FIT FOR USE PILOT COLLABORATION OF: CDISC, PHUSE, FDA

INDUSTRY FEEDBACK

PREFACE

- The content presented in this slide deck represents individual companies' feedback based on their participation during the pilot.
- Any recommendations or implied change in process should not be considered best practice.
- Follow-up actions are being performed to identify best practices in response to this feedback and will be the subject of future communication.

Fit for Use Pilot - Introduction

- Industry Collaboration between CDISC, PhUSE, and FDA
- Open call for participation in June 2016
- 13 Sponsor submissions made by September 2016
- Publicly accessible wiki site has been established: https://wiki.cdisc.org/display/NSFFUW/Nonclinical+%28SEND%29+Fit+for+Use+Workstream+Home
- Detailed learning points will continue to be shared
- Learning points will be used to inform industry PhUSE and CDISC team efforts

Fit for Use Pilot – Introduction (cont.)

- Sponsors participating: 13
- FDA Reviewers participating: 9
- PharmTox Divisions: 5
- Studies submitted: 13
- Study types: Repeat Dose and Carcinogenicity
- All study data packages included the associated Define file
- Most study data packages included the associated nSDRG and the associated Study Report (.pdf)
- No legacy Tumor.xpt files were submitted (would be in real submission), however TF domains were submitted

Fit for Use Pilot – Pilot Data Coverage

- Domains included (total number submitted across all studies, by frequency then alphabetically)

SEND V3.0 Domain	Domain Abbreviation	Total
Body Weight	BW	13
Clinical Observations	CL	13
Demographics	DM	13
Disposition	DS	13
Exposure	EX	13
Laboratory Test Results	LB	13
Macroscopic Examination	MA	13
Microscopic Findings	MI	13
Trial Design domains Trial Arms, Trial Elements, Trial Summary and Trial Sets	TA,TE, TS and TX	13 (each)
Comments	CO	12
Pharmacokinetics Concentration	PC	12
Body Weight Gain	BG	11
Pharmacokinetic Parameters	PP	11
Subject Elements	SE	11
Supplemental Qualifiers for Microscopic Findings	SUPPMI	11

Fit for Use Pilot – Pilot Data Coverage

- Domains included (cont.)

SEND V3.0 Domain	Domain Abbreviation	Total
Organ Measurements	OM	10
Related Records	RELREC	10
Supplemental Qualifiers for Clinical Observations	SUPPCL	10
Supplemental Qualifiers for Macroscopic Findings	SUPPMA	10
Electrocardiogram	EG	5
Food and Water Consumption	FW	5
Supplemental Qualifiers for Body Weight Gain	SUPPBG	5
Supplemental Qualifiers for Body Weight	SUPPBW	5
Supplemental Qualifiers for Disposition	SUPPDS	5
Supplemental Qualifiers for Laboratory Test Results	SUPPLB	5
Vital Signs	VS	4
Supplemental Qualifiers for Tumor Findings	SUPPTF	3
Tumor Findings	TF	3

Fit for Use Pilot – Pilot Data Coverage

- Domains included (cont.)

SEND V3.0 Domain	Domain Abbreviation	Total
Pool Definition	POOLDEF	2
Death Diagnosis	DD	1
Palpable Masses	PM	1
Subject Characteristics	SC	1
Supplemental Qualifiers for Exposure Findings	SUPPEX	1
Supplemental Qualifiers for Food and Water Consumption	SUPPFW	1
Supplemental Qualifiers for Pharmacokinetic Concentration	SUPPPC	1
Supplemental Qualifiers for Palpable Masses	SUPPPM	1
Supplemental Qualifiers for Vital Signs	SUPPVS	1

Scenarios Included

- Some studies included data from multiple suppliers
- Some studies included groups where main study animals served as TK animals
- One study included Anti-Drug Antibody (ADA) data in a dataset
- Some studies included satellite groups used for TK with pooled samples
- One study included a Tox arm: Group1 (control), 2, 3, 6 and TK arm: Group 4, 5, 7
- Within one study the study duration changed for some animals
- Some studies included dosing that remained constant
- One study included dried blood spot analysis in SEND that was not in the study report
- One study design was composed of 5 groups with 10/sex/group in the main study and 6 satellite animals/sex/group for TK. Dosing in the 600 mg/kg (high-dose) group discontinued on Days 11 and 6, respectively in males and female rats. These animals were continued on study without any further dosing.
- Not all findings data included in the study report pdf was submitted in SEND format
- Some studies were conducted with a single sex
- Species coverage included rats, dogs, transgenic mice, and cynomolgus monkeys

