PharmaSUG 2023 - Paper SS-224

From FDA to PMDA submission:

How to resolve CDISC non-compliance issues

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ABSTRACT

From the perspective of both the US Food and Drug Administration (FDA) and Japan's Pharmaceuticals and Medical Devices Agency (PMDA), CDISC compliance is mandatory for a submission package. At the core of CDISC compliance are the validation rules specified by each regulatory agency and also within an agency's Technical Conformance Rules. Validation rules may differ between agencies, especially with respect to the assessment of the severity of non-compliance, which can cause an application review to be suspended.

Along with a company acquisition, Lundbeck acquired a Biologics License Application (BLA) submission package that had been submitted to the FDA and that was accepted by the agency, which in time, is also intended for a PMDA submission. To prepare for the PMDA submission, we investigated the FDA package that had previously been submitted by the acquired company and discovered that, due to the difference in CDISC requirements between the FDA and PMDA, four of the trials within the FDA package would be considered CDISC non-compliant based on the PMDA's CDISC compliance rules.

The purpose of this paper is to describe a solution on how to update an existing FDA package to be CDISC compliant for a PMDA submission. Specifically, we share our approach to ensure that while modifying data for CDISC-compliance, transparency, and traceability from data collection to analysis results remains intact, and that there are no alterations to the results. In our paper, we also briefly share our interactions with the PMDA, and how we prepared for meetings with the agency.

INTRODUCTION

Lundbeck acquired a biopharmaceutical company in 2019, and along with this company acquisition, we acquired a BLA FDA submission package that had already been submitted to the FDA, and which subsequently received approval in 2020.

The submission package had been developed by the acquired company based on the FDA-accepted versions of SDTM and ADaM in relation to the CDISC requirements and the FDA's validation rules in Pinnacle 21 (P21). The data submitted to the FDA provided a consistent package of data and documentation including SDTM and ADaM data sets, programs for generating ADaM, and their documentation (Define.xml, Reviewer's Guides, and aCRF) that supported traceability by describing the path between SDTM, ADaM, and the analysis results in the Clinical Trial Reports.

Based on this FDA package, Lundbeck intend to build a submission package that can be accepted by the PMDA. However, it is observed that submission requirements may differ between agencies, and as for the PMDA and FDA, it is noted that these two agencies do not share the same set of Pinnacle 21 validation rules due to their different interpretations of CDISC standards. Even though the CDISC SDTM and ADaM Implementation Guide versions are the same in the FDA package and the one PMDA requires currently, having a submission package that has already been submitted to the FDA (and even approved by the agency) does not automatically imply that one has a submission-ready package for the PMDA.

For the above-mentioned FDA submission package, four trials were not CDISC compliant based on the PMDA's validation rules. The data from one trial was not even in CDISC format, and the data from the other three trials were CDISC compliant based on the FDA's validation rules but were not CDISC compliant based on PMDA's validation rules. This situation could have led to the need to recreate a full

SDTM and ADaM package for all 4 trials just for the PMDA submission, and which would have potentially delayed the submission to the PMDA. Hence, we explored a solution to avoid the need for recreating a full SDTM and ADaM package.

THE INITIAL PMDA MEETING

During our initial meeting with the PMDA, we asked the agency whether an exemption (waiver) for these trials was applicable. Specifically, we asked if we could submit the FDA package as is, and which would therefore have implied that the submitted package would be PMDA CDISC non-compliant. The basis for making this request was that the PMDA accepted data sets that were formatted according to CDISC SDTM version 3.1.3 and CDISC ADaM version 1.0, which were the versions of SDTM and ADaM that had been submitted to the FDA as a part of the BLA to the FDA.

We anticipated that the PMDA might not agree with our request for an exemption (waiver), and so, during that same meeting, requested permission to discuss an alternative solution to the CDISC non-compliance issues, in the event that the PMDA would not grant an exemption.

Without going into detail, we briefly laid out our alternative solution to the PMDA which was to resolve the Pinnacle 21 findings based on PMDA's validation rules through minimal modifications of the data sets that had been submitted to the FDA. Moreover, we proposed to update Define.xml files and Reviewer's Guides according to the SDTM and ADaM updates to ensure consistency and traceability between SDTM and ADaM data sets.

Eventually, the outcome of the meeting was that PMDA did not grant an exemption (waiver) for any of these four trials. So, in relation to the legacy trial that was not in CDISC format, the decision was that the trial needed to be remapped to a CDISC compliant standard, based on the standards established by the PMDA Technical Conformance guide and the PMDA CDISC SDTM and ADaM standards, to be able to pass the PMDA Pinnacle 21 Validation.

For the other three trials, the PMDA accepted our request to discuss our proposed modification approach in further details during the subsequent meeting.

In preparation for that subsequent meeting, we worked on documentation to thoroughly describe our proposed modification approach and the measures we needed to take to ensure that there would be no loss of traceability.

THE APPROACH

Overall, the SDTM and ADaM data sets that would eventually be submitted to the PMDA will be created through modification of the FDA-SDTM and FDA-ADaM data sets, respectively, by using relatively simple modification programs.

Our approach involved several steps:

1. Identification of PMDA P21 findings.
2. Assessment of the impact of the findings on the analysis results.
3. Modification of the data sets.
4. Update of the submission documents i.e., Define.xmls and Reviewer's Guides.

Figure 1 illustrates the relationships between the electronic data submission package that was submitted to the FDA and our proposed method for updating the data sets to fit the PMDA submission requirements. The boxes in dark orange represent the data, programs, and documentation that Lundbeck proposed to submit to the PMDA.

