

PhUSE SDE ADaM Review from a CDER Statistical Reviewer's Perspective

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FDA Disclaimer

- This presentation reflects the views of the authors and should not be construed to represent FDA's views or policies.

Outline

- CDER encourages use of ADaM
- ADaM Evaluation
- Usefulness of ADaM for other Statistical Reviewers
- Example Data Request from my Medical Division

CDER encourages use of ADaM

“CDER strongly encourages IND sponsors and NDA applicants to consider the implementation and use of data standards”

FDA.gov webpage

CDER encourages use of ADaM

- **Data Standard Common Issues Document**
- **Study Data Specifications**
- **eStudy Data Guidance**
Guidance for Industry: Providing Regulatory Submissions
in Electronic Format — Standardized Study Data
- **CDER eData team**

CDER encourages use of ADaM

Why Push for Study Data Standards?

Overall Improved Efficiency Analyzing Data

- Consistent data structure
- Consistent nomenclature
- Analysis-ready
- Standardize not only the data
 - Metadata
 - Representation of the relationship between data elements

CDER encourages use of ADaM

Consistent Nomenclature

– Patient identifier

- Possibilities: PTNO, STYSID1A, PATNO, PATNUM, SUBJID, PATID, PTID, PATIENT, ALLOC...
- **ADaM: USUBJID**

– Treatment assignment:

- Possibilities: GROUP, TRT1C, TRT, TREAT, RANDTRT, TRTREG, REGCODE, RANDDRG ...
- **ADaM: TRTP and TRTPN**

ADaM Evaluation

- Content Standard: CDISC Analysis Data Model (ADaM) v2.1 and corresponding Implementation Guide (ADaMIG) v1.0
- Metadata Standard: CDISC Define.XML v1.0 (draft v2.0 recently released)

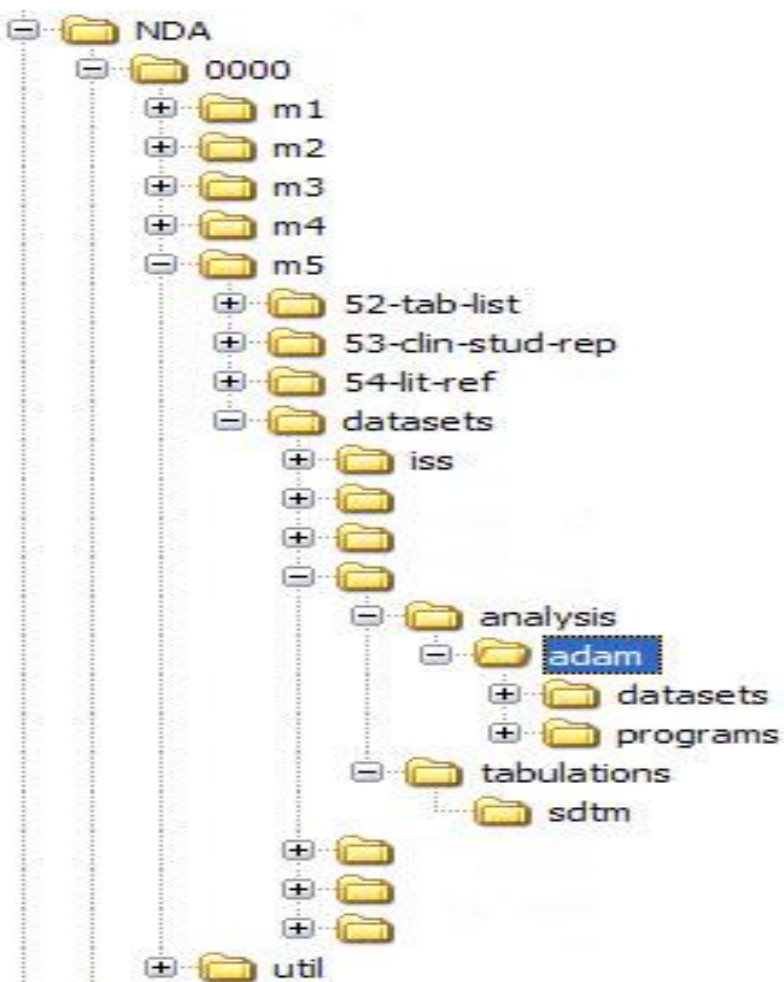
ALWAYS A WORK IN PROGRESS...