INDIVIDUAL PILOT PARTICIPANT FEEDBACK

Company 1

- What was important or impactful? any “course corrections”?
  - *The reviewer feedback prompted us to reevaluate how some of our data are collected. There are data collection practices in the lab that result in specific situations in the SEND datasets where variables were not appropriately populated.*
- What was unclear or you have questions?
  - *Feedback was very clear and easy for us to follow. We appreciate that the reviewers obviously put considerable effort into providing clear and concise feedback.*
- What value did you get by participating in Fit For Use Pilot?
  - *It was very valuable to have confirmation from the agency that for the most part the way in which we are populating our SEND datasets was compatible with the FDA’s data visualization tools and was useful to the reviewers. It was likewise valuable to receive specific feedback on areas where we can make data collection improvements at our company.*

Company 2

- What was important or impactful? any “course corrections”?
  - *Confirmed some known issues as well as identified new issues with our SEND tool; This clarified for the tool vendor that further updates were needed.*
  - *Identified additional discrepancies between study report and datasets that should be described in the nSDRG.*
  - *Surfaced finding terminology that could be improved upon to better represent data provided in STRESC variables.*
- What was unclear or you have questions?
  - *Feedback received indicated a lack of clarity regarding population of Findings (Results) versus Specimens in the MI Domain.*
  - *Some of the validator messages (warnings and/or errors) seemed to not properly represent the FDA Rules and/or SENDIG v3.0 guidance.*
- What value did you get by participating in Fit For Use Pilot?
  - *Feedback from the FDA gave us valuable clear information to influence tool vendors’ updates as well as internal process modifications.*
  - *Receiving affirmation of the general content of our nSDRG and the ability for our data to be visualized increased confidence in our process.*
  - *The ability to view feedback from all participants encompassing various endpoints and study types provided information that would have otherwise taken each individual company extensive resources and time and may not have resulted in this amount and quality of feedback.*

Company 3

- What was important or impactful? any “course corrections”?
  - *FDA expects the recovery animals to be a different trial set (TX) than the non-recovery animals. The IG demonstrates this but doesn’t appear to require this. We’ll need to add this to our dataset preparation check list.*
  - *Didn’t realize they wanted VISITDY populated in MA, MI, and OM even though the SENDIG says that these variable should not generally be used in MA and MI. We need to find a way to populate this variable and add it to our check list. When I read this requirement in the Technical Conformance Guide I recognized using VISITDY as they described was in general alignment with the variable’s intended use, but I didn’t check the IG to see that this variable is generally not to be used in the MA and MI domains. We’ll need to add this to our dataset preparation check list to make sure it is present on all studies with multiple necropsy days intended to be analyzed together.*
  - *The FDA would like to see in the SDRG a listing of the endpoints in CL, VS, and anything unusual in LB.*
  - *Didn’t realize that to get a validation report from Pinnical21 I needed to choose the define standard instead of just include the define file as input during the SEND validation.*
  - *Severity mapping to CT needs to be described in SDRG section 6.2*

Company 4

- What was important or impactful? any “course corrections”?
  - *The submission dataset package met critical FDA expectations*
  - *SDRG*
    - *Section numbering should match FDA SDRG Template*
    - *Study Design Summary should include*
      - *Dose regimen*
      - *Drug lot, if more than one lot is used*
    - *Mismatch of terminology between the dataset and the report, resulting from SEND standardization, has prompted a revision to the sponsor SDRG template to explain terminology mapping*
      - *PK*
      - *Clinical signs*
  - *Visualization Tool*
    - *Screen shots providing FDA views of sponsor data were very helpful in planning internal visualization of the data*
    - *Additional detail is required for trial set descriptions (TX domain) and standardized clinical observations (CL domain) to improve visualization of the data*

Company 4 (cont.)

- What was unclear? What do you have questions about?
  - *SDRG*
    - *Request regarding inclusion of methodology for sample collection for PC and PP domains in the SDRG is unclear, as this would be duplication of content in the Study Report*

- What value did you get by participating in Fit For Use Pilot?
  - *Confirmation that sponsor parsing of TK parameters allowed visualization of those parameters*
  - *Feedback was valuable in:*
    - *Improving visualization of standardized clinical observation data*
    - *Improving Trial Set descriptions*
    - *Understanding how sponsor data is viewed*

Company 5

- What was important or impactful? any “course corrections”?
  - *Several data capture processes were corrected*
    - *Observational data*
    - *Food consumption terminology*

- What was unclear or you have questions?
  - *Because there was no direct Q&A with the Agency, specific questions where details could be hammered out was not possible*
    - *Perhaps a Q&A document from the Agency could be generated after the first year to 18 months of submissions*
  - *There needs to be confidence that the learnings will be transferred to the CRO industry on which much of industry relies*

Company 5 (cont.)

