

RECORD OF TELEPHONE CONVERSATION

Submission Information

Application Type	BLA
STN	125428/0.0
Review Office	OVRR
Applicant	Dynavax Technologies Corporation / Lic. # 1883
Product	Hepatitis B Vaccine (Recombinant), Adjuvanted
Trans-BLA Group:	No

Telecon Details

Telecon Date/Time	03-AUG-2016 01:03 PM
Author	BERKHOUSEN, KATHERINE
EDR	No
Post to Web	No
Outside Phone Number	
FDA Originated?	Yes
Communication Categories	AD - Advice
Related STNs	None
Related PMCs	None
Telecon Summary	Discussion with Dynavax regarding the inconsistencies in the revised datasets for Study 16
FDA Participants	Andrea Hulse; Alexandra Worobec, Darcie Everett, Marian Major; Richard Daemer, Katherine Berkhausen
Applicant Participants	Robert Janssen, William Heyward, Kimberly Erby, Robert Halstead, Brit Harvey, Biao Xing, Elaine Alambra

Telecon Body: CBER opened the discussion stating that our discussion would focus on the Study HBV-16 'revised' datasets which were submitted as part of the Dynavax responses to the CRL, as well as the subsequent datasets and tabular summaries of data submitted in response to two information requests (IRs). CBER noted apparent discrepancies between the revised data

RECORD OF TELEPHONE CONVERSATION

submitted on April 8, 2016, in amendment 45, and the data submitted in response to CBER IRs dated April 27, 2016 and June 28, 2016.

CBER requested clarification of definitions for the variables contained in the ADSL dataset. It is not clear what “0” and “1” represent for the variables “LCPPFLG” and “NIPPFLG”. Dynavax agreed that as written in the defined document it wasn’t clear, but clarified that “0” corresponds to subjects who are excluded from the respective per protocol population and “1” corresponds to subjects who are included in the respective per protocol population. CBER stated that it was absolutely critical that the column variables be defined accurately and unambiguously in order for CBER reviewers to effectively and efficiently evaluate the submitted datasets. CBER requested that variable definitions be denoted within the actual columns in the column information section so that each respective definition will be viewable in the JMP program used during review and the reviewer will not have to exit the dataset to retrieve the column variable definition. CBER requested that all future dataset submissions have self-contained column definitions.

Subject 20320 was used as an example to make sure that the coding as explained made sense and remained consistent throughout the data submitted. This subject was coded as “0”, i.e., not included in the original 2012 datasets (per the response to April 27, 2016 IR); however, in the revised data submitted in response to the June 28, 2016 IR, the subject was coded as newly excluded in 2016. Dynavax clarified that the table submitted in response to the June 28, 2016 IR titled “Subjects Excluded from Per Protocol Populations in 2016” did not actually represent subjects excluded from all per protocol populations in 2016; it only represented subjects excluded from the LCPP in 2016 and the column that represents the NIPP population includes subjects excluded in 2012 as well as 2016. When CBER asked Dynavax how the reader would know that critical information, Dynavax was unable to provide an answer and agreed that the table as titled and presented was uninterpretable without that explanation.

Another example was presented to Dynavax, subject 35020, where the subject was a “1” for LCPPFLG in the original 2012 dataset indicating that the subject was included in the LCPP. In the data and datasets submitted in response to CBER’s April 7th and April 27th, 2016 IRs, subject 35020 is a “0” for LCPPFLG. However, in response to CBER’s June 28, 2016 IR, the dataset and tabular presentation of the data presented designate subject 35020 as not newly excluded in 2016, i.e., excluded originally in 2012 from the LCPP. When asked to clarify the discrepancy and explain how it came about, Dynavax was unable to provide any clarification or explanation. CBER explained that there were other data discrepancies that would be provided to Dynavax for clarification/correction in writing. Given these two examples, CBER explained to Dynavax that it is difficult to determine which, if any, of the revised data is accurate and that this raises concerns of a more extensive data quality issue.

CBER requested that Dynavax review the submitted HBV-16 datasets to determine if, in addition to the ADSL dataset, any others may have been impacted by erroneous NIPPFLG or LCPPFLG flags. Dynavax committed to providing an answer to that question within one business day. CBER stated that the clinical review team was still in the process of reviewing the data

RECORD OF TELEPHONE CONVERSATION

discrepancies but that an information request (IR) requesting clarification/correction would be forthcoming.