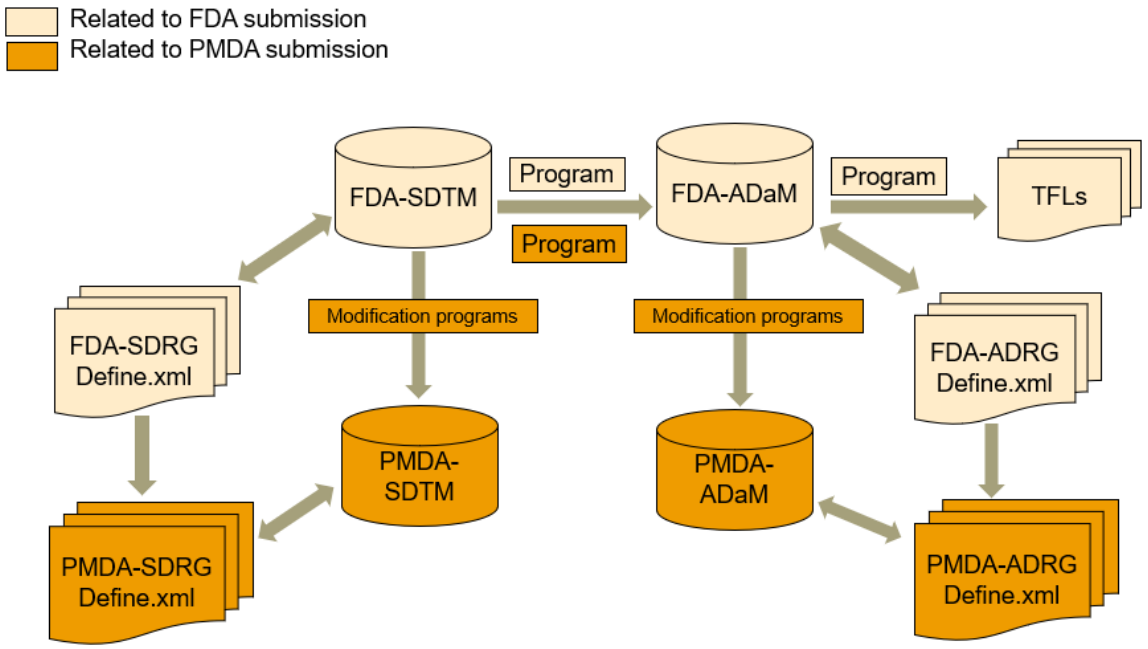


Figure 1. Traceability and data flow in the submission package

Specially, for the FDA-SDTM domains and FDA-ADaM data sets that would not give Pinnacle 21 PMDA REJECT/ERROR findings, we proposed to the PMDA not to modify these but that we would be allowed to submit them in their current form. To maintain consistency between SDTM Define.xml and the PMDA-SDTM data sets, Define.xml would be updated for SDTM, and that the same would be applied for ADaM Define.xml and the PMDA-ADaM data sets. The key benefit of our proposal was that it would keep a clear and unambiguous traceability.

IDENTIFY ALL PMDA P21 FINDINGS

Our process began with the identification of all P21 issues by running the SDTM and ADaM data sets for each trial (from the FDA package) through the PMDA P21 checker.

SDTM - Description, explanation, solution, and modification

First, we focused on SDTM, and below in **Figure 2** is an example of a SDTM P21 report for one trial:

Processed Sources								
Domain	Label	Class	Source	Records	Rejects	Errors	Warnings	Notices
GLOBAL	Global Metadata	--	--	0	0	0	0	0
AE	Adverse Events	EVENTS	ae.xpt	1421	0	3	584	0
CE	Clinical Events	EVENTS	ce.xpt	46081	0	8	22092	0
CM	Concomitant Medications	INTERVENTIONS	cm.xpt	4880	1	0	1196	0
CO	Comments	SPECIAL PURPOSE	co.xpt	102979	0	0	2	0
DM	Demographics	SPECIAL PURPOSE	dm.xpt	2413	0	0	131	0
DS	Disposition	EVENTS	ds.xpt	10329	0	54	14761	0
DV	Protocol Deviations	EVENTS	dv.xpt	324	0	0	89	0
EG	ECG Test Results	FINDINGS	eg.xpt	112547	0	0	215423	0
EX	Exposure	INTERVENTIONS	ex.xpt	3128	0	770	4	0
FA	Findings About Events or Interventions	FINDINGS	fa.xpt	954459	0	0	154783	0
IE	Inclusion/ Exclusion Criteria Not Met	FINDINGS	ie.xpt	1591	0	0	3	0
LB	Laboratory Tests Results	FINDINGS	lb.xpt, lbim.xpt	474057	0	407375	1322900	0
MH	Medical History	EVENTS	mh.xpt	5340	0	1	118	0
PC	Pharmacokinetic Concentrations	FINDINGS	pc.xpt	7977	0	10	27596	0
PE	Physical Examination	FINDINGS	pe.xpt	4146	0	0	9046	0
PP	Pharmacokinetic Parameters	FINDINGS	pp.xpt	12127	0	80	22961	0
QS	Questionnaire	FINDINGS	qs.xpt	467991	0	0	136918	0
RELREC	Related Records	RELATIONSHIP	relrec.xpt	92162	0	0	1	0
SC	Subject Characteristics	FINDINGS	sc.xpt	7245	0	0	14496	0
SE	Subject Elements	SPECIAL PURPOSE	se.xpt	3998	0	0	2193	0
SUPPAE	Supplemental Qualifiers AE	RELATIONSHIP	suppae.xpt	7158	0	0	0	0
SUPPCE	Supplemental Qualifiers CE	RELATIONSHIP	suppce.xpt	46081	0	0	0	0
SUPPCM	Supplemental Qualifiers CM	RELATIONSHIP	suppcm.xpt	5492	0	0	0	0
SUPPDM	Supplemental Qualifiers DM	RELATIONSHIP	suppdm.xpt	6100	0	0	0	0
SUPPDS	Supplemental Qualifiers DS	RELATIONSHIP	suppds.xpt	4455	0	0	0	0
SUPPDV	Supplemental Qualifiers DV	RELATIONSHIP	suppdv.xpt	634	0	0	0	0
SUPPEG	Supplemental Qualifiers EG	RELATIONSHIP	suppeg.xpt	325489	0	0	0	0
SUPPEX	Supplemental Qualifiers EX	RELATIONSHIP	suppex.xpt	3164	0	0	0	0
SUPPFA	Supplemental Qualifiers FA	RELATIONSHIP	suppfa.xpt	16255	0	0	0	0
SUPPLB	Supplemental Qualifiers LB	RELATIONSHIP	supplb.xpt, supplbim.xpt	1932887	0	132836	0	0
SUPPPC	Supplemental Qualifiers PC	RELATIONSHIP	supppc.xpt	6163	0	0	0	0
SUPPSC	Supplemental Qualifiers SC	RELATIONSHIP	suppsc.xpt	1770	0	0	0	0
SUPPXM	Supplemental Qualifiers XM	RELATIONSHIP	suppxm.xpt	157	0	0	0	0
SV	Subject Visits	SPECIAL PURPOSE	sv.xpt	11875	0	0	3781	0
TA	Trial Arms	TRIAL DESIGN	ta.xpt	12	0	0	1	0
TE	Trial Elements	TRIAL DESIGN	te.xpt	3	0	0	0	0
TI	Trial Inclusion/Exclusion Criteria	TRIAL DESIGN	ti.xpt	113	0	0	0	0
TS	Trial Summary	TRIAL DESIGN	ts.xpt	42	0	2	10	0
TV	Trial Visits	TRIAL DESIGN	tv.xpt	31	0	0	0	0
VS	Vital Signs	FINDINGS	vs.xpt	47661	0	4	6217	0
XM	Concomitant Procedures	INTERVENTIONS	xm.xpt	157	0	0	62	0
XR	Headache Ediary Findings	FINDINGS	xr.xpt	3027401	0	275217	682039	0
Total				7758295	1	816360	2637407	0