- *Issues with VISITDY vs PCTPTNUM remain*
  - *For VISITDY: If a sample was taken 24 hrs after a Day 1 dose, the CRO would display the VISITDY as 2, as that is the day that the measurement is expected to be taken, but they were told from FDA feedback that it should be Day 1 for graphing purposes. It goes against the guidance and examples shown in the SENDIG.*
  - *For PCTPTNUM: the CRO followed the guidance from the SENDIG stating that –TPTNUM should be a unique number for each unique –TPT, so they populated it with numbers starting from 1 to n, where n was the number of unique TPTs. Feedback received was that PCTPTNUM should be populated with a number representing the timepoint but, although the examples of the PC dataset does show PCTPTNUM displayed like this, what the CRO has done is not wrong and still orders the TPTs in exactly the same order (example below)*

PCTPT	TPTNUM	Suggested TPTNUM
0.25 Hr Post Dose	1	0.25
0.5 Hr Post Dose	2	0.5
1 Hr Post Dose	3	1

  - *The questions that arise from this feedback is that according to the guidance the CRO has completed these variables correctly, yet still received feedback that they needed to change things, does this mean the guidance is wrong? Would the SEND package have been rejected on these findings? If it was rejected what kind of feedback would there be to be able to get things right in the future, would it be in the same form as was presented in the FUP? It also raises the issue that SEND is meant to be a standardized submission, but there still appears to be things that can be down to interpretation making it very difficult to standardize and perhaps the guidance should be updated to not be so ambiguous in places*

Company 5 (cont.)

- What value did you get by participating in Fit For Use Pilot?
  - *Learned that there is still more to learn*
  - *Activity was VERY productive and left a positive feeling for future joint interactions*
  - *The process of correcting and updating will be iterative i.e. not done all at once*

Company 6

- What was important or impactful? any “course corrections”?
  - *We gained a better understanding of how to address early termination of dose groups in the Trial Design Domains. We will take this into consideration for the next study that has this scenario*
  - *In general, the level of information we provided in the nSDRG was appropriate but we need to do a better job in the situation when we have early termination of dosing in a particular study group*
  - *In the future we will use VISITDY for OM, MI, MA to avoid inappropriate splitting of data across multiple sacrifice days*
  - *We need to be consistent on how we map the 3 grades of severity in MI that we use to the grades used in SEND and this needs further explanation in the nSDRG*
- What was unclear or you have questions?
  - *In general, the feedback from FDA was clear. We did review the feedback with our SEND vendor who was able to clarify anything that was not clear in the feedback from FDA*

Company 6 (cont.)

- What value did you get by participating in Fit For Use Pilot?
  - *Because we have never submitted SEND datasets to FDA before, we consider the chance to submit datasets for a study to FDA to review prior to having to do this on a mandatory basis invaluable. The learnings from this exercise coupled with our learnings from our eDATA test submissions has helped us correct potential issues with our submissions now, before we plan our first submission, rather than after rejection based on technical criteria.*
  - *Because our company is based in a region where SEND will not be required for several years, several units within the company were reluctant to embrace the SEND initiative. This exercise helped these units within our company to better understand the value and utility of SEND datasets to the FDA reviewers and this in turned helped the company better understand the overall corporate value of SEND.*

Company 7

- What was important or impactful? any “course corrections”?
  - There appeared to be a conflict with the reviewers comments and the SENDIG v3.0 for the variable VISITDY for measurements over 24h – we will revise our next submission in line with this
  - In-house LIMS lexicons needed to be reviewed following FDA comments on:
    - The misuse of non 'observational' terms in internal LIMS observations lexicon (e.g. 'refer to comment')
    - The use of modifiers and areas in sometimes 'over-standardized' observational data
  - A thorough review of TK data and an understanding of internal business procedures is required to understand and explain management of LLQ and Not Reportable results
  - The importance of the nSDRG
    - The approach we took to include a comprehensive amount of detail in the nSDRG was appreciated by the FDA reviewers (gives confidence)
  - Forced us to gain experience of using Pinnacle21 and further understand the Errors/Warnings and the need to check the Define file with Pinnacle21

Company 7 (cont.)

