SEND Submissions – Pathology Best Practices

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Abstract

With FDA mandated electronic data submissions in SEND (Standard for Exchange of Nonclinical Data) format on studies starting after December 17, 2016, how confident are you that your company's Pathology dataset submission is complete and accurate on all studies? Are you familiar with electronic data formats? How are you integrating study data from multiple CRO's, vendors and LIMS, including assuring that a common Controlled Terminology was applied across the dataset, especially if you outsource Pathology data? Does the nSDRG (Nonclinical Study Data Reviewer's Guide) have the appropriate data and combine the data from all CRO's and sites involved? If incomplete or inaccurate datasets are submitted, and returned due to errors, what is your company action plan for corrections? The purpose of this poster is to share SEND experiences concerning Anatomic and Clinical Pathology dataset accuracy. SEND now in place for IND's and NDA's.

SEND Standards to Consider in a Dataset Submission

SENDIG (Standard for the Exchange of Nonclinical Data: Implementation Guide) version 3.0 is the standard for current data electronic submissions. This requires Anatomic and Clinical Pathology data be submitted in a standardized format, (SAS V5 .xpt files), for single dose, repeat dose and carcinogenicity studies electronically, this includes non-GLP studies used to select dose levels for GLP studies.

Detecting dataset and report discrepancies is a QC effort, especially when Controlled Terminology plays a critical role in the accuracy of the data submitted. The FDA is utilizing the data in STRESC of the MI domain to visualize the Microscopic incidences. The same holds true for Macroscopic and Clinical observation findings. If findings in STRESC are too vague, they may not accurately reflect incidence counts in the report, requiring FDA to revert to paper review of the data. Thus, STRESC of your MI, MA and CL domains should (in a perfect world) match the incidence tables in the final report in order for the FDA to use electronic data effectively. STRESC contains base process of microscopic evaluation, and with SENDIGv3.1, will be controlled terminology from INHAND.

If your Microscopic incidence table were to have multiple varieties of (for example) Inflammation or Necrosis in the final report, then the variable STRESC in your SEND dataset should ideally reflect these as such, not only the base process.

MIORRES (Microscopic original result)	MISTRESC (Result as reported)
Inflammation, lymphocytic, moderate	Inflammation, lymphocytic
Inflammation, granulomatous, mild	Inflammation, granulomatous
Inflammation, neutrophilic, severe	Inflammation, neutrophilic
Necrosis, marked	Necrosis
Necrosis, focal, moderate	Necrosis, focal

What has been common to find in datasets from many sources – all varietals of findings concatenated as seen below:

Inflammation, lymphocytic	Inflammation
Inflammation, granulomatous	Inflammation
Inflammation, neutrophilic	Inflammation
Necrosis	Necrosis
Necrosis, focal	Necrosis

FDA can't use these data in STRESC in the example above to calculate incidences as reported and must resort to paper report for review, causing additional time conducting data review!

Clinical Pathology (LB) utilize Controlled Terminology for both tests and units for test results, these should be verified and discrepancies noted in the nSDRG

SEND Standards to Consider in a Dataset Submission continued

The USUBJID (unique subject ID) is a critical link to the cohesive SEND dataset, whereby the same USUBJID must be used in all datasets. It is not uncommon for CRO's and Sponsors to have different USUBJID's. It is something which must be discussed, and the same USUBJID MUST be used in all domains for the same animals for all data collected.

The SENDIG V3.0 provides specific domain models, assumptions, conformance and business rules, and examples for preparing standard tabulation datasets that are based on the SDTM (Standard Data Tabulation Model). If there is uncertainty regarding SEND implementation, the sponsor should discuss the issue with the review division.

Microscopic Findings (MI) Domain

The use of the SDTM anatomic sites should be in force, and adherence to INHAND terminology should be implemented, even though not complete, there are a good number of terms which have been standardized for rodent species, and INHAND terminology will ultimately become the FDA mandated Controlled Terminology for histopathology findings.