Figure 2. SDTM P21 report for one trial

We investigated all REJECT and ERROR findings for SDTM one trial at a time to identify whether it was possible to resolve all these findings. Warnings were only looked at if they were in relation to REJECT and/or ERROR findings. These are shown in **Figure 3**.

Issue Summary				
Source	Pinnacle 21 ID	Message	Severity	Found
AE				
	CT2001	AEACN value not found in 'Action Taken with Study Treatment' non-extensible codelist	Error	3
CE				
	SD0013	CESTDTC is after CEENDTC	Error	2
	SD1331	CESTDTC is after CEDTC	Error	6
CM				
	SD0002	NULL value in CMTRT variable marked as Required	Reject	1
EX				
	SD1206	EXSTDTC date is after RFXENDTC	Error	2
	SD1207	EXENDTC date is after RFXENDTC	Error	2
	SD1249	EXDOSE does not equal 0 when EXTRT = 'PLACEBO'	Error	766
MH				
	SD1331	MHSTDTC is after MHDTC	Error	1

Figure 3. Examples of P21 REJECT and ERROR findings in SDTM

We created an appendix to the Briefing Document to detail the SDTM P21 findings for each of the three CDISC non-compliant trials. Specifically, the findings were categorised according to whether they were resolvable or non-resolvable, and for each finding, an explanation on how to resolve it, as well as an assessment on the impact on ADaM and the existing Tables, Figures, and Listings (TFLs) published in the CTR, was provided.

An example of an SDTM P21 finding from the Appendix is shown below in **Figure 4**:

Pinnacle 21 ID: SD1331

Source	MH
Message	MHSTDTC is after MHDTC
Description	Start Date/Time of Event, Exposure (--STDTC) must be less or equal to Date/Time of Collection (--DTC)
Explanation	MH.MHDTC, Date/Time of History Collection, contains information about the collection date (in this case date of screening visit), whereas MH.MHSTDTC contains the start date of the medical history event. The ERROR finding is due to one record where MHSTDTC is after MHDTC: MHTERM: OVERWEIGHT; MHDTC: 2016-07-26; MHSTDTC: 2016-08; MHDY: -29 According to SDTM IG v.3.1.3, MH.MHDTC is a permissible variable and MHDTC is not used in any ADaM datasets
Solution	This ERROR finding will be resolved by removing MH.MHDTC from SDTM.MH. Variables ending on "DY" describe the relative day of an observation, and in this case MH.MHDY, Study Day of History Collection, is related to MH.MHDTC and therefore this variable needs to be removed from the MH domain as well. MHDY is not used in any ADaM datasets
Impact ADaM	MHDTC or MHDY are not used in ADaM.ADMH
Impact TFL	None

Figure 4. Examples of resolvable P21 ERROR finding and solution

After investigating all P21 findings and providing recommendations on how to resolve them, we also

needed to see if the recommended update of the data was possible. To this end, we created a "modification.sas" program which read in the final SDTM data set submitted to the FDA and then updated the relevant domains accordingly.

The modification program for the above ERROR finding in SDTM.MH is shown below:

```
* SDTM.MH Update: Remove MHDTC and MHDY variable;
data OUT.MH;
   set SDTM.MH;
   drop MHDTC MHDY;
run;
```

ADaM - Description, explanation, solution, and modification

For the same trials, we then investigated all findings in ADaM, and a similar report was done for each finding with a description of the finding, an explanation, a proposal on how to resolve the finding and an assessment on the impact on the TFLs that have been published in the CTR.

The ADaM P21 report for the same trial is shown below in **Figure 5**:

