SEND – Common Challenges and Best Practices

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About the Presenter

Jacquice Davis is a member of the Data Standardization team at PointCross Life Sciences, which supports non-clinical trial submissions to the FDA. As a recent member, she comes from the National Institutes of Health (NIH) where she was involved in developing standards for microbiome research peer review submissions and has degrees in Biology and Bioinformatics. Since joining PointCross, she has been involved in data standardization and SEND compliance measures for customers.

Experience & Lessons Learned

- Lack of SEND submissions in 2016
  - Industry has been slow to respond and move forward with SEND
  - Not enough data to show the major issues facing industry
- FDA received only a handful of submissions during their test pilot program for technical conformance (less than 40)
  - FDA ran pilot program on data reviewability in summer 2016 to assess readiness of industry
  - Checks on quality of data, conformance to study report, and technical conformance to SEND
- PointCross has focused on ensuring consistency between study reports and SEND datasets since 2014

Quality, Consistency and Reviewability Issues

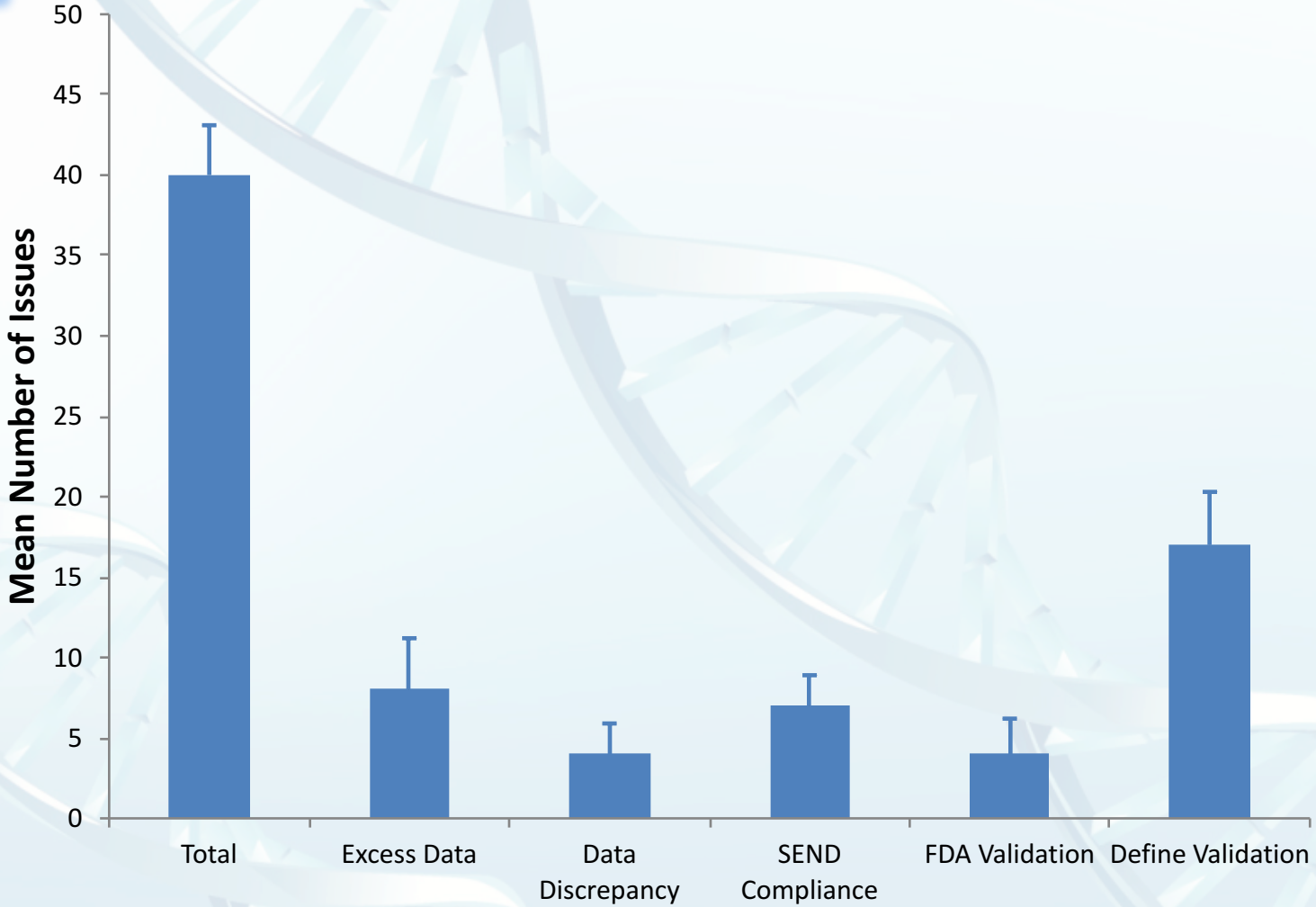


*Chart generated from QC checks of the six most recent studies for which PointCross has performed their SEND-Assure service. All studies referenced included a Define file and were prepared after the FDA's pilot program in summer of 2016.