ADaM Evaluation

- In the past, and unlike for SDTM data, primarily using judgment whether “useable”
 - We ask ourselves, “Is it useable for a reviewer?”
 - “Compliance” = “usability”
- Presently **much more** detailed in ADaM Evaluation
 - Some ADaM checks exist in the CDER DataFit Program
 - Another work in progress...
 - Still primarily an eye test

ADaM Evaluation

eCTD Check



ADaM Datasets

Analysis Programs

SDTM Datasets

ADaM Evaluation Metadata Check

- Typical Industry Process
 - Produce ADaM Datasets and then produce corresponding Metadata File
 - Same process applies for Production of SDTM Datasets
- Regulatory Review Process
 - Comprehensively Review Metadata File prior to engaging ADaM Datasets
 - Again, same process applies for utilizing SDTM Datasets during a review



ADaM Evaluation

Metadata Check – Dataset Level

Datasets
☐ Subject-Level (ADSL)
☐ Subject-Level Analysis Data - Scr. Fail. (ADSLSF)
☐ Concomitant Medications, Therapies and Procedures (ADCM)
☐ Adverse Event (ADAE)
☐ Protocol Deviations (ADDV)
☐ Antibody (ADAB)
☐ Efficacy (ADEFF)
☐ Efficacy - QS (ADEFFQS)
☐ ECG (ADEG)
☐ Infusion Vital Signs (ADIVS)
☐ Laboratory (ADLB)
☐ Medical History (ADMH)
☐ Physical Exam (ADPE)
☐ Time to Event (ADTIME)
Value Level Metadata
Controlled Terminology
☐ Code Lists
☐ STUDYID
☐ TRT
☐ TRTN
☐ ALLYN
☐ DSREAS
☐ ABSRCDOM
☐ ABSRCVAR
☐ ABPARAMCAT
☐ ABPARAMCD
☐ ABPARAM
☐ ABPARAMN
☐ ABVISITNUM
☐ ABVISIT
☐ ALLY
☐ ABAVALC
☐ ABDTYPE
☐ AGEGRP
☐ AGEGRPN
☐ SEX
☐ SEXN

Datasets for Study -ADaM

Dataset	Description	Class	Structure	Purpose	Keys	Location
ADSL	Subject-Level	SPECIAL PURPOSE	One record per subject	Analysis	USUBJID	adsl.xpt
ADSLSF	Subject-Level Analysis Data - Scr. Fail.	SPECIAL PURPOSE	One record per subject	Analysis	USUBJID	adslsf.xpt
ADCM	Concomitant Medications, Therapies and Procedures	INTERVENTIONS	One record per conmed per subject	Analysis	USUBJID, CMCAT, CMSTDTC, CMDECOD, CMTRT	adcm.xpt
ADAE	Adverse Event	EVENTS	One record per AE term per subject	Analysis	USUBJID, AESTDTC, AETERM	adae.xpt
ADDV	Protocol Deviations	EVENTS	One record per reported term per visit per subject	Analysis	USUBJID, VISITNUM, DVSTDTC, DVTERM	addv.xpt
ADAB	Antibody	FINDINGS	One record per antibody parameter per time point per subject	Analysis	USUBJID, PARAMN, VISITNUM, ADT	adab.xpt
ADEFF	Efficacy	FINDINGS	One record per efficacy parameter per time point per subject	Analysis	USUBJID, PARAMN, AVISITN, ADT	adeff.xpt
ADEFFQS	Efficacy - QS	FINDINGS	One record per parameter per time point per subject	Analysis	USUBJID, PARAMCAT, VISITNUM, PARAMN	adeffqs.xpt
ADEG	ECG	FINDINGS	One record per ECG observation per visit per subject	Analysis	USUBJID, PARAMN, VISITNUM, ADT	adeg.xpt
ADIVS	Infusion Vital Signs	FINDINGS	One record per vital sign measurement per visit per time point per subject	Analysis	USUBJID, PARAMN, VISITNUM, ADTM, SRCSEQ	adivs.xpt
ADLB	Laboratory	FINDINGS	One record per lab test per visit per time point per subject	Analysis	USUBJID, PARAMN, VISITNUM, ADTM	adlb.xpt
ADMH	Medical History	FINDINGS	One record per medical history event per subject	Analysis	USUBJID, MHGRPID, MHTERM	admh.xpt
ADPE	Physical Exam	FINDINGS	One record per body system per visit per subject	Analysis	USUBJID, PARAMN, VISITNUM, ADT	adpe.xpt
ADTIME	Time to Event	FINDINGS	One record per parameter per time point per subject	Analysis	USUBJID, PARAMN, AVAL	adtime.xpt