Pinnacle 21 Validator Report

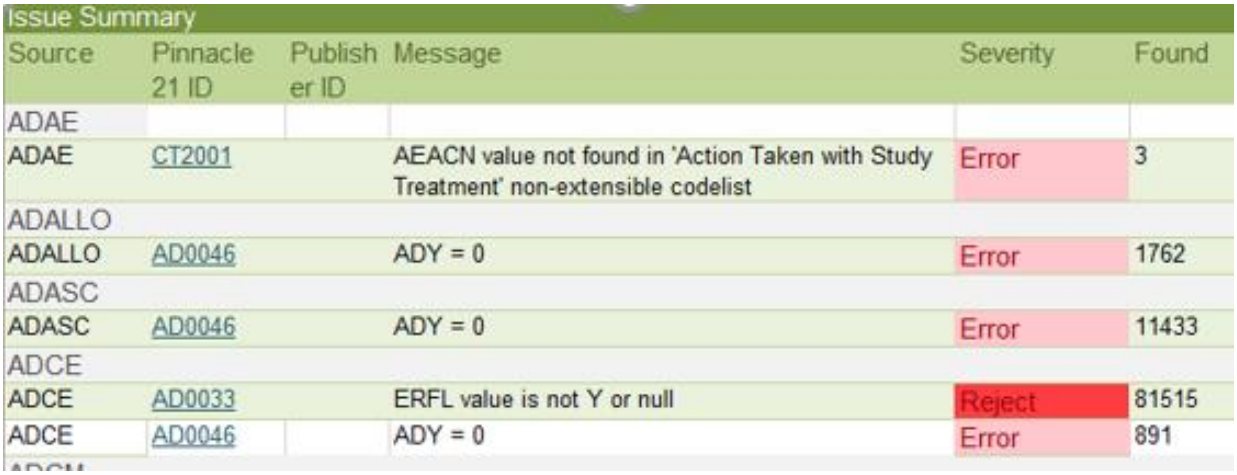
Processed Sources

Domain	Label	Class	Source	Records	Rejects	Errors	Warnings
GLOBAL	Global Metadata	--	--	0	0	0	0
ADAE	Adverse Event Analysis Dataset	ADVERSE EVENT ANALYSIS DATASET	adae.xpt	1421	0	3	0
ADALLO	Allodynia Analysis Dataset	BASIC DATA STRUCTURE	adallo.xpt	9829	0	1762	0
ADANLCE	Clinical Event Efficacy Analysis Dataset	BASIC DATA STRUCTURE	adanlce.xpt	762700	0	0	644388
ADASC	Allodynia Symptom Analysis Dataset	BASIC DATA STRUCTURE	adasc.xpt	74706	0	11433	5750
ADBDI	BDI-II Analysis Dataset	BASIC DATA STRUCTURE	adbdi.xpt	983	0	0	0
ADCE	Clinical Events Analysis Dataset	OCCURRENCE DATA STRUCTURE	adce.xpt	327088	81515	891	1
ADCM	Concomitant Medication Analysis Dataset	OCCURRENCE DATA STRUCTURE	adcm.xpt	4880	0	28	2978
ADCSSRS	C-SSRS Analysis Dataset	BASIC DATA STRUCTURE	adcssrs.xpt	140961	0	11159	100
ADDEV	Protocol Deviations Dataset	BASIC DATA STRUCTURE	addev.xpt	323	0	0	0
ADEFFCE	Events Efficacy Analysis Dataset	BASIC DATA STRUCTURE	adeffce.xpt	199800	0	0	306360
ADEG	Electrocardiogram Analysis Dataset	BASIC DATA STRUCTURE	adeg.xpt	100478	0	15795	0
ADEQD	EQ-5D-5L Analysis Dataset	BASIC DATA STRUCTURE	adeqd.xpt	34522	0	5279	0
ADEX	Treatment Exposure Analysis Dataset	OCCURRENCE DATA STRUCTURE	adex.xpt	3128	0	1776	0
ADIE	Incl./Excl. Criteria Analysis Dataset	BASIC DATA STRUCTURE	adie.xpt	1589	0	0	0
ADLB	Laboratory Analysis Dataset	BASIC DATA STRUCTURE	adlb.xpt	456478	0	38842	0
ADLBIM	Immunology Laboratory Analysis Dataset	BASIC DATA STRUCTURE	adlbim.xpt	87164	0	9768	0
ADMH	Medical History Analysis Dataset	OCCURRENCE DATA STRUCTURE	admh.xpt	5340	0	0	6350
ADPC	Analysis Dataset for PC	BASIC DATA STRUCTURE	adpc.xpt	9572	0	0	4
ADPP	Analysis Dataset for PK	BASIC DATA STRUCTURE	adpp.xpt	12195	0	0	0
ADREPCE	Clinical Events Report Analysis Dataset	BASIC DATA STRUCTURE	adrepce.xpt	393568	0	0	139600
ADSF	SF-36 Health Survey Analysis Dataset	BASIC DATA STRUCTURE	adsf.xpt	72316	0	8792	0
ADSL	Subject-Level Analysis Dataset	SUBJECT LEVEL ANALYSIS DATASET	adsl.xpt	2413	0	0	81
ADTTE	Time to Event Analysis Dataset	BASIC DATA STRUCTURE	adtte.xpt	888	0	0	0
ADVS	Vital Signs Analysis Dataset	BASIC DATA STRUCTURE	advs.xpt	51748	0	8028	6069
AE	Adverse Events	EVENTS	aesi.xpt	420	0	0	0
CM	Concomitant Medications	SYSTEM	cm.xpt	4880	0	0	1
DM	Demographics	SYSTEM	dm.xpt	2413	0	0	0
SFSCORED	Unrecognized	SYSTEM	sfscored.xpt	7238	0	0	1
Total				2769041	81515	113556	1111683

Figure 5. ADaM P21 report for one trial

Similar to what we had done for the SDTM P21 findings, we also investigated all REJECT and ERROR findings for ADaM to identify whether it was possible to resolve all these findings. Examples of these are

shown below in **Figure 6.**



Issue Summary

Source	Pinnacle 21 ID	Publisher ID	Message	Severity	Found
ADAE					
ADAE	CT2001		AEACN value not found in 'Action Taken with Study Treatment' non-extensible codelist	Error	3
ADALLO					
ADALLO	AD0046		ADY = 0	Error	1762
ADASC					
ADASC	AD0046		ADY = 0	Error	11433
ADCE					
ADCE	AD0033		ERFL value is not Y or null	Reject	81515
ADCE	AD0046		ADY = 0	Error	891

Figure 6. Examples of P21 REJECT and ERROR findings in ADaM

In the same appendix to the Briefing Document that contained the details of the SDTM P21 findings, we also provided the details of the ADaM P21 findings for each of the three CDISC non-compliant trials with a description, an explanation, and a proposal on how to resolve each finding, as well as an assessment of their impact on the existing TFL's.

