled with a ----(b)(4)----- The syringe contains a -----(b)(4)----- elastomer plunger/stopper. The syringe barrel is -----(b)(4)----- and the syringe plunger is --(b)(4)-- ----- The syringe barrels with mounted the ----(b)(4)----- are delivered ready to use. Further syringe details are supplied in the following table:

Component	Identity of material	Standard
Syringe barrel 1.25 ml	Type I ----(b)(4)--- glass	(b)(4)----- -----
Tip cap -(b)(4)-	(b)(4)----- -----	(b)(4)----- ----- -----
Plunger stopper	Formulation: (b)(4)----- -----	(b)(4)----- ----- -----

Component	Identity of material	Standard
Lubricant (plunger stopper, syringe barrel)	(b)(4)-----	(b)(4)----- ----- -----
Plunger rod	(b)(4)-----	(b)(4)----- ----- -----

Syringe barrels are sterilized by ---(b)(4)----- treatment to achieve a ----(b)(4)---- -----  
-----, stated validated per -----(b)(4)-----  
----- residue is --(b)(4)-- ----- and -----  
(b)(4)----- residue is -----(b)(4)----- revalidates the sterilization procedure quarterly.  
----- (b)(4)----- specification is less than -----(b)(4)----- assesses -----(b)(4)-----  
via the -(b)(4)- test, and was given approval for use of this test for -----(b)(4)----- and  
stoppers in 1980 and 1981, respectively. -(b)(4)- routinely tests each syringe lot for  
conformance to the --(b)(4)--- specification. -(b)(4)- reviews each lot's certificate, and  
inspects -----(b)(4)----- every -(b)(4)- years to ensure that the required  
standards continue to be met.

Plunger stoppers are -----(b)(4)----- process to achieve a --(b)(4)--,  
stated validated per -----(b)(4)-----  
----- Plunger stoppers must also pass the  
following requirements:

- USP <381> "Elastomeric Closures for Injection".
- --(b)(4)-----.
- --(b)(4)-----
- -----.
- --(b)(4)-----

Syringe barrels undergo the following in-process and final inspections to an -(b)(4)-  
according to an ISO 2859 single sample plan (standard level II): visual, dimensional,  
blocked barrel, leak test, lubrication and particulate count, functionality, packaging  
integrity/contamination. Plunger stoppers undergo the following in-process and final  
inspections to an -(b)(4)- according to an ISO 2859 single sample plan (standard level  
II): visual, dimensional, functional and particulate count and packaging integrity.  
Intercell performed studies to determine potential adsorption to container and  
leachables/extractables studies.

Adsorption to container:

Results observed during stability studies indicate absence of adsorption to container  
closure system (see Section 3.2.P.8) for the following parameters:

- (b)(4)-----  
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- (b)(4)-----  
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Leaching and Extractables:

Intercell/-(b)(4)- evaluated leachables from the final container closure by the extraction testing performed under protocol 0710/19495, Analysis of Extractables and Leachates from Container / Closure Systems (see 3.2.P.2.4-Appendix 3). Filled syringes from a technical fill of Final Bulk Vaccine Batch -----(b)(4)----- were stored upright to ensure no product contact with the rubber stopper or inverted to ensure to ensure product contact with the rubber stopper.

Batch -----(b)(4)----- was formulated on 14 July 2005 and filled on 24 March 2006 (- -----(b)(4)-----), so was stored in syringes for approx 15 months (inverted or upright) before to analysis. Prior to analysis the content of the samples was ----(b)(4)-----  
-----  
----- (b)(4)-----  
----- for plasticisers and other semi-volatile organic species amenable to the method.

The results of the testing performed are summarized below:

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

The complete list of tests, sans those performed by Intercell and -(b)(4)- and described above, may be found in the crossed referenced master file, and Intercell provided a detailed summary of all testing (Section 3.2.S.6). Review of Master File (CDER) -(b)(4)- indicates that -(b)(4)- complies with the stated reference standard with respect to sterilization and ---(b)(4)--- determination.

*Container Closure Integrity (CCI):*

**Bulk Container:**

Note: Intercell did not respond to the initial IR (see **Questions for Applicant:** Questions/requests submitted with the Filing Letter, Question 1) prior to the PLI, and was cited (FDA form 483, observation #11) during the PLI for lack of adequate integrity testing for their final bulk container. The firm's response is reviewed in the 483 response review memorandum.

**Final Container:**

-(b)(4)- performed CCI testing by subjecting -----(b)(4)-----  
-----  
-----

----- positive were also incorporated into the testing, and were prepared by -----(b)(4)-----  
These reference/control units do not undergo the test, and -(b)(4)- negative controls were prepared but did not undergo testing. Units were inspected visually for --(b)(4)--, and results of testing observed that none of the test units demonstrated a --(b)(4)--.

