

The Standard for the Exchange of Nonclinical Data (SEND): History and Basics

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ABSTRACT

The CDISC SEND model is an implementation of the Study Data Tabulation Model (SDTM) for the submission of nonclinical studies. The SEND Model was first developed in 2002, utilizing domains described in the CDER 1999 Guidance and the SDTM as its basis. The first pilot with the FDA was conducted in 2003, but the real stimulus that gained the model widespread recognition was the announcement of an FDA pilot project in 2007. Since that time, more than forty volunteers representing pharmaceutical companies, vendors, and CROs have created close to thirty domains for general toxicology and pharmacology, carcinogenicity, and reproductive toxicology studies. This paper will provide an overview of the history of SEND and its close ties with the development of the SDTM and the SDTMIG. It will also cover some of the basics of the SEND model and how the nonclinical implementation is different from the clinical implementation.

INTRODUCTION

NOTE TO READERS: In an attempt to make wading through the alphabet soup of acronyms easier, some of the more frequently used ones are listed at the end of this paper.

SEND BACKGROUND

Relationship to the SDTM

SEND is an implementation of the SDTM for nonclinical studies. The initial work product was known simply as the Standard for the Exchange of Nonclinical Data (SEND). The term, SEND Implementation Guide (SENDIG), was not to appear until much later. In December of 2002, work began to model the nonclinical domains from the CDER 1999 Guidance (1) to be consistent with the newly emerging standard for clinical data called the Study Data Tabulation Model (SDTM).

The SDTM is the product of the CDISC Submission Data Standards (SDS) Team, a group of individuals from pharmaceutical companies, vendors, and CROs whose initial work product was known as the CDISC Submission Data Standards (Version 1.0 [October 2000] through v2.0 [December 2001]). Included in these versions were standardized representations of the safety domains listed in the CDER 1999 Guidance (1). In December 2001, CDER announced a pilot project to test the Patient Profile Viewer (PPV), a tool developed under a Cooperative Research and Development Agreement (CRADA) with PPD Informatics to display tabulation data submitted in a standardized electronic format.

Success with the PPV pilot in 2002 was followed by two activities, one for clinical data, and one for nonclinical data. For clinical data, the idea of a standard that could be applied to more than just the safety domains was proposed by the FDA to the SDS Team in October of that year. While early versions had various names, this standard evolved to become the Study Data Tabulation Model, and the basis for the Version 3.x submission standards. The detailed history of the SDTM and the SDTM Implementation Guide (SDTMIG) has been described previously (2, 3). For nonclinical data, the signing of a CRADA with PharmQuest for the development of analysis tools for the evaluation of nonclinical datasets resulted in the announcement of a pilot project for standardized nonclinical data in January 2003. This announcement stated the following:

“Recently, FDA received recommendations for a standard presentation of certain clinical data from the Clinical Data Interchange Standards Consortium, Inc. (CDISC), a nonprofit organization including members from pharmaceutical companies, biotechnology companies, contract research organizations, and software vendors. CDISC is currently facilitating the work on similar standards for nonclinical datasets. Where possible, the standards developed for clinical datasets and metadata should be used in the development of standardized presentations of the datasets for routine toxicology studies (e.g., chronic toxicology and carcinogenicity studies).”

The Development of SEND

The SEND Team was formed in the first quarter of 2003, with a list of more than fifty people and all work being conducted via biweekly teleconferences. The submission of nonclinical data in an electronic format had not been widespread, with the exception of the tumor.xpt Tumor Analysis dataset for carcinogenicity studies. The idea of submitting data in electronic format on a regular basis was new (and maybe even scary) to more than a few people at the time. As a result, many teleconference attendees either had a regulatory background and/or were attending mostly to stay informed. Against this backdrop, SEND was still considered to be a “Consortium”, and had not yet become an official CDISC team.