Pinnacle 21 ID: AD0046

Source	ADCE
Message	ADY = 0
Description	A variable with a suffix of DY (day) must not equal zero. Variables whose names end in DY are relative day variables. In ADaM as in the SDTM, there is no day 0. If there is a need to create a relative day variable that includes day 0, then its name must not end in DY
Explanation	The issue is present for 891 records. In this study, patients were infused at Day 0 and there is a need to include Day 0 in the analyses. ADY is not used in TFLs
Solution	To accommodate the need for Day 0 (zero) as an analysis day, the solution of this ERROR finding will be to rename ADY to ADAY (label = Analysis Day)
Impact TFL	None

Figure 7. Example of resolvable P21 ERROR finding and solution

Pinnacle 21 ID: AD0033

Source	ADCE
Message	ERFL value is not Y or null
Description	A variable with a suffix of RFL must have a value that is Y or null (R = record level flag variable)
Explanation	ADCE.ERFL in ADAM.ADCE is a flag indicating "Evening Report Available" and contains "Y" or "N". It is not a record level flag, which is only allowed to contain "Y" or " ". In ADCE, ADCE.ERFL = "N" for 81515 records
Solution	The solution for resolving this ERROR finding will be to rename the variable to EVEFL (a Lundbeck project standard variable name for this information). This would be a sponsor defined variable, since there is no CDISC ADaM variable defined for this. The variable, ADCE.ERFL, is used in the derivation of ADREPCE.AVAL (where PARAMCD = "REDDAY" and "MEDDAY"). The renaming of ERFL to EVEFL hence implies that an update in this derivation will be needed as well
Impact TFL	None. By only renaming the variable and not change the content of the variable, no impact occurs on TFLs

Figure 8. Example of resolvable P21 REJECT finding and solution

After investigating all the P21 findings and providing recommendations on how to resolve them, we also created a "modification.sas" program as we had done for SDTM. This modification program reads in the final ADaM data set submitted to the FDA, and subsequently, an update according to the findings from the PMDA Pinnacle 21 report is executed, as shown below for the ADaM data set ADCE (ADAM.ADCE).

```
* ADCE - renaming of variables acc. to ADaMIG;
data OUT.ADCE;
   set ADAM.ADCE(rename=(ADY=ADAY ERFL=EVEFL));
   label ADAY = "Analysis Day";
run;
```

Output 1 and **Output 2** below illustrate the modifications to ADAM.ADCE, before and after modification, respectively.

	ADT	ADY	AVISIT	ERFL
35	15DEC2015	-1		N
36	16DEC2015	0	Weeks 1-4	Y
37	17DEC2015	1	Weeks 1-4	Y
38	18DEC2015	2	Weeks 1-4	Y
39	19DEC2015	3	Weeks 1-4	Y
40	20DEC2015	4	Weeks 1-4	Y

Output 1. Output from ADAM.ADCE BEFORE the modification

	ADT	ADAY	AVISIT	EVEFL
35	15DEC2015	-1		N
36	16DEC2015	0	Weeks 1-4	Y
37	17DEC2015	1	Weeks 1-4	Y
38	18DEC2015	2	Weeks 1-4	Y
39	19DEC2015	3	Weeks 1-4	Y
40	20DEC2015	4	Weeks 1-4	Y

Output 2. Output from ADAM.ADCE AFTER the modification

As illustrated above, the content of the ADCE ADaM data set remains exactly the same and only the naming of the variables ADY and ERFL have been changed to adhere to the PMDA validation rules.

After modifying the SDTM and ADaM data, we needed to update the Define.xml and the ADRG accordingly while ensuring consistency and traceability between SDTM and ADaM data sets.

Figure 9 illustrates the update to ADaM Define.xml in relation to the above modification of ADCE, while **Figure 10** illustrates the update to ADRG:

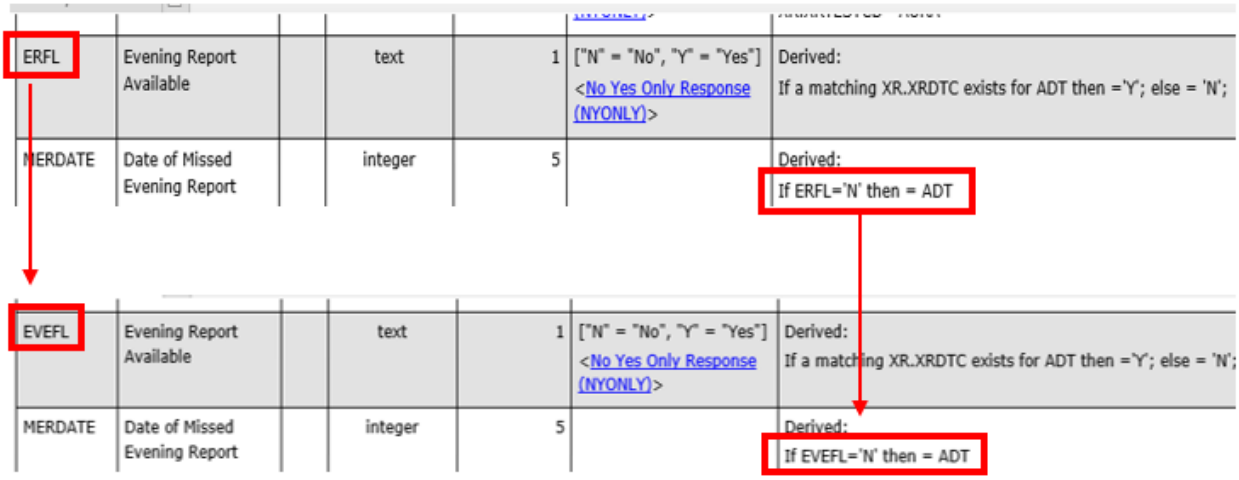
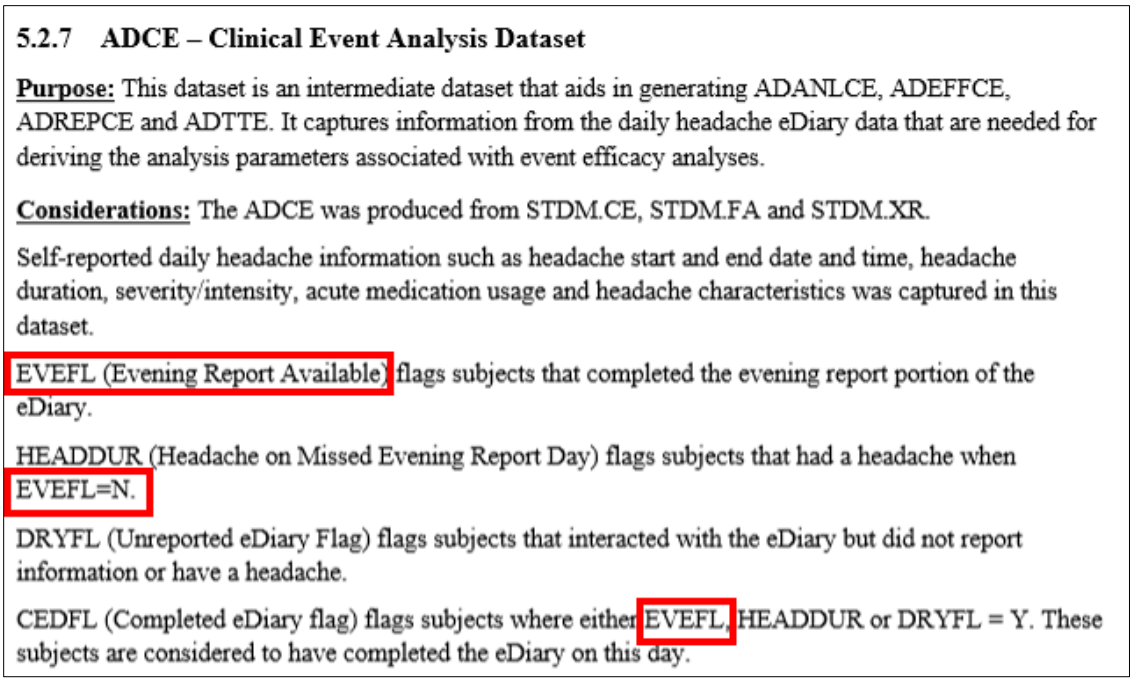


