**CBER SEND Pilot 4 – Standardized data validation review**

Ref: Pilot Submission files and DataFit validation reports reviewed:

\\cbsfs03\CBER\_CASA-CV\Validation BLAs, supplements for 2020\SEND\_Pilot\JnJ

**I. Comments for CBER Nonclinical Reviewers:**

1. The nSDRG sections **4.2.6** says “LBDTC is populated with the actual dates/times of analysis and not the sample collection date/time.”

This seems a deviation from the definition and intended use of LBDTC. Not sure why LBDTC is not based on the collection date/times.

This is common for most of the SEND system, because the collection is done from different system. Usually the date is correct, might not be the time. Depending on what is important for use, can make some suggestion for improvement. Usually it is important to know the elapse time from dose data and sample collection. Consistency is the key issue. Recommendation: IF the date is the same, it is meant to be the sample collection date, put whatever information is correct.

1. Datasets SUPPMA and SUPPMI do not seem to provide real additional information supplemental to MA and MI. In other words, the information captured by MARESMOD in SUPPMA is already found in the MAORRES.

xxRESMOD is specifically needed in data (for discoloration in this instance), pathologist thinks this is clear to identify it, computationally analyzed, xxORRES contains everything. Reports might contain incidence count. Same principal applies to MI.

1. BW (Body Weight) dataset –BWSTRESU variables: these variables values are currently represented in both ‘g’ and ‘kg’ but should those should’ve been standardized into a single unit? Currently BWTESTCD=TERMBW, the units are ‘kg’; BWTESTCD=BW, the units are ‘g’.

Different system comes out with different unit, the same with report. The rule with SENDIG is unit is consistent with specific test. TERMBW will not compare with regular weight. This might be differently across different studies.

1. Define file – Microscopic Findings (MI) section:

MISEV has missing value in the data. The Define file associates MISEV with codelist <[SEND Severity](file:///H:\SEND%20Projects\Pilot4\define.xml#CL.CL.SEV)> ["1 OF 5", "2 OF 5", "3 OF 5", "4 OF 5"]. But in SENDIG V3.1, MISEV is associated with codelist <SEV> [‘MILD’, ‘MODERATE’, ‘SLIGHT’, ‘SEVERE’, ‘MINIMAL’, ‘MARKED’]. Is it a deviation?

Issue with SENDIG is aware, controlled terminology has been changed based on different version.

1. CL (Clinical Observation) dataset – CLNOMLBL (Label for Nominal Study Day) variable:

Comment: Some of the values appear a bit too cryptic and should be made more explicit (see examples below). Additional guidance or convention may be helpful. What is the definition of nominal day? This seems specific to non-clinical study.

Submitted value Suggested value for more explicit meaning

Day 1 PostRx1 1 hour postdose

Day 1 PostRx5 4 to 8 hours postdose

Nominal Day was developed for V3.1, it was to address the clarity of the report and dataset, so the data showed in report is nominal day. Because of the staggered days happened, on report table it is all reported on the same date, but individual data is on different day.

1. CL (Clinical Observation) dataset – CLTPT and CLTPTNUM variables:

Comment: these two variables have real values for some records but null values for the other records (even for the same type of CLTEST names). This does not seem the best practice.

It seems that CLTPTNUM/CLTPT are null for Day -1, -2, -7, 2, 3 and Day 30.  There is only one record each per subject on these days so it seems there is only one assessment done on that day that were not dictated by a planned timepoint within a day.  If that is the case, it makes sense that CLTPTNUM/CLTPT would be null in this instance. What is “CSO” or “SIRT”?

In Section 4.8.2.2 of the study report, it states that on non-dosing days, clinical signs were recorded at least once.  On days 1, 15, and 29, which were dosing days, assessments were done at specific timepoints.

Ophthalmology doesn’t have timepoint. CSO stands for Cage Side Observation on non-dosing days. SIRT stands for Detailed Clinical Observation non-dosing days. PostRX is immediate postdose.

1. BW, DS, CL, LB datasets - xxNOMLBL (Label for Nominal Study Day) variables:

Comment: the xxNOMLBL variables values seem to adopt quite different conventions (see examples below). Some general naming convention for this could be helpful.

DSNOMDY=31 and DSNOMLBL=Week5

CLNOMDY=31 and CLNOMLBL=Day 31 CSO

BWNOMDY=31 and BWNOMLBL=Day 31

BWNOMDY=-7 and BWNOMLBL=Day -7

LBNOMDY=-5 and LBNOMLBL=Day -5 Pretreatment

Because of different data collection. Protocol drives report, report drives xxNOMLBL. Is that important to look at cross different domains? xxNOMDY is expected, xxNOMLBL is permissible.

1. EX (Exposure) dataset – EXDOSE / EXDOSTXT / EXDOSU variables:

Comment: EXDOSE / EXDOSTXT / EXDOSU provides “the amount of test material administered to the subject”. However, the way the unit data value is presented in this pilot (see below) essentially specifies the concentration of the study material as opposed to ‘the amount of test material administered to the subject’.

EXDOSE=null; EXDOSTXT=1x10^11; EXDOSU=vp/ml

One may argue that if you take the vehicle solution variables (EXVAMT/ EXVAMTU) into consideration, you can derive the amount of test material administered. This is true, However, it deviates the original specific definitions of EXDOSE/EXDOSTXT/EXDOSU in SENDIG (i.e., these variables refer to treatment amount but not treatment concentration). It specifies in the study report that the concentration is based on the concentration administered to human subjects, as in, it is the same amount.  OVRR reviewers want to see concentration, volume and dose in EX.