Sponsors should ensure that the transformation of findings from MIORRES to MISTRESC closely adheres to the instructions in the SENDIG and TCG (Technical Conformance Guide). Modifiers for which there are variables available (e.g. MISEV, MILAT, etc.) should be placed appropriately in their respective domains. Severities (e.g., 1of5, 2of5, or 1of4 2of4 etc.) should be placed in MISEV, and not duplicated in MISTRESC or SUPPMI. Non-neoplastic findings in MISTRESC, where Controlled Terminology has not yet been established, should be standardized in a way to ensure traceability between counts in tables, listings, and figures and the terms in MISTRESC should also be standardized across studies. Controlled Terminology has removed minimal, mild, moderate, marked and severe, and replaced with 1of5, 2of5, 3of5, 4of5, 5of5 where a 5 grade scale is used, and 1,2,3,4 of 4 as well as 1,2,3 of 4 for 3 and 3 level severity scoring scales.

Tumor Dataset
Carcinogenicity studies should include an electronic dataset of tumor findings (tumor.xpt and define file) to allow for a complete review and statistical analysis of the tumor data. This is the same tumor data file which has been mandated for submissions since 1991, detailing the file content as outlined on pages 61&2 of the guidance document. It was discussed at the Spring 2018 face to face meeting with the FDA, and the statisticians require this file in order to conduct PETO analysis, and this remains an expected analysis dataset until it can be modeled from the SEND submission data. The correlation of onset dates to tumor data at histopathological evaluation needs some manual interventions and verification in order to provide this file. This needs to be explained in the define file. While SENDIGv3.0 defines TF.xpt, the entire domain is currently being reevaluated, as it provides little to no benefit to FDA and varies in data reported in the document (option to include metastatic tumors vs primary tumors only)

Variables in SDTM and SEND: Required, Expected, and Permissible
CDISC data standards categorize SDTM and SEND variables as being Required, Expected, and Permissible. In some instances, sponsors have interpreted Permissible variables as being optional and, in other cases, sponsors have excluded Expected variables. For the purposes of SDTM and SEND submissions, **all Required, Expected, and Permissible variables that were collected, plus any variables that are used to compute derivations, should be submitted.**

SEND Standards to Consider in a Dataset Submission continued

CDISC Controlled Terminology
Sponsors should use the terminologies and code lists in the CDISC Controlled Terminology, which can be found at the NCI (National Cancer Institute) Enterprise Vocabulary Services. For variables for which no standard terms exist, or if the available terminology is insufficient, the sponsor should propose its own terms. The sponsor should provide this information in the define.xml file and in the nSDRG.

FDA recognizes that studies are conducted over many years, during which time versions of Controlled Terminology may change. Generally, FDA expects sponsors to use the most current version of an FDA-supported terminology available at the time of coding, or dataset generation. It is acceptable to have different studies use different versions of the same dictionary within the same application. There are some situations where it may be acceptable to use a single older version of Controlled Terminology across multiple studies, even though that version may NOT be the most current for the later studies. The study data submission should describe the impact, if any, of the older version on the study results in the nSDRG. For example, if the sponsor anticipates pooling coded data across multiple studies, then it may be desirable to use a single version across those studies to facilitate pooling. If a sponsor selects this approach, then the approach and the justification should be documented in the *Study Data Standardization Plan*, or in an update to the plan.

Regardless of the specific versions used for individual studies, pooled analyses of coded terms across multiple studies (e.g., for an integrated summary of safety) should be conducted using a single version of a terminology. This will ensure a consistent and coherent comparison of clinical and scientific concepts across multiple studies. Sponsors should specify the terminologies and versions used in the study in the SDRG.

Conclusions

As SEND datasets are intended to allow FDA reviewers to more rapidly review data electronically, quality is an important factor. Part of any quality driven process includes the definition of processes, responsibilities, and education. This is true of SEND dataset generation and verification as well. Defining thorough processes and ownership early, greatly reduces costly delays and complications when creating and submitting SEND datasets.

In conclusion:

Does your Study Pathologist unit take part in the assurance of compliance with regard to SEND electronic data submissions? Is any QC performed? Is a compliance statement issued?

The Study Sponsor is responsible for data accuracy and what Quality measures are taken to review and ensure all data is present in regard to the electronic data submission, be it internally or outsourced in terms of data review/ completeness. FDA stance is that SEND data is owned by the study sponsor, and they are responsible for the completeness and accuracy of the data in electronic submissions. Does your organization have measures in place to assure this is data completeness and accuracy check is done? It can be through either internal or outsourced data review for data integrity and completeness

SENDIGv3.1 becomes effective in March 2019 along with INHAND Controlled Terminology. Are you ready?

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