Figure 9. Define.xml for ADaM before and after the update



5.2.7 ADCE – Clinical Event Analysis Dataset

Purpose: This dataset is an intermediate dataset that aids in generating ADANLCE, ADEFFCE, ADREPCE and ADTTE. It captures information from the daily headache eDiary data that are needed for deriving the analysis parameters associated with event efficacy analyses.

Considerations: The ADCE was produced from STDM.CE, STDM.FA and STDM.XR.

Self-reported daily headache information such as headache start and end date and time, headache duration, severity/intensity, acute medication usage and headache characteristics was captured in this dataset.

EVEFL (Evening Report Available) flags subjects that completed the evening report portion of the eDiary.

HEADDUR (Headache on Missed Evening Report Day) flags subjects that had a headache when EVEFL=N.

DRYFL (Unreported eDiary Flag) flags subjects that interacted with the eDiary but did not report information or have a headache.

CEDFL (Completed eDiary flag) flags subjects where either EVEFL, HEADDUR or DRYFL = Y. These subjects are considered to have completed the eDiary on this day.

Figure 10. Updated ADRG

Finally, the section about “Data Conformance Summary” in the Reviewer’s Guide for both SDTM and ADaM needed to be replaced with the findings from the PMDA P21 report.

P21 findings affecting both SDTM and ADaM

For a few P21 findings, the updates in SDTM had an impact on ADaM as well, which therefore required updates to both SDTM and ADaM. Below, we provide examples of P21 findings that required updates to both SDTM and ADaM data, some of which were resolvable, while others were unresolvable.

Resolvable P21 finding

Here, we illustrate a P21 findings that required updates to both SDTM and ADaM data, and which was resolvable. Specifically, it involved the resolution of a REJECT finding in both SDTM and ADaM.

Pinnacle 21 ID: SD0002

Source	CM
Message	NULL value in CMTRT variable marked as Required
Description	Required variables (where Core attribute is 'Req') cannot be NULL for any records
Explanation	CM.CMTRT is NULL in 1 record. According to cSDRG, the explanation for this finding is as follows: *"Missing in database, DM response: CRA asked site to remove medication and Medication History page answer was not queried to be changed to No. Record was verified this way. During listing review, inconsistency was missed"*
Solution	Since it is documented that this record should never have been present in SDTM.CM, this REJECT finding will be resolved by deleting this record from SDTM.CM.
Impact ADAM	This record is transferred directly from SDTM.CM to ADAM.ADCM, so as the record is removed from SDTM.CM, it will also be removed from ADAM.ADCM
Impact TFL	There is NO impact, since "where non-missing CMTRT" is used in selection of data from ADAM.ADCM when creating TFL output

Figure 11. Example of resolvable P21 REJECT finding and solution

The modification of SDTM.CM due to the REJECT finding is shown below:

```
* SDTM.CM update: Remove record where CMTRT = " " acc. to SDRG, a mistake
that the query was not fixed (i.e. removed from database);
data OUT.CM;
   set SDTM.CM;
   if USUBJID = "123456789" and CMDECOD = "" and CMTRT = " " then delete;
run;
```

The modification of ADAM.ADCM due to the update in SDTM.CM above is shown below:

```
*  ADCM Update acc. to update in SDTM;
data OUT.ADCM;
   set ADAM.ADCM;
   * Due to update in SDTM from ERROR finding in SDTM P21 report;
   if USUBJID = "123456789" and CMDECOD = "" and CMTRT = " " then delete;
run;
```

Next, we illustrate another P21 findings that was resolvable, this time involving an ERROR finding the affected both SDTM, ADaM, and TFL.

Pinnacle 21 ID: SD1249

<table>
<tr><td>Source</td><td>EX</td></tr>
<tr><td>Message</td><td>EXDOSE does not equal 0 when EXTRT = 'PLACEBO'</td></tr>
<tr><td>Description</td><td>EXDOSE must be equal to 0 when EXTRT = 'PLACEBO'</td></tr>
<tr><td>Explanation</td><td>766 records have EX.EXDOSE = 0 when EX.EXTRT = “PLACEBO”</td></tr>
<tr><td>Solution</td><td>To resolve the ERROR finding in EX.EXDOSE (Dose exposed) in SDTM.EX, the content of the variable should be updated from 100 to 0 for PLACEBO in the updated EX.EXDOSE.

