

Cell Substrate Review -IXIARO

BLA STN#: 125280

Sponsor: Intercell

Product: IXIARO (Japanese encephalitis vaccine, purified, inactivated)

To: The File – 125280/0

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Subject: Cell substrate review and approval recommendation.

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Cell substrates/adventitious agents overview.

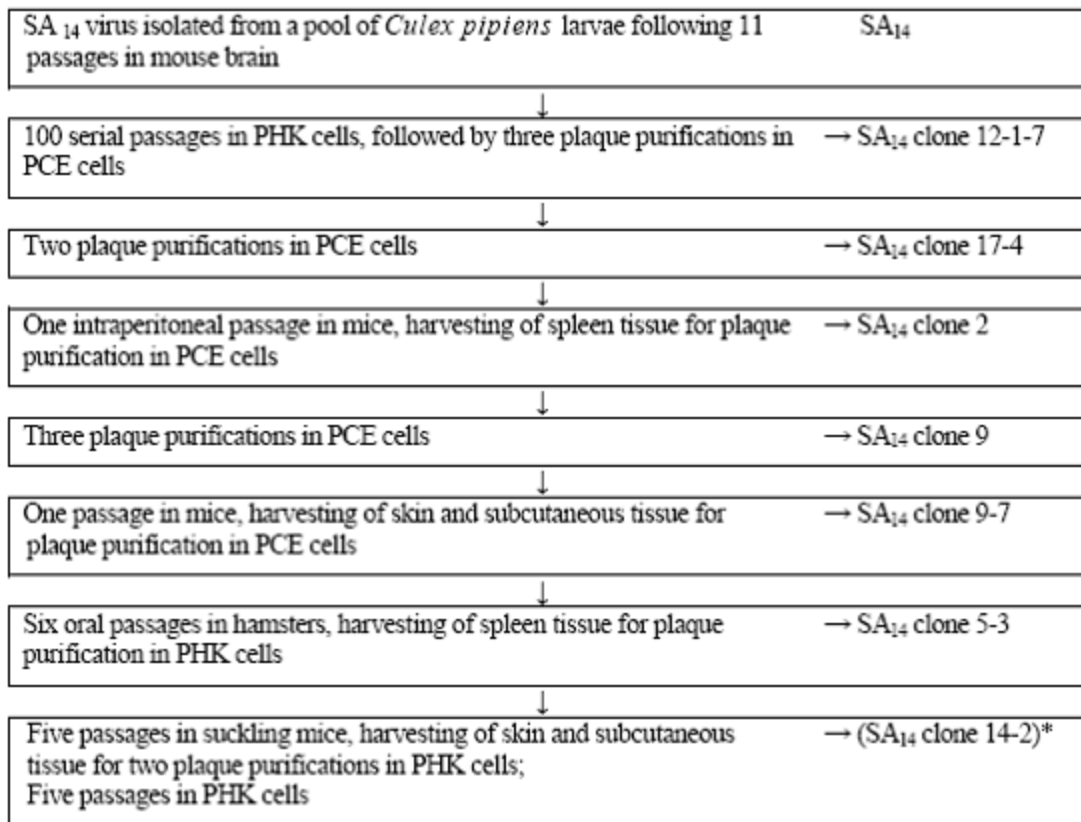
IXIARO is JE virus strain SA 14-14-2 grown in Vero cells, -(b)(4)--purified, formalin inactivated, then adjuvanted with alum. Adventitious agent contamination of the product could theoretically come from three sources: the virus seed, the Vero cell bank used to grow the virus, or accidental introduction during the manufacturing process itself. The first two potential concerns are the subject of this review, the manufacturing process and its controls are reviewed elsewhere by Dr. Li Yu.

In summary, the information in the BLA documents that the JE SA 14-14-2 working virus seed bank and the Vero cell banks are well made, well-characterized, and are free of adventitious agent concerns. Based on this, I recommend approval of this BLA.

Passage history of the JE SA 14-14-2 virus.

The parental JE virus was originally isolated from mosquitoes and then passaged a large number of times, in China. This is summarized in Figure 3.2.S.2.3.1-2, shown below.

Figure 3.2.S.2.3.1-2: Development History of SA₁₄ 14-2 Virus



Notes: PCE: primary chicken embryo; PHK: primary hamster kidney.
* The notation SA₁₄ clone 14-2 is abbreviated to SA₁₄-14-2

In 1986, the SA 14-14-2 virus was adapted to grow in primary dog kidney cells by researchers at WRAIR, -----(b)(4)-----

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

The risks of adventitious agent contamination will be considered separately for the JE SA 14-14-2 virus prepared in China, the dog kidney cell adaptation at WRAIR; the Vero cell bank, Vero cell adaptation, and master virus seed process at -(b)(4)-, and finally the working virus seed preparation at Intercell.

Isolation of JE SA 14-14-2 in China

There is no information in the BLA about the preparation or testing of the JE SA 14-14-2 virus from China. Given that the virus was passaged in numerous cell types and animals over the course of many years - see Figure 3.2.S.2.3.1-2 above – there were plenty of opportunities to pick up viral (or microbial) contaminants. Still, these concerns are alleviated by the fact that the eventual virus seeds are well-tested for adventitious

agents. Also, the product is formalin-inactivated, and section 3.2.A.2 presents data validating that the inactivation process kills between -(b)(4)- and -(b)(4)- logs of three different test viruses. Therefore, there are no concerns regarding adventitious viral agents.

With regard to the possibility of TSE contamination, the work leading up to the penultimate SA 14 clone 5-3 was completed and published in the literature by 1973, and thus is not a concern. The work describing the last passages in mice and primary hamster kidney cells leading to JE SA 14-14-2 was published in 1981. Given that the passaging likely occurred in China in 1980 or before, there are no concerns regarding TSE agents in preparations sourced from China.

Adaptation of JE SA 14-14-2 to growth in primary dog kidney (PDK) cells.

There is a very brief description of the process used to make the PDK cells, and the passaging of the JE SA 14-14-2 virus, in a 1988 paper from the literature reproduced as Annex II of 3.2.A.2.2.1 Appendix 9. The PDK cells were prepared by the Salk Institute from healthy 9-week old male Beagles, and were frozen on liquid nitrogen until use. Animals were necropsied to confirm the absence of any obvious diseases or neoplasms. Cells were tested by broth and agar inoculation for microbial sterility and absence of mycoplasma. Cells were also shown not to react with a polyvalent antiserum specific to four canine adventitious viral agents. Despite the absence of details, the testing done provides some assurance that the cells were not contaminated with microbes or viruses.

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(b)(4)----- seed still induces neutralizing antibodies in the -(b)(4)- potency assay similar to the original virus seed.

**19 pages determined to be not releasable:
(b)(4)**