Telephone Conference Memorandum - 5/2/2007 - AFLURIA

- **TELEPHONE CONFERENCE MEMORANDUM**

STN 125254: CTD BLA for Influenza Virus Vaccine
SPONSOR: CSL Limited
PRODUCT: Influenza Virus Vaccine
DATE: May 2, 2007
Facsimile sent: May 2, 2007
CBER REPRESENTATIVE:
Katherine Berkhousen
CSL REPRESENTATIVE:
Paul Hartman
Tel: 610-878-4644
Fax: 610-878-4182
SUMMARY:
CBER has identified some problematic areas of the ---- data sets which are communicated to CSL via facsimile. Listed below are some examples of the problems we are encountering. CBER has requested a telephone conference call as soon as possible to discuss these concerns.

1. The variable 'SEX' is defined in the "Define.pdf" document as:
2. 0=male
   1=female.

When examining the PATIDD dataset, the sex variable includes only values of 1 or 2. Thus we are unsure what numerical value is associated with either gender.
We suggest you resubmit the dataset with a variable sex_c (i.e. a categorical version of sex);
Sex_c: "Male"
"Female"

2. There are many variables with responses indicated with numerical values (0, 1, 2, 3, etc.) in many cases. Utilizing text to clearly describe the response values would be helpful.

For example, in many variables that include treatment (trt, trttrue, treatrand, etc) the following notation is used: T1, T2, T3, T4, T5, this does not provide a clear indication of the type of treatment administered or received. **We suggest using the following responses would be more helpful then the integer values**:
Treatment_c: "Bulk Lot #1"
"Bulk Lot #2"
"Bulk Lot #3"
"Syringe"
"Placebo"

Similarly for antigen, rather than the numerical values of 1, 2, 3 it would be more helpful to use an accurate descriptor of the antigen which is being assayed:

> Antigen_c: "H1N1"
> "H3N1"
> "B-strain"

We would prefer the sites be more self explanatory. Thus we suggest creating a variable site_c that includes information about the specific site.

> Site_c: "St. Louis"
> "Cincinnati"
> "U. Rochester"
> "U. Maryland"
> "Baylor"
> "U. Iowa"
> "Vanderbilt"
> "Duke"
> "Stanford"

Many other variables in the various datasets utilize numerical values rather than more obvious categorical responses (this includes but is not limited to: discont, pos_pro, conmed, faltern, head, etc.).
Please provide datasets which include categorical variables which represent more clearly the response provided.

3. Please provide a clearly labeled variable which represents the assay value of the various antigens in the HAIDD dataset.

We are unclear what the GMT variable represents, in the HAIDD dataset. This value should be the combined log(titer) of all observations in a treatment group. We assume you have simply pooled all titers for each treatment group. If this is not the case, please indicate what "GMT" is.

4. When providing these revised datasets, it would be helpful if each dataset could include basic demographic information including (but not necessarily limited to):

Race_c (we would prefer this variable include all races represented: Caucasian, Asian, Black, Hispanic, Pacific, Native American)

> Age,
> Sex_c,
> Discont_c

5. The variable sero_con includes only the response if the subjects were sero_negative at baseline. Please generate a variable that combines the results of sero_con and sign_inc and establishes if a subject "sero_responded" (i.e. if they sero-converted or had a significant increase in titer over time).
6. Please provide all statistical programs necessary to properly incorporate the use of the CSL defined ***formats*** in all dataset provided in the submission.
7. Please provide any statistical programs utilized in the analysis of efficacy, reactogenicity and adverse event responses. Additionally please provide

documentation of any of these programs as well as any Macro's used to perform statistical analysis.

8. The original Case Report Forms (CRF) do not appear to be available in any submissions. Please provide all CRFs. Specifically we request the following data which we are unable to locate:
   CSL FLU-05-09

a. CRF for subject 27FVD137: serum sickness, unsolicited AE, vaccine-associated, moderate intensity, ongoing at end of study.
b. Subject 27FVD153 (request CRF)had a negative screening pregnancy test, then tested positive on study day 21. Was to be followed to term.
c. We do not see CRFs other than for the single SAE. Please comment.

9. Please explicitly provide the 5 treatment group information in all data sets. Additionally please create a variable which combines all 3 lot data. We suggest that this categorical variable be defined as:
   Reductetrt_c= "Syringe"

"Bulk Lot"
"Placebo"

10. In the .xtp dataset PATINFDD, please provide insight as to why the pre-blood and post blood dates the are the same?
11. We note that the Per Protocol population excluded the 101 subjects at the Vanderbilt site whose vaccine was stored improperly, but that the immunogenicity analysis is based on the Evaluable Population. Please repeat the immunogenicity analysis on the Per Protocol population using the same endpoints as was done for the Evaluable Population. Alternatively, you could perform the immunogenicity analysis on the subset of the 101 subjects above who were excluded from the per protocol analysis.
12. For each subject in the HAIDD database, please calculate and provide to us the study day on which the post-vaccination titer was drawn, e.g. Day 24, in addition to the actual date of visit 3.