Data Merging Issues

- **Data collected using different LIMS Systems**
  - Creating SEND from one type of source file can typically be handled by a LIMS' SEND solution or third party
  - Merging data from multiple LIMS systems requires intimate knowledge or experience with all data sources
- **Data collected at different test sites**
  - Data issues can escalate quickly when there is more than one type of source file for merging, for example:
    - SEND formatted data from CRO
    - LIMS extract from in-house lab
    - Data from specialty lab in Excel, CSV, PDF
- **Bioanalysis and Pharmacokinetic data**
  - Not typically collected or reported in SEND or digital format
  - Requires conversion to SEND format and then merging with other source data

Examples of Data Merging Issues

- **Using older versions of LIMS**
  - Outputs may be in formats that are difficult to merge
- **Merging DMPK domains only**
  - Getting PP or PC data from different CROs

Validators Today, and What to look for Tomorrow

- Validators available on the market today now were created to check a wide range of rule sets (nonclinical & clinical as well as FDA & PMDA) due largely to the fact that many rules are still being developed
- Current validators developed based on clinical standards and have now incorporated checks for SEND conformance
- Validators for SEND should include FDA Validation rules as well as FDA Business rules
- FDA Business Rules
  - Complementary with Technical Rejection and Standard Conformance
  - Supersedes FDA Validation Rules
  - Consists of 45 Clinical and 41 Non-clinical rules
  - No longer contains severity (Errors and Warnings)

Critical Errors Found by PointCross Validator

FDAN039: Value of Duration, Elapsed Time, and Interval variables (--DUR, --ELTM, --EVLINT) must conform to the ISO 8601 international standard

FDAN032: Variable Data Types in the dataset should match the variable data types described in SEND

Domain	RuleID	Message	Severity	Found	Category
PP					
	FDAN039	Invalid ISO 8601 value for (PPDUR, PPELTM, or PPEVLINT) variable	Error	82	Standard Compliance
	FDAN032	SEND/dataset variable type mismatch	Error	82	Standard Compliance

PointCross Validation Report Warnings from SEND Public Test Study

Rule:	Domain:	Warning:
FDAN158	CO	Inappropriate usage of variables in CO domain
FDAN212	OM	Duplicate records
FDAN148	SC	Missing values for both SCDTC and SCDY variables
PC-NONCLIN-0010	TA	Domain in dataset is not present in define.xml
FDAN026	TA	Variable in dataset is not present in define.xml
PC-NONCLIN-0010	TE	Domain in dataset is not present in define.xml
FDAN026	TE	Variable in dataset is not present in define.xml
FDAN055	TE	Permissible variable with missing value for all records
FDAN026	TX	Variable in dataset is not present in define.xml
PC-NONCLIN-0010	TX	Domain in dataset is not present in define.xml

Define.XML Versions 1.0, 2.0, and 2.1

- Key enhancements include:
  - Support for CDISC Controlled Terminology
  - Flexible definition of Value Level Metadata
  - Enhanced documentation of data origin or source
  - Improved handling of comments
  - In 2.1, enhanced origin values

Define.XML - Common Errors

Common Define.XML validation rules broken in recent SEND datasets

Rule	Description	Severity	Rule Description	Comment
DD0003	'Coded Comment Definitions' is not a valid value for 'NCName'.	Error	Required attributes must be included in Define.xml and cannot be empty.	Space not allowed for NCName. Value should be ''CodedCommentDefinitions''.
OD0031	Duplicate ItemDef OID	Error	The OID attribute for ItemDef element must be unique within a single MetaDataVersion.	Definition for VISITDY present twice
DD0055	Invalid Class value	Error	The Class attribute must have a value of 'SPECIAL PURPOSE'	Class was 'SPECIAL-PURPOSE'. Hyphon (-) not allowed
DD0068	Invalid use of Length	Error	The Length attribute must be empty when DataType is not integer, float, or text.	Length attribute should not present for Date (DTC) variables
OD0071	Missing Significant Digits value	Error	The Significant Digits attribute is required when DataType is float.	For Float data type variables, significant digit should present. Eg, STRESN

