

Telecon with CBER and Dynavax Sept 30, 2016

Dynavax Participants:

Biostats / Biometrics

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Dynavax contacted CBER on September 22, 2016 and requested a telecon to discuss the draft version of the Dataset and Excel spreadsheet, to confirm the format, and to help orient the CBER reviewers once the actual datasets and spreadsheets are submitted. Dynavax agreed that this was the intent of the telecon and stated they wanted to review the structure of the datasets/spreadsheets with the review team to clarify any potential CBER questions about the proposed structure. CBER stated that they cannot make any commitment that the data sets are acceptable and meet expectation without a full review. Dynavax concurred.

Dynavax attempted to clarify the per protocol definitions for the Non-Inferiority Per Protocol Population (NIPPFLG) and the Lot Consistency Per Protocol Population (LCPFLG) by projecting a slide that listed the criteria and time points that if met made a subject eligible for inclusion in the relative per protocol analysis populations. .

Dynavax also projected a slide that listed submissions, submission timelines, and whether or not the submission was accurate. Dynavax reminded us that revised datasets for Study HBV-10 and HBV-16 were submitted on the following dates: March 15, 2016, April 8, 2016, and May 27, 2016, and that a manual spreadsheet entitled HBV016_EX.XPT was submitted on July 12, 2016. They noted that the revised datasets submitted on May 27th and July 12th were correct but the other submissions contained some errors.

CBER asked if Dynavax re-reviewed all the data themselves to look for additional errors or if they only focused on identifying and corroborating the errors that CBER had identified.

Dynavax responded that they performed a 'spot check' of the ADSL dataset and did not find any errors in addition to what CBER already identified. Dynavax added that they did not look at other data/datasets for inaccuracies. .

Dynavax projected the master-dataset that concatenated the 2012 ADSL and 2016 ADSL datasets and included the identifiers and columns that CBER requested in the IR dated September 9, 2016. CBER asked that Dynavax include an additional column that identifies the unique subject ID and year (e.g. 101_2016), so that reviewers can manipulate the data and retain the ability to easily discriminate between each data row by subject ID_year.

Discussion continued regarding the Excel file. Dynavax projected the demo Excel file and a specific subject was used as an example to highlight and explain the various columns. CBER made several comments regarding the Excel file:

1. CBER pointed out that the Excel datasets seemed to only address subjects for which changes were made; however, CBER's IR of Sep 9, 2016 requested a separate Excel file that replicates each dataset and provides additional information to describe changes from 2012 to 2016. CBER requested that Dynavax add a new 'tab' with data from all subjects which would mirror the dataset.
2. CBER asked Dynavax to highlight the entire row if any change was made.
3. CBER asked that all per protocol outcomes be moved to the 2016 row, as opposed Dynavax's proposal to have subjects who were originally excluded in 2012 have outcomes listed in the 2012 row and subjects who were newly excluded in 2016 have outcomes listed in the 2016 row. Dynavax explained their rationale for doing it the way they did; however, since all outcomes in the revised datasets occurred in 2016 and none occurred in 2012, CBER requested the modification to facilitate accurate interpretation and ease of manipulation of the data.

CBER questioned why Dynavax had denoted Engerix-B subjects as included in the LCPFLG column, as they would not have been part of the data analysis population for the lot consistency evaluation. Dynavax stated that they applied NIPP and LCPP flags to everyone who was 'eligible' for inclusion in the populations. CBER asked Dynavax what variable specified whether subjects were actually included in the respective analysis populations, rather than merely being eligible for inclusion in the analysis. Dynavax said there wasn't such a variable. CBER asked how one would know which subjects were actually included in the analysis populations. Dynavax stated it wasn't possible and acknowledged that that wouldn't have been apparent. Dynavax confirmed that this was the case for both the LCPP and the NIPP but that this was only the case for study HBV-16, and not for studies HBV-10 and HBV-23. They offered to revise the spreadsheets to exclude Engerix-B subjects but the spreadsheets then would differ from the datasets. CBER reiterated that the spreadsheets and the datasets should be consistent, and that the datasets should be structured so that CBER could use them to obtain accurate analyses. Dynavax discussed their logic of including the Engerix-B subjects and offered to provide their logic for preparing the datasets. CBER stated that it needed to be clear which subjects were included in any analysis populations, not just which subjects were eligible for inclusion but might not have been ultimately excluded from the analyses. Dynavax offered to add additional columns to the HBV-16 ADSL dataset to denote the subjects that were actually included in the NIPP and LCPP per protocol populations. Dynavax agreed to provide the following:

Master ADSL Datasets (response to Item 24a):

- HBV-10 (2012 and 2016 merged)
- HBV-16 (2012 and 2016 merged).
 - Additional variable for **SUBJID** that will include the year (2012 or 2016).
 - For example, Subject 20301 will show: 20301-**2012** and 20301-**2016**
 - Two additional variables: One to indicate whether or not a subject was included in the non-inferiority analysis and a separate variable to indicate whether or not the subject was included in the lot-consistency analysis

Excel Files (response to Item 24b)

- HBV-10 (2012 and 2016 merged)
 - One Worksheet (mirror of Master ADSL Dataset) which represents the Per-Protocol Population and changes between 2012 and 2016
- HBV-16 (2012 and 2016 merged)

- An additional tab/worksheet containing a mirror of Master ADSL Dataset (Excel Master File)
 - highlight the entire row for a subject where their Status changed from 2012 to 2016
- 2nd worksheet (extracted from the Excel Master File, subset for those subjects with changes to NIPP and/or LCPP)
 - Two additional variables: One to indicate whether or not a subject was included in the non-inferiority analysis and a separate variable to indicate whether or not the subject was included in the lot-consistency analysis
- 3rd NIPP worksheet (for only those with changes to NIPP)
 - Additional variable to indicate whether or not a subject was included in the non-inferiority analysis
- 4th LCPP worksheet for only those with changes to LCPP)
 - Additional variable to indicate whether or not a subject was included in the lot-consistency analysis

Also, as part of their response to Item **24c**, Dynavax will provide an explanation of the methodology / logic for preparing the datasets.

This concluded the call.