A small group (<20) of active SEND Team members forged on, and developed SEND v1.0 (August, 2003), which served as the specification of the FDA Pilot Project. It contained domains for the following: Exposure, Animal Characteristics, Body Weights, Clinical Pathology, Clinical Signs, Drug/Metabolite Levels, Food Consumption, Fetal Data, Female Fertility, Group Characteristics, Group Observations, Macroscopic Findings, Male Fertility, Microscopic Findings, Organ Weights, Rodents Micronucleus, Study Summary, Study Timing, Tumor Analysis, and Water Consumption. SEND v1.0 was a single document, containing both information about the model (SDTM) and its implementation (modeled after the initial, but never-implemented, v3.0 of the SDTM). The submission of datasets for the pilot was essentially completed by the end of 2004.

Input from the pilot, as well as efforts to more closely align this implementation with that for human clinical trials, resulted in the Version 2.x standards. The last of these was v2.3, posted in November 2005, at which time the SEND initiative began to lose momentum. As was the case with the SDTM/SDTMIG, many companies were unwilling to commit resources without some type of public statement from the FDA regarding the future of SEND. A small subteam worked throughout 2006 and early 2007 on modeling safety/pharmacology domains for hemodynamic measurements (e.g., intra-arterial diastolic and systolic pressures, arterial pulse pressure, left ventricular inotropic state, arterial heart rate), respiratory measurements (e.g., breathing rate, tidal volume, minute volume), and CNS (central nervous system) assessments (e.g., body temperature, tail flick, locomotor activity, sleep time, grip strength). The main focus of this group was to determine how easily data modeled according to the SDTM could be utilized for statistical analysis. The success of this effort was presented by the subteam leads in 2008 (4).

There was a resurgence of SEND activity in April and May of 2007. This came from two fronts: 1) there was an industry effort, led largely by people from Lilly and Covance, to develop and improve the SEND model for use as a data-transfer standard (vendor to sponsor), and 2) there was renewed interest from the FDA, not only from CDER but also from the Office of the Commissioner, for its use in submissions. The word spread, and a re-formed SEND Team held its first full-team face-to-face meeting in Washington, DC in September of 2007. This meeting had a number of purposes, including the following:

- Re-energize efforts to improve consistency with the SDTM and the SDTMIG. This was at a time when work was being done by the SDS Team to improve upon SDTM v1.1 and SDTMIG v3.1.1. SEND also needed to be able to address more complicated trial designs and create a Demographics domain, the data for which had been previously represented only in Subject Characteristics.
- Begin the development of specifications for a regulatory (live submission) pilot, the announcement of which was expected within a month or two (the announcement came in October)(5). The pilot was to involve up to eight sponsor companies who would be submitting nonclinical data to an IND (Investigational New Drug) or NDA (New Drug Application) in both the current PDF format as well as the electronic SEND format.
- Continue the development of domains for safety/pharmacology studies.
- Renew the efforts begun in 2005 to develop domains for reproductive toxicity studies. These studies can be complex due to 1) the staggered timing of the phases of gestation and weaning within treatment groups, resulting in event-based data collection, and 2) the relationships that need to be maintained between mating partners and between parents and offspring, possibly through multiple generations.
- Continue momentum for the development of comprehensive sets of standard terminology, leveraging the work from the CDISC Controlled Terminology Team, and the National Cancer Institute's Enterprise Vocabulary Services (NCI EVS).

Each of these responsibilities was assigned to a subteam with a designated leader. Since 2007, the SEND Team has seen its largest and most active membership, with tremendous commitment from pharmaceutical companies, vendors, CROs, and FDA representatives. The SEND Team has had three or four 4- 5-day face-to-face meetings each year.

Throughout 2008, the SEND Team worked on creating what was called Version 3.0 Draft A of the SEND Implementation Guide (SENDIG), intended to be used as a specification for the CDER Pilot described above. In March 2009, it was posted for public awareness. Continuing improvements and new domains led to work on developing Version 3.0 Draft B, to be used primarily as a working draft for Team review, in early 2010. In December 2010, the first version intended for production use (Version 3.0) was posted as a draft for public review and comment. The SEND Team is currently addressing comments from the review period, and a final production version is expected to be posted sometime in April 2011.

Within the FDA, there has been interest in expanding the use of the SEND standard to other FDA Centers. In December 2009, CVM (Center for Veterinary Medicine) announced a pilot project to test the ability of SEND to support the review of margin of safety and nonclinical toxicology study data submitted for Investigational New Animal Drug Exemptions (INADs) and New Animal Drug Applications (NADAs)(6).

