DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

Our Reference: BL 125426/0

Cangene Corporation
Attention: Mr. Steve McGregor
January 22, 2015
Sent by email

Dear Mr. McGregor:

We are reviewing your biologics license application (BLA) dated April 5, 2012 for Coagulation Factor IX (Recombinant). We determined that the following information is necessary to continue our review:

1. Regarding your response to Item 1a in the IR letter dated December 10, 2014, we agree that the two one-sided t-test (TOST) is an appropriate test to evaluate statistical equivalency between two datasets. However, if you replace the EAC value from equations v and vi (on page 2 of 12) into equations ii and i (on page 2 of 12), respectively, your testing procedure is simply reduced to assess whether the mean of dataset 2 falls between the LEDL (minimum of dataset 1) and UEDL (maximum of dataset 1). The parameters ME and EAC play none to minimal role indeed. This can be further confirmed from the example you provide on page 3 of 12.
   We don't agree with this approach for the following reasons.

   a. The range of dataset 1 may be very large in the presence of extreme values.

   b. Comparing the mean of dataset 2 to the minimum and maximum values of dataset 1 is an extremely loose test. For example, in a rare situation, if 50% of dataset 2 points have values less than the minimum value of dataset 1, and the other 50% of dataset 2 points have values greater than the maximum value of dataset 1, then it is likely that equivalence will still be established.

   c. It indeed does not take the variability of dataset 1 into account as ME gets cancelled out in the substitution mentioned above.

   Therefore, your procedure poses a great risk to falsely claim equivalence for two potentially very different datasets. Please propose a more strict testing procedure which takes the data variability into account.

The review of this submission is on-going and issues may be added, expanded upon, or modified as we continue to review this submission.

Please submit your response to this information request as an amendment to this file by February 5, 2015 referencing the date of this request. If you anticipate you will not be able to respond by this date, please contact the Agency immediately so a new response date can be identified.

If we determine that your response to this information request constitutes a major amendment, we will notify you in writing.

The action due date for this file is April 29, 2015.

Please send an acknowledgement message for receipt of this request.

If you have any questions, please contact me at (240) 402-8443.

Sincerely,

Edward Thompson
Regulatory Project Manager
FDA/CBER/OBRR/RPMS