ADaM Evaluation

Metadata Check – Variable Level

Efficacy Dataset (ADEFF)							adeff.xpt
Variable	Label	Type	Controlled Terminology	Origin	Role	Comment	
STUDYID	Study Identifier	text	STUDYID	Derived	Subject Identifier	SDTM involved domain STUDYID.	
USUBJID	Unique Subject Identifier	text		Derived	Subject Identifier	SDTM involved domain USUBJID.	
TRT1P	Planned Treatment	text	TRT	ADSL.TRT1P	Treatment		
TRT1PN	Planned Treatment Number	integer	TRTN	ADSL.TRT1PN	Treatment		
TRT1A	Actual Treatment	text	TRT	ADSL.TRT1A	Treatment		
TRT1AN	Actual Treatment Number	integer	TRTN	ADSL.TRT1AN	Treatment		
ITTFL	Intent-To-Treat Population Flag	text	ALLYN	ADSL.ITTFL	Indicator		
SAFFL	Safety Population Population Flag	text	ALLYN	ADSL.SAFFL	Indicator		
MITTFL	Modified Intent-To-Treat Population Flag	text	ALLYN	ADSL.MITTFL	Indicator		
PPROTFL	Per Protocol Population Flag	text	ALLYN	ADSL.PPROTFL	Indicator		
DSREAS	Completion Status/Why Terminated (CRF)	text	DSREAS	ADSL.DSREAS	Analysis-Enabling		
SEX	Sex	text	SEX	ADSL.SEX	Analysis-Enabling		
SEXN	Sex, Numeric	integer	SEXN	ADSL.SEXN	Analysis-Enabling		
BRTHDT	Date/Time of Birth	integer		ADSL.BRTHDT	Timing		
AGEGRP	Age Group	text	AGEGRP	ADSL.AGEGRP	Analysis-Enabling		
AGEGRPN	Age Group, Numeric	integer	AGEGRPN	ADSL.AGEGRPN	Analysis-Enabling		

Datasets

☐ Subject-Level (ADSL)

☐ Subject-Level Analysis Data - Scr. Fail. (ADSLSF)

☐ Concomitant Medications, Therapies and Procedures (ADCM)

☐ Adverse Event (ADAE)

☐ Protocol Deviations (ADDV)

☐ Antibody (ADAB)

☐ Efficacy (ADEFF)

☐ Efficacy - QS (ADEFFQS)

☐ ECG (ADEG)

☐ Infusion Vital Signs (ADIVS)

☐ Laboratory (ADLB)

☐ Medical History (ADMH)

☐ Physical Exam (ADPE)

☐ Time to Event (ADTIME)

Value Level Metadata

Controlled Terminology

☐ Code Lists

☐ STUDYID

☐ TRT

☐ TRTN

☐ ALLYN

☐ DSREAS

☐ ABSRCDOM

☐ ABSRCVAR

☐ ABPARAMCAT

☐ ABPARAMCD

☐ ABPARAM

☐ ABPARAMN

☐ ABVISITNUM

☐ ABVISIT

☐ ALLY

☐ ABAVALC

☐ ABDTYPE

☐ AGEGRP

☐ AGEGRPN

☐ SEX

☐ SEXN

☐ AESEV

☐ AEACN

☐ AEREL

Metadata Check – Variable Level

Analysis Parameter	Analysis Value	Unit	Derived	Analysis Parameter	Analysis Parameter
AVALE	Analysis Value	float	Derived	Analysis Parameter	Analysis Parameter
AVALEC	Character Analysis Value	text	Derived	Analysis Parameter	Analysis Parameter
BASE	Baseline Value	float	Derived	Analysis Parameter	Analysis Parameter
BASEC	Character Baseline Value	text	Derived	Analysis Parameter	Analysis Parameter
CHG	Change from Baseline	float	Derived	Analysis Parameter	Analysis Parameter
PCHG	Percent Change from Baseline	float	Derived	Analysis Parameter	Analysis Parameter
DTYPE	Derivation Type	text	Derived	Analysis Parameter	Analysis Parameter
CRIT	Analysis Criterion	text	Derived	Analysis Parameter	Analysis Parameter