SEND BASICS

SENDIG ORGANIZATION

The SEND implementation of the SDTM as described in the SENDIG v3.0 has many similarities to the implementation for human clinical trials described in the SDTMIG v3.1.2, including the following:

- At a high level, the SENDIG is laid out in the same way as the SDTMIG, with introductory sections (Sections 1-3) and sections on assumptions for all domains (Section 4), subject-related special-purpose domains (Section 5), general-observation-class domains (Sections 6.1, 6.2, and 6.3), trial design (Section 7), and relationships (Section 8).

- Within the relevant sections, domain metadata models are displayed in exactly the same format, with columns for variable name, variable label, data type, controlled terminology or format, and role. Likewise, there are the same columns with information to sponsors: CDISC notes, Core, and References.
- SEND utilizes an extensive set of controlled terminology that is maintained by CDISC and NCI EVS, and described outside of the implementation guide. SEND uses the same controlled terminology lists used for human clinical trials whenever possible.

SENDIG DOMAIN CONTENT

The domain content of the SENDIG is shown in Figure 1. Those familiar with the SDTMIG will recognize a number of differences, which include the following:

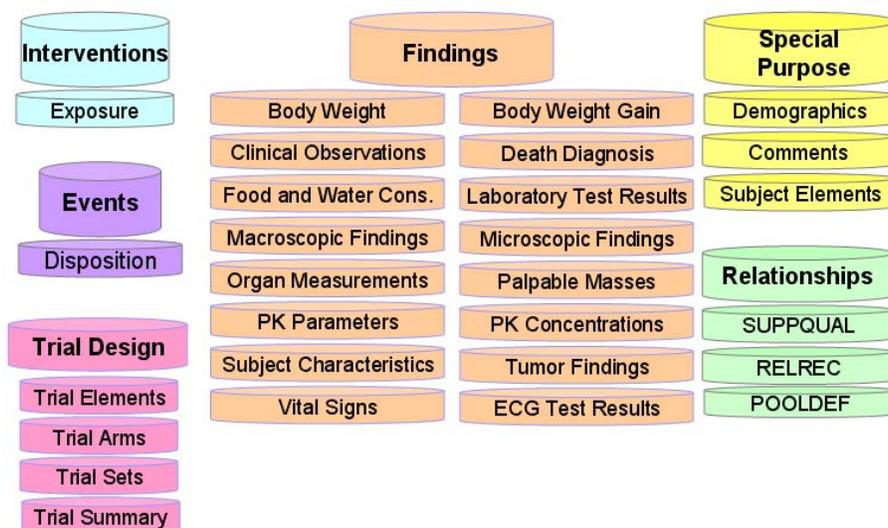
- The Interventions general-observation class has only one modeled domain, Exposure. Concomitant Medications and Substance Use do not apply to toxicology studies, but Concomitant Medications may be relevant as SEND begins to be applied to veterinary-drug studies.
- The Events general-observation class has only one modeled domain, Disposition. The Adverse Events, Medical History, and Protocol Deviations domains have not been modeled in the SENDIG.
- The Findings general-observation class contains a number of new domains:
 - Body Weights
 - Body Weight Gains
 - Clinical Observations
 - Death Diagnosis
 - Food and Water Consumption
 - Macroscopic Findings
 - Microscopic Findings
 - Organ Measurements
 - Palpable Masses
 - Tumor Findings

Note that SEND utilizes Laboratory Test Results, Pharmacokinetics Concentrations, Pharmacokinetics Parameters, Subject Characteristics, Vital Signs, and ECG Test Results in the same way that the SDTMIG does.

- Subject Visits is not included in the Special-Purpose Domains, nor is Trial Visits in the Trial Design section. Since animals are observed at least daily in almost all toxicology studies, the concept of documenting these encounters adds little value to the understanding of the data. The Timing variable VISITDY is, however, used in the general observation class domains as it is in the SDTMIG to facilitate the grouping of data within and across domains.
- A new table, POOLDEF (Pool Definition), appears in the Relationships section. This allows for the identification of the individual animals that comprise data collected for a group or pool of animals. Examples where this is needed are for food and water consumption of group-housed animals, and when blood samples from small animals need to be combined in order to have a quantity sufficient for analysis. This table will be discussed in more detail later.
- A new table, Trial Sets, appears in the Trial Design section. This allows for the subsetting of animals within an Arm (treatment path) as well as for multiple Arms to be “grouped” together. The Trial Design concepts will be discussed in more detail later.