(See **Questions for Applicant** section)

**Shipping Validation:**

Intercell qualified shipment using -----(b)(4)----- filled with ----(b)(4)-----, according to protocol JEV/VP9-01. Each filled -(b)(4)- was conditioned at -(b)(4)- before being placed inside the standard shipping packaging system -----(b)(4)-----  
-- temperature monitors were located within the container, to ensure that all areas were temperature-mapped. The monitors were programmed to record temperature at --(b)(4)- intervals and had been conditioned at --(b)(4)-- prior to use. Once the monitors had been positioned and recording initiated, the container lid was secured in position and sealed with a tamper evident fastening. The containers were then sited in the GMP Quarantine Stores area, at an --(b)(4)-- temperature of --(b)(4)-- and left undisturbed for -(b)(4)--. Intercell claims that this adequately simulated the packaging of Final Bulk Vaccine and shipment in a -(b)(4)- temperature-controlled vehicle to the filling contractor. However, Intercell also demonstrated actual transport of the Final Bulk Vaccine from Livingston to ---(b)(4)--- using three ----(b)(4)----- filled with ----(b)(4)---- and -----(b)(4)----- as used for Final Bulk Vaccine. The --(b)(4)-  
- -----, in the same manner as Final Bulk Vaccine. Following shipment to -(b)(4)- using the validated temperature-controlled packaging and vehicle described above, the -(b)(4)- were inspected for integrity. The surface of the -(b)(4)- were -----(b)(4)----- . Following this, the -----(b)(4)----- and, after an -----(b)(4)----- , no growth within the -(b)(4)- could be seen. Samples, aseptically removed from the -(b)(4)- , confirmed this result.

This validation method would not normally be considered acceptable since Intercell did not actually ship and monitor temperature during shipment. However, Intercell stated that, although they considered the shipment method satisfactorily validated, the method was not found to be totally appropriate. A more robust method is to be used for commercial batches (described in Section 3.2.P.7.1.3), placing the ----(b)(4)----- Final Bulk Vaccine -(b)(4)- into a plastic container, security/tamper sealed and maintained at -(b)(4)- during transportation using -----(b)(4)----- . Calibrated data loggers will be used to monitor the temperature inside the container -----(b)(4)----- . Intercell stated that the results of this study would be provided as soon as available. The results of this study were reviewed during the PAI; results were acceptable.

#### **Facility Utilities:**

##### *HVAC:*

The HVAC system serving the JEV clean rooms is comprised of -(b)(4)- independent air handling units (AHUs), AHU -----(b)(4)-----  
-----, their associated changes and also pass through -----(b)(4)----- (Zone -(b)(4)-). -(b)(4)- dedicated extract fan units exhaust the air to atmosphere. Each supply air handling unit -----  
----(b)(4)----- . A supply fan and motor move the air through each system. The supply air handling units have ----(b)(4)-----  
----- allows the system to provide the cleanrooms with particulate free air at the required quality. Each room served by the HVAC systems has an air quality grade designed to comply with EU GMP requirements. All Grade -(b)(4)- rooms have been designed with a minimum of -(b)(4)- air changes per -(b)(4)-, all Grade -(b)(4)- rooms are designed with a minimum of -(b)(4)- air changes per -(b)(4)- and the Grade -(b)(4)- room is designed with a minimum of -(b)(4)- air changes per -(b)(4)-. Intercell states that



each HVAC system has been designed to condition the rooms, via its own -----(b)(4)-----, to a temperature of -(b)(4)- and a relative humidity of -(b)(4)- .

Differential pressures between rooms have been designed to provide a positive pressure cascade, with the exception of the Change Rooms for -(b)(4)- and -(b)(4)-. In general, the differential pressure is -(b)(4)- between each subsequent level in the pressure cascade. The exceptions to this are the JEV Change Lobby which is an uncontrolled area and as such the differential pressure to ambient is not specified; the differential pressure between JEV Clean Corridor and JEV Prep Area which is -(b)(4)- and the differential pressure between JEV Returns Corridor to the Exit Change/Lobby which is also -(b)(4)-.

The Change Rooms for -(b)(4)- and -(b)(4)- rooms are designed to be negative pressure sinks. They have a pressure lower than the -----(b)(4)----- and -(b)(4)- and -(b)(4)- to ensure that live virus does not contaminate the ----(b)(4)----- or other cleanrooms where live virus is not handled (-(b)(4)- and -(b)(4)- are the rooms where live virus is handled). Refer to the Establishment Inspection Report for review of HVAC validation, to include -- --- (b)(4)----- and HEPA filter validation, and all Facility Utilities validation.