ADaM Evaluation

Metadata Check – Controlled Terminology

Laboratory (ADLB)

Medical History (ADMH)

Physical Exam (ADPE)

Time to Event (ADTIME)

+

Value Level Metadata

+

Controlled Terminology

-

Code Lists

STUDYID

TRT

TRTN

ALLYN

DSREAS

ABSRCDOM

ABSRCVAR

ABPARAMCAT

ABPARAMCD

ABPARAM

ABPARAMN

ABVISITNUM

ABVISIT

ALLY

ABAVALC

ABDTYPE

AGEGRP

AGEGRPN

SEX

SEXN

AESEV

AEACH

AEREL

AEOUT

AECMTRT

AEAVISIT

CMCMCAT

DVVISNM

DVVISTX

DVDECOD

DVACAT

DVCAT

ABVISITNUM, Reference Name (ABVISITNUM)

Code Value	Code Text
0.9	Baseline Visit
3.01	Unscheduled Labs
7	Week 7
9.01	Unscheduled Labs
13	Week 13
19	Week 19
23.01	Unscheduled Labs
25	Week 25
31	Week 31
33.01	Unscheduled Labs
35.01	Unscheduled Labs
37	Week 37
41.01	Unscheduled Labs
43	Week 43
49	Week 49
53	Week 53/EOS
99999	Overall

ABVISIT, Reference Name (ABVISIT)

Code Value	Code Text
Baseline Visit	Baseline Visit
Overall	Overall
Unscheduled Labs	Unscheduled Labs
Week 13	Week 13
Week 19	Week 19

ADaM Evaluation

Dataset Check

- ADSL, Any ADaM BDS dataset, etc.
 - Data Structure is key
- Modeling analysis data in general is more ‘gray’ than ‘black and white’
 - Multi-purpose (a dataset may support many different analyses)...hence less modeling rules

ADaM Evaluation

Dataset Check

- ADaM delicately tries to balance ‘Traceability’ and ‘Analysis-Ready’ with a predictable structure
 - Contains derived data along with data directly imported from SDTM datasets
 - In lieu of dropping records/observations not used for analyses (e.g. data from unscheduled visits), it implements various analysis flags
- ‘Traceability’ is the key for reviewers
 - Less is NOT more
 - ADaM appropriately emphasizes this

ADaM Evaluation Dataset Check

Quick Side-Note

(remember my disclaimer!)

- Derived Variables SHOULD ONLY exist in ADaM datasets
- SDTM Datasets SHOULD ONLY present the observed data from the CRF