Because the POOLDEF and Trial Sets tables have not been previously defined in the SDTM, they will need to be added to the next version, or included in an amendment (the exact mechanism to be determined by the SDS Team and CDISC management).

Figure 1. SENDIG Observation Classes and Special-Purpose Domains



SENDIG VARIABLE CONTENT

SEND utilizes all of the variables described in v1.2 of the SDTM, but also required the addition of new variables that represent new concepts. These new variables will be added to the next version of the SDTM (or an amendment) as follows:

SDTM Table 2.2.3, Findings

--LAT	Laterality	Example values: LEFT, RIGHT
--DIR	Directionality	Example values: DORSAL, VENTRAL
--DSTRBN	Distribution	Example values: ENTIRE, PARTIAL
--CSTATE	Consciousness State	Example values: CONSCIOUS, UNCONSCIOUS
--LEAD	Lead Identified to Collect Measurements	Example values: Lead I, LEAD CV5RL
--SPCUFL	Specimen Usability for the Test	Y, N
--EXCLFL	Exclude from Statistics	Y
--REASEX	Reason for Exclusion from Statistics	Text
--ANTREG	Anatomical Region	Example values: CORTEX, MEDULLA, MUCOSA, SEROSA

SDTM Table 2.24, Identifiers

POOLID	Pool Identifier	Used in place of USUBJID when measurements are collected for a group of animals rather than by subject
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SDTM Table 2.2.5, Timing Variables

--DETECT	Time in Days to Detection of Tumor	Needed for the creation of the tumor.xpt file from SEND datasets from carcinogenicity studies
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SDTM Table 2.2.6, Demographics

SPECIES	Species	Example values: RAT, MOUSE
STRAIN	Strain/Substrain	Example values: FISCHER 344, B6C3F1
SBSTRAIN	Strain/Substrain Details	Example values: ENTIRE, PARTIAL
AGETXT	Age Text	Example value: 4-6 weeks
SETCD	Set Code	Used to divide or group Arms

SENDIG SPECIAL-PURPOSE DOMAIN USAGE

Related Records

The Related Records (RELREC) dataset is used to represent relationships between records across two (or more) datasets. As a special-purpose domain, it has a fixed structure. In the SENDIG, this is most often needed when tissue masses are identified. For example, a mass may be first observed as part of clinical observations, then be measured periodically, observed macroscopically at necropsy, be examined histologically, and then be used in tumor analysis. In this case, the mass would have data in five domains: Clinical Observations, Palpable Masses, Macroscopic Findings, Microscopic Findings, and Tumor Findings. A dataset-to-dataset relationship might look like this if the same mass was given a single identifier (--SPID value, in this case) for use across all domains.

STUDYID	RDOMAIN	USUBJID	POOLID	IDVAR	IDVARVAL	RELTYPE	RELID
2010-001	MA			MASPID		ONE	A
2010-001	MI			MISPID		ONE	A
2010-001	PM			PMSPID		ONE	A
2010-001	CL			CLSPID		ONE	A
2010-001	TF			TFSPID		ONE	A

Some sponsors may chose to use RELREC to represent record-to-record relationships for individual animals. Such an example would be this:

STUDYID	RDOMAIN	USUBJID	POOLID	IDVAR	IDVARVAL	RELTYPE	RELID
2010-001	MA	2001-001-1005		MASEQ	15	ONE	A
2010-001	MI	2001-001-1005		MIGRPID	GRP 3	ONE	A
2010-001	PM	2001-001-1005		PMSEQ	2	ONE	A
2010-001	CL	2001-001-1005		CLSEQ	55	ONE	A
2010-001	TF	2001-001-1005		TFSEQ	3	ONE	A

Note that the SEND implementation of RELREC includes the variable, POOLID, which is an Expected variable (an Expected variable in the SDTMIG domains must be in the data structure even if the value is Null). Either USUBJID or POOLID must be populated in all cases where there is not a dataset-to-dataset relationship.