#### *Plant Steam:*

Plant steam is used to provide humidification and heating for the Zone -(b)(4)- and Zone -(b)(4)- HVAC system. The humidity control is provided via steam injection humidifiers. The heating control is provided using a Low Pressure Hot Water system, which services the Air Handling Unit's frost and re-heat coils with -(b)(4)- water. The JEV clean rooms are maintained at environmental conditions of -(b)(4)- and a relative humidity of -(b)(4)- -(b)(4)-. Plant steam is also supplied to the -----(b)(4)----- autoclave. The Plant steam is supplied by a -----(b)(4)----- boiler.

#### *Compressed Air:*

Compressed air is used to actuate the pneumatically operated valves, -----(b)(4)-----, and for filter integrity testing. It is supplied by -(b)(4)- air compressors operating on a duty/standby set-up. The compressed air is provided at -----(b)(4)----- grade. -----(b)(4)----- . The particulate level is further reduced in the ----(b)(4)----- stream with the addition of a ----(b)(4)----- filter to remove any potential microbiological contaminants. Compressed air to the integrity tester in -(b)(4)- is passed through an activated carbon filter and two hydrophobic sterile grade filters prior to the point of use. Compressed air is routinely tested to assure physical and microbial quality. ----(b)(4)----- *Water:*

The -(b)(4)- unit is used to provide ----(b)(4)----- water for the Zone -(b)(4)- and Zone -(b)(4)- HVAC system. The -(b)(4)- supplies --(b)(4)-- water to the AHU's cooling coil at a temperature of -(b)(4)- enabling the AHU to maintain the environmental conditions described. The ----(b)(4)----- water system also provides primary cooling via -----(b)(4)----- to the -----(b)(4)----- filtration system and the -----(b)(4)----- autoclave.

#### *Standby Power Generation*

A standby generator will supply electricity to critical equipment within the clean rooms, facility and HVAC in the event of loss of mains electricity.

## Cleaning Validation:

### *Cleaning Validation of Major Process Equipment:*

The -----(b)(4)----- is the only major product contact equipment present for the manufacturing process. Cleaning of the system is accomplished as follows:

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

Intercell stated in the initial BLA submission that qualification of the cleaning of this equipment, according to the draft protocol provided in 3.2.S.2.5-Appendix 7, was on-going at the time of submission (see Filing Letter Questions, **Questions for Applicant** section). During the PLI, it was noted on FDA form 483 that the cleaning validation was still not completed, as Intercell's first attempt at cleaning validation had not 1) met final rinse acceptance criteria for bioburden, post cleaning, and 2) provided appropriate rationale for conductivity acceptance criteria. Intercell had attributed out of specification bioburden to a sampling error, but did not perform additional runs post corrective action. Intercell subsequently repeated testing in response to the FDA form 483 observation. Repeat cleaning validation met all acceptance criteria, and Intercell provided appropriate rationale for conductivity limits, post-cleaning.

Storage conditions and validated storage duration, as well as cleaning of filter --(b)(4)-- are not applicable to Intercell's -(b)(4)- system, as all --(b)(4)-- are replaced --(b)(4)-- -----.

### *Cleaning Validation – -(b)(4)- Fill Facility:*

Intercell did not initially submit fill facility cleaning validation studies for review (see Filing Letter Questions, **Questions for Applicant** section, Question #4). Intercell supplied the fill facility cleaning validation on July 24, 2008 and September 30, 2008. Filling of JEV vaccine at -(b)(4)- in performed in clean room -(b)(4)- using dedicated --- (b)(4)--, filling pumps and filling needles. Aseptic connectors and all tubing are ----- (b)(4)----- has performed a cleaning validation that assures that no more than ----- (b)(4)----- product carry-over from each batch. Initially, a risk assessment was performed to evaluate equipment parts critical or with highest potential risk of product contamination. -(b)(4)- determined that the -----(b)(4)-----, filling pumps and filling needles are most critical, as a whole system, and evaluated rinse samples from them.

Briefly, cleaning procedures are as follows:

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

Acceptance criteria were as follows:

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

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

Intercell failed to provide the final report and summary data for these cleaning validation studies. (see **Questions for Applicant** section)

**Process Equipment/Equipment Validation:**

The -----(b)(4)----- is the only major product contact equipment present for the manufacturing process. These systems include a -----(b)(4)----- -----  
-----  
-----  
The system's -----(b)(4)---- is compatible with the recommended  
suspended screen -----(b)(4)---- recommended.