ADaM Evaluation

Dataset Check - ADSL

	USUBJID	AGEGRP	AGEGRPN	SEX	SEXN	TRT1PN	TRT1AN	ITTFL	SAFFL	MITTFL	PPROTFL	ICFDT	RANDDT	TRTSTD	TRTEND	DS
1		>= 18 years		2 F	2	2	2 Y	Y	Y	Y	Y	04APR2007	20APR2007	22APR2007	08APR2008	Completed
2		>= 18 years		2 M	1	1	1 Y	Y	Y	Y	N	04APR2007	20APR2007	22APR2007	06APR2008	Completed
3		>= 18 years		2 M	1	2	2 Y	Y	Y	Y	Y	11APR2007	01MAY2007	02MAY2007	16APR2008	Completed
4		>= 18 years		2 F	2	2	2 Y	Y	Y	Y	Y	03FEB2008	21FEB2008	24FEB2008	13FEB2009	Completed
5		>= 18 years		2 F	2	2	2 Y	Y	Y	Y	Y	25FEB2008	17MAR2008	17MAR2008	05MAR2009	Completed
6		2 - 17 years		1 F	2	2	2 Y	Y	Y	Y	Y	26FEB2008	20MAR2008	20MAR2008	05MAR2009	Completed
7		2 - 17 years		1 M	1	2	2 Y	Y	Y	Y	Y	26FEB2008	20MAR2008	20MAR2008	05MAR2009	Completed
8		>= 18 years		2 M	1	1	1 Y	Y	Y	Y	N	10MAR2008	26MAR2008	02APR2008	16MAR2009	Completed
9		>= 18 years		2 M	1	2	2 Y	Y	Y	Y	Y	11MAR2008	28MAR2008	03APR2008	17MAR2009	Completed
10		>= 18 years		2 M	1	1	1 Y	Y	Y	Y	N	12MAR2008	28MAR2008	04APR2008	18MAR2009	Completed
11		>= 18 years		2 M	1	1	1 Y	Y	Y	Y	N	11JAN2007	14FEB2007	15FEB2007	14FEB2008	Completed
12		>= 18 years		2 M	1	2	2 Y	Y	Y	Y	Y	24FEB2007	14MAR2007	15MAR2007	28FEB2008	Completed
13		2 - 17 years		1 M	1	2	2 Y	Y	Y	Y	Y	24FEB2007	14MAR2007	15MAR2007	28FEB2008	Completed
14		>= 18 years		2 F	2	1	1 Y	Y	Y	Y	N	13MAR2007	27MAR2007	29MAR2007	13MAR2008	Completed
15		2 - 17 years		1 M	1	1	1 Y	Y	Y	Y	N	09APR2007	25APR2007	25APR2007	08APR2008	Completed
16		>= 18 years		2 F	2	2	2 Y	Y	Y	Y	Y	09APR2007	07MAY2007	08MAY2007	22APR2008	Completed
17		>= 18 years		2 F	2	1	1 Y	Y	Y	Y	N	09MAY2007	15JUN2007	18JUN2007	03JUN2008	Completed
18		2 - 17 years		1 F	2	1	1 Y	Y	N	N	N	09MAY2007	28JUN2007	29JUN2007	10JUN2008	Completed
19		>= 18 years		2 M	1	2	2 Y	Y	Y	Y	Y	03JUL2007	25JUL2007	26JUL2007	10JUL2008	Completed
20		2 - 17 years		1 M	1	2	2 Y	Y	N	N	N	10SEP2007	04OCT2007	05OCT2007	18SEP2008	Completed
21		2 - 17 years		1 M	1	1	1 Y	Y	Y	Y	N	23JAN2008	05FEB2008	08FEB2008	20JAN2009	Completed
22		>= 18 years		2 M	1	1	1 Y	Y	Y	Y	N	22OCT2007	26NOV2007	27NOV2007	17NOV2008	Completed
23		>= 18 years		2 F	2	1	1 Y	Y	Y	Y	N	07FEB2008	13MAR2008	14MAR2008	02MAR2009	Completed
24		>= 18 years		2 M	1	1	1 Y	Y	Y	Y	N	28FEB2008	20MAR2008	21MAR2008	06MAR2009	Completed
25		>= 18 years		2 F	2	1	1 Y	Y	Y	Y	N	11MAR2008	26MAR2008	28MAR2008	13MAR2009	Completed