Supplemental Qualifiers

Supplemental Qualifiers (known also as SUPPQUAL) is used for the submission of non-standard variables. "Non-standard" in this context means there isn't an existing SDTM variable for this data. While SDTMIG v3.1.1 allowed for a single SUPPQUAL dataset for a study or individual SUPP-- datasets for each domain having Supplemental Qualifiers, SDTMIG v3.1.2 permits only the latter. The SENDIG v3.0 follows suit. The only flexibility permitted in the SUPP-- datasets is in the inclusion or exclusion of POOLID, which is Permissible (a Permissible variable in the SDTMIG domains can be dropped from the submission dataset only if no data have been collected for it).

Pool Definition

In some animal studies, it's not possible to get certain types of data for individual subjects. One example of such data is food and water consumption for group-housed animals, where measurements are for a cage of animals. Another example is when blood samples from more than one animal are needed in order to have a quantity sufficient for analysis.

The POOLDEF table is a lookup table to be used with subject-based domains. Its sole purpose is to identify animals that make up pools. Whenever the composition of the group of animals used for pooling changes, the group must be assigned a new, unique POOLID. The example below shows three animals that were in Cage 1 comprised a pool at some point (Rows 1-3), and that later Animal 2009-008-002 was removed from the pool (Rows 4 and 5). It also shows that some of these same animals were included in another pool (Rows 6-10). The POOLID is sponsor defined, but in the example below, the sponsor used values that convey some type of meaning (cage data and PK samples).

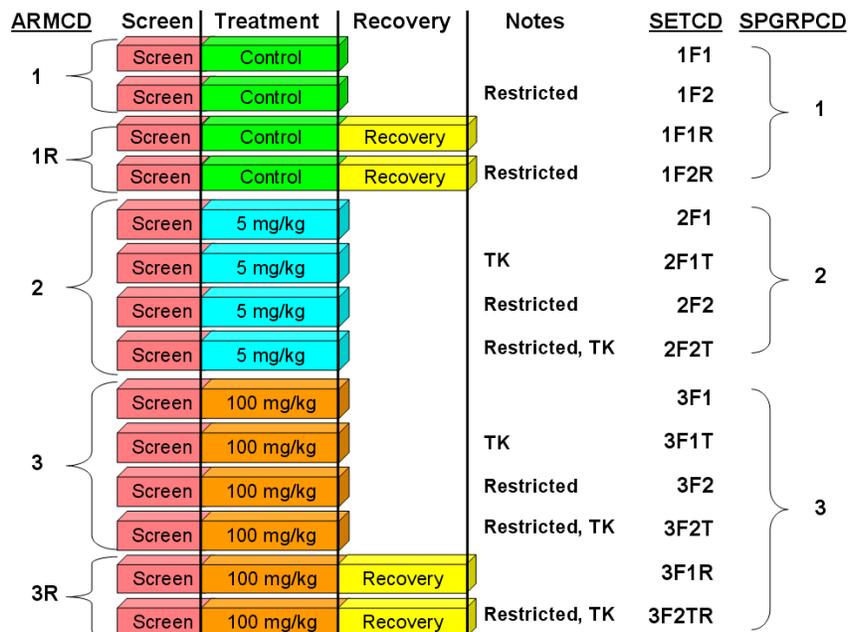
Row	STUDYID	POOLID	USUBJID
1	2009-008	CAGE 1	2009-008-001
2	2009-008	CAGE 1	2009-008-002
3	2009-008	CAGE 1	2009-008-003
4	2009-008	CAGE 1-A	2009-008-001
5	2009-008	CAGE 1-A	2009-008-003
6	2009-008	PK1	2009-008-001
7	2009-008	PK1	2009-008-002
8	2009-008	PK1	2009-008-003
9	2009-008	PK1	2009-008-004
10	2009-008	PK1	2009-008-005

THE TRIAL DESIGN MODEL (TDM)

Overview

SEND uses the SDTM Trial Design Model (TDM) tables of Trial Arms (TA), Trial Elements (TE), and Trial Summary (TS). As mentioned previously, SEND requires the addition of a Trial Sets (TX) table, and does not utilize the Trial Visits (TV) table. SEND also doesn't use Trial Inclusion/Exclusion (TI), since the screening of animals rarely requires the documentation of inclusion/exclusion exceptions. This section will analyze the rather complicated study design shown in Figure 2 and the table below (both adapted from the SENDIG) to illustrate the use of the TDM concepts.