- What was unclear or you have questions?
  - *There appeared to be a conflict with the reviewers comments and the SENDIG v3.0 for some variables? What is correct?*
  - *Some FDA comments referred to issues that were already highlighted in the nSDRG?*
  - *Reviewers had differing opinions on the same submission (e.g. nSDRG content)*
  - *Clarification required re: use of --TPTNUM --RFTDTC, --TPTREF, --DY variables*
  - *We had a request to show Body weight gain for a different period than presented in the final report – is this an expected comment? Our position is that the data in the SEND file represents the final report data (and nothing more)*

- What value did you get by participating in Fit For Use Pilot?
  - *A reassurance gained in the knowledge that other participants received similar questions/comments from FDA (it was good to feel less isolated)*
  - *An understanding of what the FDA reviewer is looking for*
  - *Confidence from the data set we provided*

Company 8

- What was important or impactful? any “course corrections”?
  - *The “real” submission conditions greatly helped the review/test of our internal processes, and prompted improvements*
  - *Confirmed some known issues as well as identified new issues with our SEND conversion process, as well as source data entry:*
    - *These issues were used to update user requirements for improving the SEND tool in a current IT project*
    - *Helped define areas to discuss with lab staff to change data collection practices to better enable SEND*
      - *The representation of standardized pathology results were not sufficient for reviewer visualizations*
      - *LB domain – capture of specimen type needed to be changed; verification that all study data was included*
      - *Data extraction practices needed to be adjusted for broader population requirements of SEND (i.e.TK animals)*
  - *Gained better understanding of impact of nSDRG*
    - *Value of explaining non-SEND data handling (i.e. ADA data)*
    - *nSDRG is time-consuming to complete, but it became apparent this is a valued deliverable for reviewers*
    - *We’ve realized the need for a more efficient, effective process to assure a complete nSDRG*
  - *Improved understanding of define file creation and validation*
    - *Previously did not realize the feedback would include validation of Define*
    - *In the nonclinical world (at least ours) there was not a lot of expertise internally on Define. Used the pilot feedback to better learn the Define requirements, on the fly….*

Company 8 (cont.)

- What was unclear or you have questions?
  - *A few validator warnings seemed to conflict with SENDIG (version 3.0) – will the rules be changed?*
    - *i.e. Variable order,* Define.xml/CDISC variable mismatch*,* Invalid origin type
  - How should we address a comment that our explanations of warnings in SDRG were "too technical", considering the Validation Rules are quite technical?
  - Should the explanations of Define validation be included in nSDRG?
  - Concern that parsing modifiers from base findings, among pathologists is high – especially for findings which have a modifier incorporated in incidence tables. How can we allay their fears?

- What value did you get by participating in Fit For Use Pilot?
  - *Appreciation from project teams to pilot the process before their submission!*
  - *Actionable information to provide tool vendors to use in future releases as well as impact our internal processes*
  - *Affirmation that the data provided to the FDA could be visualized using our processes*
  - *Ability to collectively share and learn from a larger pool of data*
  - *Insight into how the data are used by a reviewer*

Company 9

- What was important or impactful? any “course corrections”?
  - *Receiving source data from other systems and vendors in compliant format*
  - *Stress testing our SEND system helped to realize the discrepancies with the pc and pp domains*
  - *Furthering our knowledge of the Define file*

- What was unclear or you have questions?
  - *CL Terminology*
    - *Not a lot of terminology control around this domain, so more challenging to implement*
  - *Proper designation of the TK arm and how best to clarify the study design*
  - *FDA Feedback is unclear: “Would also have been helpful to provide change in BW gain changes from Day 1 to Day 17. The BW data in the study report matches that in the SEND dataset.”*
    - *We provide absolute BW gain changes*
    - *We did not provide percentage gain changes*

Company 9 (cont.)

- What value did you get by participating in Fit For Use Pilot?
  - *Able to streamline our workflow and business processes*
  - *Agreement with FDA on implementation*
  - *Established new regulatory procedures*
  - *Provided confidence to our organization that our SEND implementation strategy was on track*

Company 10

- What was important or impactful? any “course corrections”?
  - *Gave us confidence that our implementation is on the right track for being useful in an actual FDA review*
  - *Confirmed that there are still several implementation details that need to be addressed*
  - *Gained some insight into what the agency considers to be the more inconsistencies between a dataset and study report (helps to determine which things are best handled in SDRG in short term vs. the need to manually modify datasets until additional automation solutions are in place)*
- What was unclear or you have questions?
  - *Generally clear. A few comments could have been more detailed, e.g. examples to demonstrate the issue*
  - *There is some confusion over how much of the CT should be included in Define.xml file*
  - *For certain datasets and variables it is not clear whether “planned” or “actual” data are expected (e.g. TS, EX)*
  - *Still some questions on appropriate use of –TPT and related variables (e.g. being a timing variable, are they restricted to time, or can they also be used to show scheduled events without a time component?)*
- What value did you get by participating in Fit For Use Pilot?
  - *Knowing how CDER OCS plans to use the datasets in the FDA Kickstart phase to bring reviewers up to speed quickly on a study was helpful for defining several implementation ‘best practices’*