ADaM Evaluation

Dataset Check - ADEFF

	USUBID	SRCDOM	SRCVAR	SRCSEQ	PARAMCD	PARAM	PARAMN	VISITNUM	AVISITN	AVISIT	ADT
1		LB	LBSTRESN	65	HGB	Hemoglobin (g/dL)	1	0.5	-2	Screening	04APR2007
2		LB	LBSTRESN	146	HGB	Hemoglobin (g/dL)	1	0.9	-1	Baseline Visit	17APR2007
3		LB	LBSTRESN	.	HGB	Hemoglobin (g/dL)	1	.	0	Modified Baseline	.
4		LB	LBSTRESN	172	HGB	Hemoglobin (g/dL)	1	3	3	Week 3	07MAY2007
5		LB	LBSTRESN	203	HGB	Hemoglobin (g/dL)	1	5	5	Week 5	21MAY2007
6		LB	LBSTRESN	232	HGB	Hemoglobin (g/dL)	1	7	7	Week 7	05JUN2007
7		LB	LBSTRESN	260	HGB	Hemoglobin (g/dL)	1	9	9	Week 9	18JUN2007
8		LB	LBSTRESN	290	HGB	Hemoglobin (g/dL)	1	11	11	Week 11	02JUL2007
9		LB	LBSTRESN	371	HGB	Hemoglobin (g/dL)	1	13	13	Week 13	16JUL2007
10		LB	LBSTRESN	394	HGB	Hemoglobin (g/dL)	1	15	15	Week 15	30JUL2007
11		LB	LBSTRESN	423	HGB	Hemoglobin (g/dL)	1	17	17	Week 17	13AUG2007
12		LB	LBSTRESN	452	HGB	Hemoglobin (g/dL)	1	19	19	Week 19	27AUG2007
13		LB	LBSTRESN	481	HGB	Hemoglobin (g/dL)	1	21	21	Week 21	10SEP2007
14		LB	LBSTRESN	510	HGB	Hemoglobin (g/dL)	1	23	23	Week 23	24SEP2007
15		LB	LBSTRESN	591	HGB	Hemoglobin (g/dL)	1	25	25	Week 25	08OCT2007
16		LB	LBSTRESN	615	HGB	Hemoglobin (g/dL)	1	27	27	Week 27	22OCT2007
17		LB	LBSTRESN	645	HGB	Hemoglobin (g/dL)	1	29	29	Week 29	06NOV2007
18		LB	LBSTRESN	676	HGB	Hemoglobin (g/dL)	1	31	31	Week 31	20NOV2007
19		LB	LBSTRESN	705	HGB	Hemoglobin (g/dL)	1	33	33	Week 33	04DEC2007
20		LB	LBSTRESN	734	HGB	Hemoglobin (g/dL)	1	35	35	Week 35	18DEC2007
21		LB	LBSTRESN	812	HGB	Hemoglobin (g/dL)	1	37	37	Week 37	02JAN2008
22		LB	LBSTRESN	840	HGB	Hemoglobin (g/dL)	1	39	39	Week 39	15JAN2008
23		LB	LBSTRESN	869	HGB	Hemoglobin (g/dL)	1	41	41	Week 41	29JAN2008
24		LB	LBSTRESN	898	HGB	Hemoglobin (g/dL)	1	43	43	Week 43	12FEB2008
25		LB	LBSTRESN	927	HGB	Hemoglobin (g/dL)	1	45	45	Week 45	26FEB2008
26		LB	LBSTRESN	956	HGB	Hemoglobin (g/dL)	1	47	47	Week 47	11MAR2008
27		LB	LBSTRESN	985	HGB	Hemoglobin (g/dL)	1	49	49	Week 49	25MAR2008
28		LB	LBSTRESN	1014	HGB	Hemoglobin (g/dL)	1	51	51	Week 51	08APR2008
29		LB	LBSTRESN	1095	HGB	Hemoglobin (g/dL)	1	53	53	Week 53	29APR2008
30		LB	LBSTRESN	56	PLAT	Platelets (10 ⁹ /L)	2	0.5	-2	Screening	04APR2007
31		LB	LBSTRESN	137	PLAT	Platelets (10 ⁹ /L)	2	0.9	-1	Baseline Visit	17APR2007
32		LB	LBSTRESN	.	PLAT	Platelets (10 ⁹ /L)	2	.	0	Modified Baseline	.
33		LB	LBSTRESN	163	PLAT	Platelets (10 ⁹ /L)	2	3	3	Week 3	07MAY2007
34		LB	LBSTRESN	194	PLAT	Platelets (10 ⁹ /L)	2	5	5	Week 5	21MAY2007
35		LB	LBSTRESN	223	PLAT	Platelets (10 ⁹ /L)	2	7	7	Week 7	05JUN2007
36		LB	LBSTRESN	251	PLAT	Platelets (10 ⁹ /L)	2	9	9	Week 9	18JUN2007
37		LB	LBSTRESN	281	PLAT	Platelets (10 ⁹ /L)	2	11	11	Week 11	02JUL2007
38		LB	LBSTRESN	362	PLAT	Platelets (10 ⁹ /L)	2	13	13	Week 13	16JUL2007
39		LB	LBSTRESN	385	PLAT	Platelets (10 ⁹ /L)	2	15	15	Week 15	30JUL2007
40		LB	LBSTRESN	414	PLAT	Platelets (10 ⁹ /L)	2	17	17	Week 17	13AUG2007
41		LB	LBSTRESN	443	PLAT	Platelets (10 ⁹ /L)	2	19	19	Week 19	27AUG2007
42		LB	LBSTRESN	472	PLAT	Platelets (10 ⁹ /L)	2	21	21	Week 21	10SEP2007
43		LB	LBSTRESN	501	PLAT	Platelets (10 ⁹ /L)	2	23	23	Week 23	24SEP2007
44		LB	LBSTRESN	582	PLAT	Platelets (10 ⁹ /L)	2	25	25	Week 25	08OCT2007
45		LB	LBSTRESN	606	PLAT	Platelets (10 ⁹ /L)	2	27	27	Week 27	22OCT2007