Figure 2. Design of Study with Multiple Arms and Sets



Group Number	Group Label	Dose Level	Number of Animals (both sexes combined)							
			Fed Ad Libitum				Restricted Feeding			
			Non-Toxicokinetic		Toxicokinetic		Non-Toxicokinetic		Toxicokinetic	
			Non-recovery	Recovery	Non-recovery	Recovery	Non-recovery	Recovery	Non-recovery	Recovery
1	Group 1, Control	Vehicle Control	10	10			10	10		
2	Group 2, 5 mg/kg	5 mg/kg/day	14		6		14		6	
3	Group 3, 100 mg/kg	100 mg/kg/day	8	6	6		8		6	6

Trial Elements

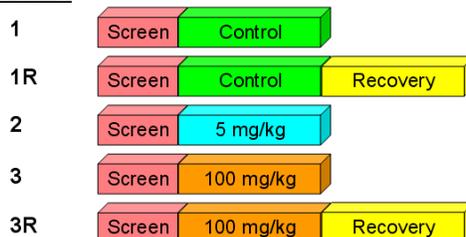
An Element is the basic building block for a discrete treatment period within a study. Planned Elements are described in the Trial Elements (TE) table, which includes a description of the planned treatment(s) for each Element, rule for starting the Element, a rule for ending the Element, and a planned duration (if it's fixed and has no dependencies). In Figure 2, the Elements are each represented by a different color, and include Screen, Control, 5 mg/kg, 100 mg/kg, and Recovery, as shown here:



Trial Arms

An Arm is a planned sequence of Elements, and is usually equivalent to a treatment group. The Trial Arms (TA) table describes the sequence of elements within each Arm, as well as rules for branching and transitions. The Demographics domain contains the name of the Arm to which the subject was randomized. In Figure 2, there are actually five distinct treatment paths. Other experimental variables such as food restriction and the assignment of animals for toxicokinetic measurements do not affect the treatment path. The Arms are therefore these:

ARMCD



Epochs

The term Epoch is used to describe a period of time that cuts across Arms. Epochs may contain the same number or a different number of Elements for each Arm. Epochs are defined in the TA table. The study in Figure 2 has three Epochs: Screen, Treatment, and Recovery.

Trial Sets

Trial Sets was expressly created for the SENDIG. It will be incorporated into the next version of the SDTM, and it's been implemented for the first time in the SENDIG. The Trial Sets table provides a mechanism for representing two aspects of a study's design: 1) the subdivision of Arms, and 2) the "grouping" of multiple Arms. Some example data will be used to facilitate the explanation of Trial Sets.

A Trial Set represents the most granular subdivision of all the experimental factors, treatment factors, inherent characteristics, and distinct sponsor designations as specified in the design of the study. It does so by allowing as many rows per Set as there are parameters of interest. The table below shows the rows excerpted from the SENDIG that describe first Trial Set (1F1) in this study. Of note are parameters (TXPARMCD values, Column 6) for dose level of test material (TRTDOS), feeding regimen (FEEDREG), and Toxicokinetic Description (TKDESC).