IQ/OQ included Documentation Verification, Drawing Verification, Installation Verification, Utility Verification, Product Contact Parts Verification, Control System Checks, Input/Output Verification/Alarm Verification, Calibration Verification, Operational Verification, a Riboflavin Clearance Test, Operator Training Verification, and an SOP check. IQ/OQ testing was satisfactory.

The PQ for the -(b)(4)- system was performed as part of execution of the conformance lots. Conformance lots met acceptance criteria, post ultrafiltration.

**Questions for Applicant:**

Questions/requests submitted with the Filing Letter:

1. Please provide any container closure integrity testing protocols and final reports for studies performed by Intercell for the -----(b)(4)----- used to store sterile filtered bulk, if any. If no testing has been performed, please provide a justification why leak testing, as performed by -(b)(4)-, adequately satisfies this requirement.
2. In section 3.2.S.2.4, appendix 7, you state that validation of your method to determine --(b)(4)-- total available count is ongoing. Please state when the validation for this method will be complete and submitted to the Agency.
3. Similar to question 2, when will the cleaning validation for equipment be complete and submitted? (See section 3.2.S.2.5.6, page 22 of 23)
4. Please submit cleaning, cleaning validation and fill changeover procedures for the fill line at -(b)(4)-.

Submitted to Intercell July 24, 2008:

1. Please provide a list of other products filled in Clean Room -(b)(4)-, Building -----  
------(b)(4)-----.
2. Please provide the pharmacological criteria, as stated in -(b)(4)- cleaning validation protocol 1750507-1, used to establish -(b)(4)- maximum allowable carryover limits for cleaning.
3. Please provide the complete sterilization validation for the final container and plunger stopper used with the final container.
4. Please provide the complete container closure integrity test protocol and final report for the final JEV container. Please also provide a correlation between visual detection of ----(b)(4)---- and an analytical method that provides quantitative results.
5. Please comment on the similarity of the placebo solution, used for samples in the -(b)(4)- syringe leachables/extractables study, to the final JEV drug product.
6. Please provide all details (defect limits, -(b)(4)-, ect) for -(b)(4)- visual inspection program.
7. Please clearly state that ------(b)(4)----- sterilization is accomplished via -----  
(b)(4)----- as described in section 3.2.P.5.5.

8. Please comment on similarity of the syringes used in -(b)(4)- media fills are of similar type to that used as the final JEV container.

Submitted to Intercell September 5, 2008:

1. Please submit the final report for adjuvant -----(b)(4)-----.
2. Please submit the final report for -(b)(4)- Validation protocol document number 1750507-1, Cleaning Validation, Initial Validation, JEV.

### **Applicant Responses:**

Questions submitted with the filing letter were submitted to the Product Office on February 29, 2008. The deficiencies noted here were not resolved prior to the PLI and so were also reflected as observations on FDA form 483 issued at the close of the PLI. Questions 1 through 3 were satisfied in Intercell's responses to FDA form 483, issued to the firm May 15, 2008. Please see the 483 response review memo entitled for a more detailed review of these responses.

Intercell provided the response to Question 4 on August 11, 2008. Cleaning, cleaning validation and fill changeover procedures appear acceptable (see descriptions of procedures, above). -(b)(4)- "Pharmacological Criteria stated in validation protocol 1750507-1, used to establish -(b)(4)- maximum allowable carryover limits for cleaning, appeared unclear (see July 24, 2008, **Questions for Applicant** section, Question #2). The -(b)(4)- Cleaning Validation Final Report was not submitted (see September 5, 2008, **Questions for Applicant** section, Question #2).

Intercell responded to the July 24, 2008 questions on August 11, 2008.

1. Intercell stated that a complete list was provided in the BLA in section 3.2.A.1. They also noted that no beta-lactams, no cytotoxic products, nor live or attenuated virus and microorganism products, are handled at the -----(b)(4)----- plant. Review of the list and this response indicates that filling of the JEV vaccine in Room -(b)(4)- is appropriate.
2. Intercell stated that the pharmacological criterion used for cleaning validation at -(b)(4)- is defined as -----(b)(4)-----, and provided a link to calculations made to determine the evaporation residue limit for cleaning validation. This response is acceptable.
3. Please see **Container Closure/Closure Integrity: Final Container/Final Container Closure** for a detailed review. Intercell referred to the crossed referenced DMF. This DMF has been reviewed, additionally; information contained in this DMF appeared acceptable after my review. Therefore, this response is acceptable.
4. Please also see **Container Closure/Closure Integrity: Final Container/Final Container Closure**

Intercell responded as follows:

The -----(b)(4)----- test method was validated independent from the container closure system. The test method validation included:

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

The results of the validation demonstrated that:

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

This response was not acceptable because it did not provide a link between the minimum amount of -(b)(4)- detectable and the amount of -(b)(4)-- resulting from a worst case leak of approximately --(b)(4)-- under the overpressure conditions used during the container closure integrity evaluation. This was communicated to -(b)(4)- and Intercell personnel.