Company 11

- What was important or impactful? any “course corrections”?
  - Most important for us was the fact the FDA was going to perform a comprehensive review of our SEND package. This included a data fitness check of our SEND domains and a review by FDA toxicologists, who provided their feedback not only in reports but also in person at the Fall 2016 SEND F2F held at White Oaks. Some of the issues that were identified and we are working on to correct:
    - Ensure that you are using the same version of FDA validation checks when validating your SEND data.
    - If Food Assessment data is collected qualitatively instead of quantitatively, ensure that you are presenting it in the correct domain.
    - We experienced several situations where our SEND output was not correct due to the way the data was collected in our data capture system. For example, the way hours post dose information was collected resulted in a separate record for each animal for each time point in the CL and VS domains.

Company 11 (cont.)

- What was unclear or you have questions?
  - We thought the pilot was well managed. There were frequent meetings to hear new announcements and where any questions could be answered. Also, Dave Epstein did a great job guiding the participants through the process and was always available when needed.
- What value did you get by participating in Fit For Use Pilot?
  - The key value from the pilot for us was the acknowledgement that we were on the right path to becoming SEND ready. Our situation was different from many of the sponsors and CROs who participated since we, back in Aug. 2016, were still in the process of implementing computer systems and business processes required to support the SEND mandate. This resulted in some manual work that, now that we are ready, is no longer needed. But the pilot and the results we received provided valuable insights into some best practices we now follow, such as:

    - If your SEND generation application is tightly integrated with your study data capture application, ensure that all required SEND data, or as much as possible, is entered and collected during the setup and conduct of the study. This will reduce manual intervention during the SEND output process.
    - Adjust your lexicons in your study data capture system to align with SEND controlled terminology lists where possible to reduce the amount of manual term mapping required.
    - Work closely with your CRO partners, both the in-life and BA/PK providers, to establish guidelines on what is expected in terms of the SEND deliverables.
    - Communicate well within your organization, not only in your nonclinical Drug Safety group, but also with your clinical colleagues responsible for submitting SDTM data.

Company 12

- What was important or impactful? any “course corrections”?
  - *The decision to participate the pilot program prompted us to closely test and review the process for generation of high quality SEND data both internally and externally. Even though internal dataset was not submitted to the pilot, the modifications and improvements as a result of this exercise were very instrumental for building a robust process.*
- What was unclear or you have questions?
  - *Feedback from the reviewers was quite straightforward and easy to follow. We appreciate the effort that FDA reviewers put into in providing clear and concise feedback.*
- What value did you get by participating in Fit For Use Pilot?
  - *It was very valuable to have confirmation from the agency that the SEND datasets by our preferred CRO providers conformed with SENDIG and met expectations from the agency.*
  - *It was very valuable to see how SEND data are visualized and analyzed by the agency using their visualization tools.*
  - *It was very valuable to see some of the findings are common amongst sponsors due to validator errors.*
  - *It was very valuable to see industry works together to share the learnings.*

Company 13

- What was important or impactful? any “course corrections”?
  - *The pilot made CDISC-SEND submission “real” for the teams involved. The past technical pilot with the FDA had way less impact.*
  - *We consolidated our internal SEND “todo” list (code lists, way to enter data into LIMS, manual tasks, …) and our (long) wish list for IT providers.*
- What was unclear or you have questions?
  - *We still have to learn what really matters in validator reports. One data format issue had to be solved to enable data load in the FDA system while it was no problem in our internal data warehouse.*
- What value did you get by participating in Fit For Use Pilot?
  - *We got and external benchmark including statement from the FDA reviewers that the SEND package did reflect the study report we submitted. It was an important milestone for our internal SEND project.*
  - *Many great discussions during the PhUSE fit for use meetings. It helped consolidating a community of interested SEND users.*
  - *The FDA report contained comment and screenshots of visualization they used. It is helpful 1) to understand the philosophy of the FDA review and 2) to reinforce internally the need to use “modern” tools. SDTM standardization is helping us to improve our data analysis capacities on the study and the project level but it requires efforts to transition to it.*