Since EXDOSE must be the same variable in SDTM.EX and ADAM.ADEX, updating EX.EXDOSE in SDTM.EX to resolve the ERROR findings would also require an update of ADEX.EXDOSE. Since ADEX.EXDOSE = 100 was used in the programs that generated the statistical output for the CSR, a new variable should be added to match the output in the CSR.

The solution will be to derive a new variable, VOLUMINF (“Volume Infused”), in ADAM.ADEX to specify the original content of EXDOSE (=100).
<table>
<tr><th></th><th>SDTM.EX</th><th>ADAM.ADEX</th></tr>
<tr><td>Original EXDOSE in SDTM.EX and ADAM.ADEX</td><td>100</td><td>100</td></tr>
<tr><td>Updated EXDOSE in SDTM.EX and ADAM.ADEX for Placebo patients only</td><td>0</td><td>0</td></tr>
<tr><td>New ADaM variable, VOLUMINF</td><td>--</td><td>100</td></tr>
</table>
</td></tr>
<tr><td>Impact ADaM</td><td>EX.EXDOSE from SDTM.EX is copied directly into ADAM.ADEX, so updating EX.EXDOSE in SDTM.EX also requires an update of ADEX.EXDOSE. A new variable, (VOLUMINF, Volume Infused), will be created with the content of the “original” EX.EXDOSE for use when creating TFL output</td></tr>
<tr><td>Impact TFL</td><td>ADEX.EXDOSE = 100 is used in TFL, so TFL program needs to be updated to select the new created variable, VOLUMINF, to produce the same output</td></tr>
</table>

Figure 12. Example of resolvable P21 ERROR finding and solution

The modification of SDTM.EX due to the ERROR finding is shown below:

```
* SDTM.EX Update: If EXTRT = PLACEBO, then EXDOSE should be = 0;
data OUT.EX;
   set SDTM.EX;
   if EXTRT = "PLACEBO" and EXDOSE ne 0 then EXDOSE = 0;
run;
```

The same modification is done in ADAM.ADEX is shown below:

```
* ADEX Update: Changes made to SDTM.EX that require update in ADaM as well;
data OUT.ADEX;
   set ADAM.ADEX;
   * Before update EXDOSE=0, create new variable containing the old EXDOSE;
   VOLUMINF = EXDOSE;
   label VOLUMINF = "Volume Infused";
   * SDTM.EX Update: If EXTRT = PLACEBO, then EXDOSE should be = 0;
   if EXTRT = "PLACEBO" then EXDOSE = 0;
run;
```

A selected part of ADEX before and after the update, is presented below:

BEFORE:

USUBJID	AVISIT	EXTRT	EXDOSE
XX01	Day 0	PLACEBO	100
XX02	Day 0	DRUG ZZZ	100
XX02	Week 12	DRUG ZZZ	100
XX02	Week 24	DRUG ZZZ	100
XX03	Day 0	DRUG YYY	100
XX03	Week 12	DRUG YYY	100

AFTER:

USUBJID	AVISIT	EXTRT	EXDOSE	VOLUMINF
XX01	Day 0	PLACEBO	0	100
XX02	Day 0	DRUG ZZZ	100	100
XX02	Week 12	DRUG ZZZ	100	100
XX02	Week 24	DRUG ZZZ	100	100
XX03	Day 0	DRUG YYY	100	100
XX03	Week 12	DRUG YYY	100	100

Output 3. Output from ADAM.ADEX before and after the modification

Unresolvable P21 ERROR finding affecting both SDTM, ADaM, and TFL

We also identified P21 findings that were unresolvable. In many cases, the reason that they were unresolvable was that attempts to resolve them would affect the already published output, as illustrated by the example below in **Figure 13**.

Pinnacle 21 ID: CT2001

Source	AE
Message	AEACN value not found in 'Action Taken with Study Treatment' non-extensible codelist
Description	Variable must be populated with terms from its CDISC controlled terminology codelist. New terms cannot be added into non-extensible codelists
Unresolvable explanation	Three subjects have "Action Taken with Study Treatment", AE.AEACN = "MULTIPLE", which is not found in the non-extensible "Action taken" codelist. According to the cSDRG, section 4.2 Issue Summary from SDTM datasets, the following is stated: *"Multiple" actions were taken, and each action was mapped in AE.SUPPAE, and "MULTIPLE" was marked in AE.AEACN*". **SDTM.AE:** ents) AESEQ | AESER | AEACN | AEACNOTH | AEOUT | AESTDTC | AEENDTC 1 N MULTIPLE RECOVERED/RESOLVED 2016-05-13 2016-05-13 **SDTM.SUPPAE:** emental Qualifiers AE) RDOMAIN | IDVAR | IDVARVAL | QNAM | QLABEL | QVAL AE AESEQ 1 AEACNINT Study Drug Infusion Interrupted DRUG INTERRUPTED AE AESEQ 1 AEACNWT Study Drug Infusion Withdrawn DRUG WITHDRAWN AEACN is presented in ADaM but not used in TFL output. Instead, **ADAE.AEINFL** (Study Drug Infusions Interrupted Flag) and **ADAE.AEWTFL** (Study Drug Infusion Withdrawn Flag) are used to create TFL output. **ADAM.ADAE:** Event Analysis Dataset) AESEQ | AESER | AESTDTC | AEENDTC | TRTEMFL | AEACN | AEACNOTH | AEINFL | AEWTFL 1 N 2016-05-13 2016-05-13 Y MULTIPLE Y Y The presentation of data in SDTM.AE and SDTM.SUPPAE are exactly as described in the SDTM IG v.3.1.3 for non-result qualifiers, where AE.AEACN is used as an example (see SDTM IG 3.1.3 section 4.1.2.8.3), so this ERROR finding is considered unresolvable.

