

REVIEW MEMORANDUM

Date: 12/15/2012

Reviewer: Phil Krause, M.D., FDA/CBER/OVRR

Through: Robin Levis, Ph.D., FDA/CBER/OVRR/DVP

To: File

Potency assay

Varizig (Cangene)

Material reviewed: BLA 125430 original submission plus amendment 15 submitted 12/7/12

Executive summary:

The ---b(4)----- is fit for use in evaluating b(4) drug substance and assigning potency to drug product. Additional variability could be introduced by using non-WHO standards, so the sponsor has agreed to use only the WHO standard until sufficient data can be provided and evaluated (in a subsequent supplement) to qualify an alternative standard for use. The -b(4)----- assay provides a reasonable surrogate for product effectiveness, meeting the key criterion for a potency assay.

Summary of data provided:

-b(4)- potency assays are proposed for use with VARIZIG. A Varicella -b(4)----- is the primary assay proposed for use. It will be used at the -b(4)----- level to determine dilution factors, and at the drug product level with a specification of b(4) 125 I.U./vial. The -b(4)----- is being used for information purposes (report results) only at this stage, and is proposed for later use subject to future validation. Thus, the current proposal hinges on the -b(4)-----, which is the assay on which this review focuses.

The -b(4)----- was recalled in -b(4)-----, due to difficulties with the positive control standard. However, the positive control that is supplied with the b(4) is not used in these assays, since a -b(4)----- product is used instead. Thus, the recent recall has no impact on the use of this b(4) for this purpose. The -b(4)----- is the same as the --b(4)-----, which was always manufactured by -b(4)----- but responsibility for marketing was recently returned from -b(4)-----

The -b(4)-- measures anti VZV antibodies based on the mix of VZV antigens present on the plate. Because the most abundant anti-VZV antibodies in humans with anti-VZV antibodies are directed against gE (the major neutralizing target), and gE is also a highly abundant virus glycoprotein, this assay measures antibodies that are likely to correlate with product effect. Even if the assay detected antibodies other than those directly linked to the mechanism of action, because those antibodies would (on average) be present in concentrations roughly proportional to anti-gE neutralizing antibodies in immune human

serum, an –b(4)-- that measures anti VZV antibodies in human serum (or a serum-derived IgG product) is expected to correlate well with neutralization. Thus, a VZV –b(4)----- is a reasonable assay to use for the purpose of testing Varizig potency.

The –b(4)---- is a considerably more sensitive assay than a standard –b(4)---, because the ---b(4)----- . In our experience with the VZV vaccine, ---b(4)----- at levels that correlated even with undetectable antibody levels by –b(4)- showed some evidence of protection. Thus, use of the less sensitive –b(4)---- is not expected to cause any problems relative to the use of the more sensitive –b(4)-----, since protective levels of antibodies are within the range of this assay.

This assay is also likely to be useful if vaccinees were used as donors. Substituting vaccinees for naturally infected donors would not likely cause a change in the antibody specificity or efficacy, since we know that vaccine induced antibody levels correlate with protection. Because VZV is a DNA virus, the VZV polymerase has high fidelity and there are no known strains that escape the vaccine. Thus, as long as quantity of antibody is held constant, quality of antibody from vaccinees is not expected to cause any difficulties.

In theory, an –b(4)-- assay could potentially measure some kind of non-specific immune response that is also present in the international standard (for instance, to some cellular antigen). However, this is very unlikely in this instance because the international standard used to standardize the assay is prepared from humans who would not have immune responses to non-varicella components of these cell lysates.

The proposed assay control is either the WHO international standard (at 50 I.U./vial) or a lot of Cangene product. Data regarding lot 407501 that was used in the clinical trials and that has been standardized to the WHO international standard (based on 5 replicates, potency is 94 I.U./ml) is provided, but the manufacturer clarified in a telephone call that this lot is no longer available for use as a standard. Other unspecified lots of Cangene product are also proposed for use as a reference standard in the future. At least –b(4)----- - points of the assay reference must be included in the standard curve. In the validation studies, both the WHO standard and –b(4)----- of Cangene product were used. Because the b(4) of Cangene product was standardized to the WHO standard, there is a risk of propagation of errors if a b(4) of Cangene product were to be used as assay standard. Thus, until additional information is provided about the potency assignment for an alternative standard, I do not recommend using any standard other than the WHO standard

The following table 1 summarizes the result of the –b(4)----- validation.

[b(4)]

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b(4)

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b(4)

Table 1. $\neg b(4)$ ----- validation results

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b(4)

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b(4)

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b(4)

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The underlying data support the conclusions of the assay validation as shown in the above tables. While the general statistical success criteria for the assay validation are not those that I would recommend (in particular, those for which $p > 0.05$ is used are not ideal), the overall validation conclusions are nonetheless valid and show fitness of this assay for use.

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

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