STUDYID	DOMAIN	SETCD	SET	TXSEQ	TXPARMCD	TXPARAM	TXVAL
TDM4	TX	1F1	Control Group, Control Article Name once daily, Fed Ad Libitum	1	ARMCD	Arm Code	1
TDM4	TX	1F1	Control Group, Control Article Name once daily, Fed Ad Libitum	2	SPCGRPCD	Sponsor-Defined Group Code	1
TDM4	TX	1F1	Control Group, Control Article Name once daily, Fed Ad Libitum	3	GRPLBL	Group Label	Group 1, Control
TDM4	TX	1F1	Control Group, Control Article Name once daily, Fed Ad Libitum	4	TRTDOS	Dose Level	0

STUDYID	DOMAIN	SETCD	SET	TXSEQ	TXPARMCD	TXPARM	TXVAL
TDM4	TX	1F1	Control Group, Control Article Name once daily, Fed Ad Libitum	5	TRTDOSU	Dose Units	mg/kg/day
TDM4	TX	1F1	Control Group, Control Article Name once daily, Fed Ad Libitum	6	CTLTYPE	Control Type	Vehicle Control
TDM4	TX	1F1	Control Group, Control Article Name once daily, Fed Ad Libitum	7	FEEDREG	Feeding Regimen	Ad Libitum
TDM4	TX	1F1	Control Group, Control Article Name once daily, Fed Ad Libitum	8	TKDESC	Toxicokinetic Description	NON-TK
TDM4	TX	1F1	Control Group, Control Article Name once daily, Fed Ad Libitum	9	PLANSUB	Planned Number of Subjects	10

The “grouping” of multiple Arms is accomplished by assigning each Set a Sponsor-Defined Group Code as a parameter (TXPARMCD = SPCGRPCD) for each Set. In referring to Figure 2, it can be seen that the sponsor has defined three groups for this study:

SPCGRPCD	ARMCD Values	SETCD Values
1	1, 1R	1F1, 1F2, 1F1R, 1F2R
2	2	2F1, 2F1T, 2F2, 2F2T
3	3, 3R	3F1, 3F1T, 3F2, 3F2T, 3F1R, 3F2TR

In summary, this is a study in which there are fourteen distinct Sets, each represented by non-blank, number-containing cell of the data portion of the study design table as well as a linear sequence of bars with a unique value of SETCD in the figure. The full Trial Sets table for this study, as shown in the SENDIG, contains 116 rows.

THE FUTURE

The team’s efforts in creating what will be the first production version of the SEND standard (in the form of the SENDIG) have been supported by FDA personnel from CDER, CVM, and The Office of the Commissioner. As the first standard for structured nonclinical data, SEND will be the foundation for:

- Companies who want to develop internal standards or exchange standards for electronic data
- The submission of structured nonclinical datasets in regulatory applications
- A more effective review of the data by regulatory authorities
- Allow for more-efficiently mining of data across studies within specific therapeutic areas
- The expansion of nonclinical capabilities (in the form of viewing and data-analysis tools)
- The creation of additional domains for nonclinical data
- Further improvements in the standardized submission of nonclinical data

As has been the case with clinical data standards, the extent of adoption by pharmaceutical companies will vary until potential implementers recognize that the benefits of standardization outweigh the perceived disadvantages.

CONCLUSION

SEND is an implementation of the SDTM, designed specifically for use in toxicology and pharmacology studies. Its development began in 2002, and evolved through various 1.x and 2.x versions, culminating in v2.3 in November, 2005. At this time, the vision for the use of SEND became less clear, and most development activities ceased. In 2007, efforts resumed, driven by renewed FDA interest for a submission standard, and for industry interest and need to have a data-exchange standard. Efforts focused on creating a SEND Implementation Guide that would accompany the SDTM as the basis for the submission and transfer of nonclinical data. The renewed effort resulted in several Version 3.0 drafts and the posting of the first version intended for production use in December of 2010. A final version is expected in April of 2011. Interest from FDA, pharmaceutical companies, and vendors has been very high. Both SEND adoption and the expansion of its capabilities will be increasing over the next few years.

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SOME OF THE ACRONYMS USED IN THIS PAPER

CDER	Center for Drug Evaluation and Research (FDA)
CDISC	Clinical Data Interchange Standards Consortium
CRADA	Cooperative Research and Development Agreement
CVM	Center for Veterinary Medicine (FDA)
eCTD	electronic Common Technical Document
FDA	Food and Drug Administration (U.S.)
SDS	Submission Data Standards
SDTM	Study Data Tabulation Model
SDTMIG	SDTM Implementation Guide: Human Clinical Trials
SEND	Standard for Exchange of Nonclinical Data
SENDIG	SEND Implementation Guide
TDM	Trial Design Model

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