Figure 13. Example of unresolvable P21 ERROR finding

The output related to the above finding is shown below in **Figure 14**:

Category	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Subjects with Any TEAE	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Number of TEAEs	xx	xx	xx	xx	xx	xx
Subjects with Any Study Drug Related TEAE	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Number of Study Drug Related TEAEs	xx	xx	xx	xx	xx	xx
Subjects with Any Severe TEAE	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Number of Severe TEAEs	xx	xx	xx	xx	xx	xx
Subjects with Any Serious TEAE	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Number of Serious TEAEs	xx	xx	xx	xx	xx	xx
Subjects with Any TEAE Leading to Study Drug Withdrawal	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Number of TEAEs Leading to Study Drug Withdrawal	xx	xx	xx	xx	xx	xx
Subjects with Any TEAE Leading to Study Drug Interrupted	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Number of TEAEs Leading to Study Drug Interrupted	xx	xx	xx	xx	xx	xx

Figure 14. Adverse Event table affected by the P21 finding

Unresolvable P21 ERROR finding affecting only ADaM

Here is an example of a P21 finding that only affects ADaM, but yet, has a large impact, since the finding involves variables that are used in all other ADaM data sets.

Pinnacle 21 ID: AD0073 and AD0062

Source	ADSL
Message	Illegal variable name: xx is not in [01-99] for TRTxxP / TRTxxA
Description	AD0073: For TRTxxP (Planned treatment), xx must be the treatment period (01 to 99). AD0062: For TRTxxA (Actual treatment), xx must be the treatment period (01 to 99)
Unresolvable explanation	These ERROR findings are due to TRTP and TRTA being included in ADSL. Also, the required variables, ADSL.TRT01P and ADSL.TRT01A are present. In ADSL, TRTP = TRT01P and TRTA = TRT01A.

TRT01P	Planned Treatment for Period 01	text	50	TRT	Derived Derived from ARM
TRT01A	Actual Treatment for Period 01	text	50	TRT	Derived Derived from ACTARM
TRTP	Planned Treatment	text	50	TRT	Derived =TRT01P
TRTA	Actual Treatment	text	50	TRT	Derived =TRT01A

ADSL.TRTP and ADSL.TRTA are used in other ADaM datasets as predecessors from ADSL as shown in below example from ADEG

TRTP	Planned Treatment	text	50	TRT	Predecessor: ADSL.TRTP
TRTA	Actual Treatment	text	50	TRT	Predecessor: ADSL.TRTA

Hence TRTP and TRTA cannot be removed from ADSL without impacting derivations in several datasets. Keeping data as is has no impact on TFL since TRT01P is always equal to TRTP and TRT01A is always equal to TRTA

Figure 15. Example of unresolvable P21 ERROR finding

We performed this thorough investigation of all P21 REJECTS and ERROR findings in both SDTM and ADaM for the three trials. In total there were 65 findings for ADaM and 184 for SDTM, of which some required an update to data and documentation whereas the unresolvable findings only required an explanation. We estimate this work to be approximately 3 months' work for 2 employees.

THE METHOD CONSULTATION MEETING WITH PMDA

Prior to the Electronic Data Preparation (Method) Consultation Meeting, a Briefing Document, a cover letter, a completed Form A (Explanatory Materials for Electronic Data to be Applied), and an Appendix containing an overview of REJECT and ERROR findings (as well as solutions for all findings) for all three trials were prepared and sent to the PMDA.

Traceability and transparency are essential for the regulatory agencies to understand the relationship or path between data collection, SDTM, and ADaM data sets, and the analysis results. This is the main reason that we made it a priority to provide a thorough documentation on the maintenance of traceability that followed modification of SDTM and ADaM.

Scientific Officers from the PMDA and participants from Lundbeck (specifically, those from functional areas that included Regulatory [from headquarters as well as the local Japanese affiliate], Biometrics, and Medical Documentation) participated in the meeting. During the meeting, the PMDA provided their position on Lundbeck's consultation items.

Overall, the PMDA accepted our strategy of modifying legacy data (i.e. data that had been submitted to the FDA) so that the data could comply with the PMDA P21 validation rules, as long as we could clearly document and ensure that traceability was intact.

CONCLUSION

The cornerstone for any data submission is traceability. When building confidence in a result, traceability and transparency are essential for regulatory agencies to understand the relationship or path between data collection, SDTM, ADaM data sets, and the analysis results.

The SDTM and ADaM data sets and their associated metadata (Define.xmls and Reviewer's Guides) provide the important sources of traceability to clearly describe how the source or derivation of the analysis data sets and variables are performed. Our suggested modification approach was tied very closely with the traceability of metadata and data points. Indeed, we consider that it is one thing to update the SDTM and ADaM data sets to be CDISC compliant, but another thing to properly document these updates i.e. in the Define.xmls (SDTM and ADaM) and Reviewer's Guides (cSDRG and ADRG).

Overall, we have developed a method for modifying a data package (that was originally submitted to the FDA) for PMDA submission that meets the PMDA's submission requirements, and without needing to remap all data. It must be said that the development, implementation, and documentation of this modification approach was time-consuming and tedious. However, the alternative scenario (i.e. a remapping of the SDTM and ADaM for 3 large trials) would have been even more time-consuming and could have resulted in a submission delay.

During the process, we thoroughly investigated all P21 REJECTS and ERROR findings in both SDTM and ADaM for the three trials for the potential for modification and assessed their implications down-stream to the analysis results. We also assessed how the modification to solve the findings impacted the submissions documents (Define.xmls and Reviewer's Guides) that ensures this traceability. The documentation of this work resulted in an appendix of 60 pages that was sent to the PMDA together with the Briefing document prior to the consultation.

Nonetheless, we believe that this work was key to achieving a positive feedback from the PMDA, as through the documentation that we provided, we were able to clearly demonstrate the relationship between analysis results and the collected data, and thereby demonstrate the robustness of our modification and verification strategy to the PMDA.

At Lundbeck, we were very pleased that the PMDA had accepted our solution on how to make the FDA submission package PMDA CDISC compliant and PMDA submission-ready, without having to recreate a full SDTM and ADaM package for all three trials.

ACKNOWLEDGMENTS

We would like to thank our great colleagues across Lundbeck for the good collaborations, their invaluable input, and for reviewing this paper.

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