Generating Define.XML for legacy studies

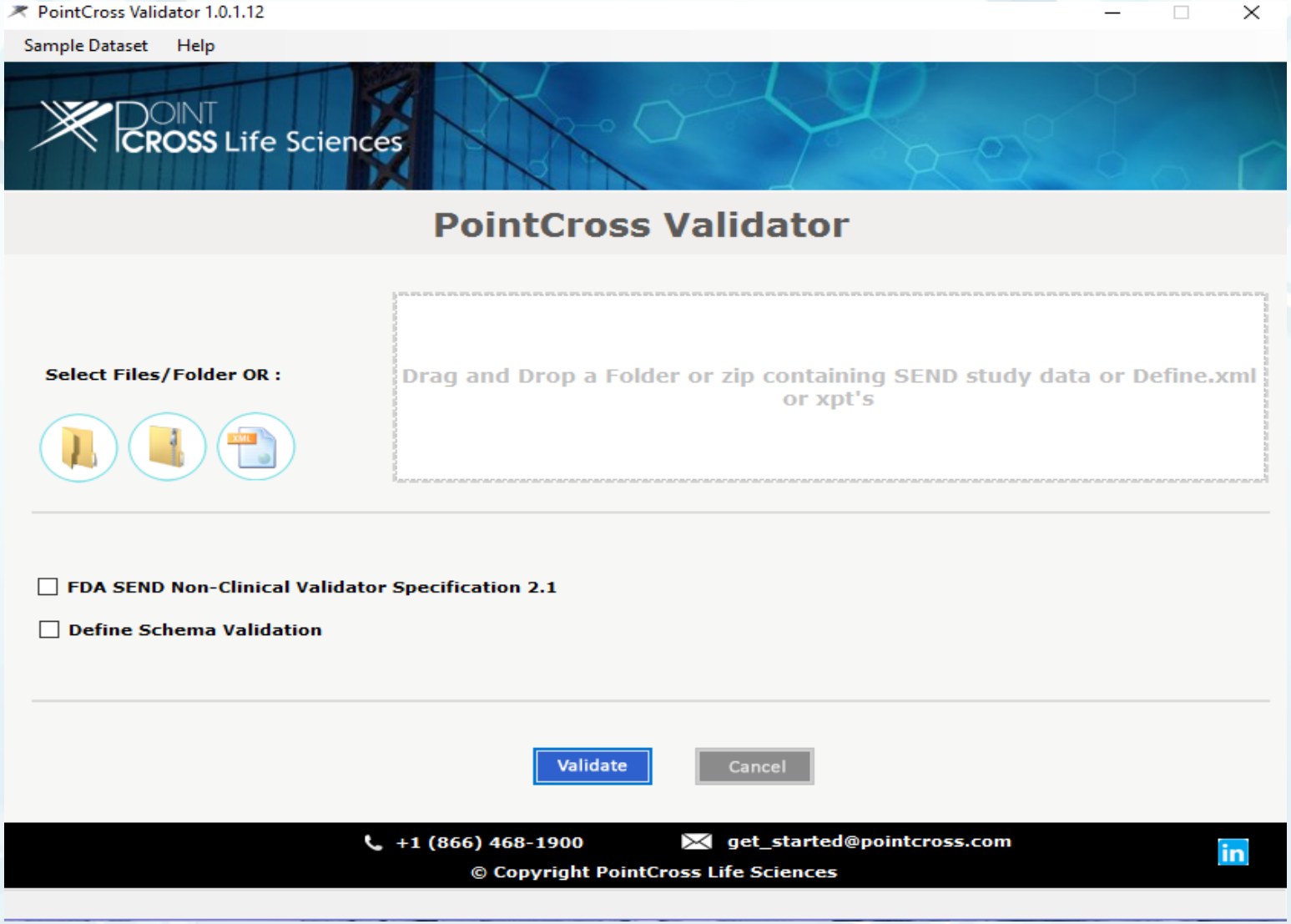
- Some sponsors are being cautious and wanting to still generate a define.xml file along with the required TS.xpt when standardizing legacy studies.

SEND & Define

- Regardless of the approach it will always require extensive knowledge of SEND and time/resources
  - Validators only identify issues, they can't fix them. Validation without human intervention may miss data consistency, trial design, and data modeling errors

PointCross Validator

- Remove confusion by being able to run validation checks on only nonclinical rules published by FDA and CDISC
- Increase efficiency by having both SEND and Define.xml validation in a single tool
- Supports SEND CT lists back to 2013



In Conclusion

- There are still many challenges around merging data from multiple sites and achieving data consistency and SEND conformance
- Today's validators don't always pick up all the issues/problems in SEND datasets and are not able to parse out which issues are relevant for your submission
- With the new FDA's submission requirements, there is another level of complexity in developing an acceptable SEND dataset

Contact Us

If you have any questions on our services or products reach out to John. Do you have questions on the material presented or would like to schedule a call with a PointCross representative?

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