On September 5, 2008 Intercell provided -(b)(4)- response, as follows:

During this CCI challenge, the -----(b)(4)----- containing -----  
(b)(4)----- solution. Using -----(b)(4)-----, it can be shown that the test is  
sensitive enough to pass the threshold -(b)(4)- concentration of ---(b)(4)-- which can be  
detected visually.

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

[ --(b)(4)-- ]

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

[ -----(b)(4)----- ]

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

[ -----(b)(4)-----  
----- ]

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

(b)(4)  
 \_\_\_\_\_  
 \_\_\_\_\_  
 \_\_\_\_\_  
 (b)(4)  
 \_\_\_\_\_  
 \_\_\_\_\_  
 \_\_\_\_\_  
 \_\_\_\_\_

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

5. Intercell stated that the placebo solution used in the -(b)(4)- syringe leachables / extractables study was an -----(b)(4)-----

(b)(4)----- solution is equivalent to those in the final JEV drug product. Hence, it can be considered -(b)(4)- formulation for the actual drug product with regards to leachables/extractables. This response is acceptable.

(b)(4)

- \_\_\_\_\_  
 \_\_\_\_\_
- \_\_\_\_\_  
 \_\_\_\_\_  
 \_\_\_\_\_  
 \_\_\_\_\_  
 \_\_\_\_\_

-----  
-----  
After finalization of the inspection, the total number of defects per defect class is calculated. A plausibility calculation is made taking into account the size of the incoming lot, the number of good pieces and the number of the rejects after visual inspection. - (b)(4)- defect limits are provided in Amendment 8 of the BLA.

-(b)(4)- current -(b)(4)- levels are as follows:

- Minor: -----(b)(4)-----  
-----
- Major: -----(b)(4)-----  
-----
- Critical: -----(b)(4)-----  
----- (b)(4)-----

If the -(b)(4)- of the -(b)(4)- pieces of one inspector does not conform to set limits, but the limit for the whole batch (i.e. a sample of -(b)(4)- pieces) is not exceeded, then the good pieces of the inspector in question must be re-inspected by another inspector. However, if the limit for the whole batch is exceeded, then the whole batch is of course being re-inspected.

-(b)(4)- Visual Inspection Program appears acceptable.

7. Intercell confirmed that the Aluminum Hydroxide used in the formulation of JEV is --  
----- (b)(4)----- . A -----

---(b)(4)----- is administered. (see September 5, 2008, **Questions for Applicant section**, Question #1)

8. Intercell confirmed that the syringes with ----- (b)(4)----- closure part - as well as the stoppers – used in the media fills are identical to those to be used for the commercial JEV production process at -(b)(4)-. This response is acceptable.

Final question contained within the Complete Response letter (see also the **Summary** section, above):

- As per our previous conversation earlier this month, the final report for adjuvant -----  
---(b)(4)----- has not been submitted to your BLA. Please submit this final report for review.

Intercell responded as follows:

In order to determine the efficacy of the ----- (b)(4)----- sterilization process, biological indicators were placed in packaged loads of ----- (b)(4)----- raw material, subjected to the standard ---(b)(4)--- process and returned for incubation in the appropriate medium, to determine the survival of the organisms. Intercell Biomedical prepares and packages ----- (b)(4)----- , which are sent to -(b)(4)- for ----- (b)(4)----- . The delivered dose in the ----- (b)(4)----- packs achieves the requested dose specification of ----- (b)(4)----- .

Intercell prepared ----- (b)(4)----- per standard procedure into -----(b)(4)----- . These -(b)(4)- were shipped to -(b)(4)- who conducted testing that included placement of -(b)(4)- bioindicator strips ( ----- (b)(4)----- ) internally within the standard sterilization load ( ----- (b)(4)----- ), and an additionally -(b)(4)- bioindicator strips on -----(b)(4)----- of

the cardboard box used to hold the load. External ---(b)(4)--- were also utilized in the testing.

Results of testing observed that no bioindicator strip demonstrated growth, post-cycle, that all positive controls exhibited growth, and that all negative controls demonstrated no growth. Therefore, this response is acceptable.