ADaM Evaluation

Dataset Check - ADEFF

ADY	ABLFL	AVAL	AVALC	BASE	BASEC	CHG	PCHG	DTYPE	CRIT	ANLFL	ANL1F
-18		10.6									
-5		10.4									
	Y	10.5		10.5		0	0	AVERAGE		Y	Y
16		11.2		10.5		0.7	6.7				Y
30		11.2		10.5		0.7	6.7				Y
45		11.4		10.5		0.9	8.6				Y
58		11		10.5		0.5	4.8				Y
72		10.6		10.5		0.1	1				Y
86		11.3		10.5		0.8	7.6		Moderate	Y	Y
100		11.7		10.5		1.2	11.4				Y
114		11.8		10.5		1.3	12.4				Y
128		12.1		10.5		1.6	15.2				Y
142		11.7		10.5		1.2	11.4				Y
156		11.7		10.5		1.2	11.4				Y
170		12.1		10.5		1.6	15.2		Good	Y	Y
184		11.6		10.5		1.1	10.5				Y
199		11.9		10.5		1.4	13.3				Y
213		11.6		10.5		1.1	10.5				Y
227		11.6		10.5		1.1	10.5				Y
241		13.8		10.5		3.3	31.4				Y
256		11.8		10.5		1.3	12.4		Moderate	Y	Y
269		11.7		10.5		1.2	11.4				Y
283		13.3		10.5		2.8	26.7				Y
297		12		10.5		1.5	14.3				Y
311		11.3		10.5		0.8	7.6				Y
325		11.3		10.5		0.8	7.6				Y
339		11.2		10.5		0.7	6.7				Y
353		12		10.5		1.5	14.3				Y
374		12.1		10.5		1.6	15.2		Good	Y	Y
-18		54									
-5		40									
	Y	47		47		0	0	AVERAGE		Y	Y
16		38		47		-9	-19.1				Y
30		50		47		3	6.4				Y
45		48		47		1	2.1				Y
58		55		47		8	17				Y
72		63		47		16	34				Y
86		59		47		12	25.5		No Response	Y	Y
100		86		47		39	83				Y
114		82		47		35	74.5				Y
128		65		47		18	38.3				Y
142		71		47		24	51.1				Y
156		88		47		41	87.2				Y
170		96		47		49	104.3		Good	Y	Y
184		105		47		58	123.4				Y



ADaM Evaluation

Dataset Check - ADTTE

USUBJID	TRT1PN	TRT1AN	PARAMCD	PARAM	AVAL	CENSORFL
	2	2	DY2HGBRP	Days to HGB Response	100	0
	2	2	DY2GCBAB	Days to Anti-GCB Antibody Positive	374	1
	1	1	DY2HGBRP	Days to HGB Response	183	0
	1	1	DY2GCBAB	Days to Anti-GCB Antibody Positive	374	1
	2	2	DY2HGBRP	Days to HGB Response	83	0
	2	2	DY2GCBAB	Days to Anti-GCB Antibody Positive	370	1
	2	2	DY2HGBRP	Days to HGB Response	113	0
	2	2	DY2GCBAB	Days to Anti-GCB Antibody Positive	367	1
	2	2	DY2HGBRP	Days to HGB Response	56	0
	2	2	DY2GCBAB	Days to Anti-GCB Antibody Positive	368	1
	2	2	DY2HGBRP	Days to HGB Response	141	0
	2	2	DY2GCBAB	Days to Anti-GCB Antibody Positive	362	1
	2	2	DY2HGBRP	Days to HGB Response	71	0
	2	2	DY2GCBAB	Days to Anti-GCB Antibody Positive	362	1
	1	1	DY2HGBRP	Days to HGB Response	84	0
	1	1	DY2GCBAB	Days to Anti-GCB Antibody Positive	366	1
	2	2	DY2HGBRP	Days to HGB Response	82	0
	2	2	DY2GCBAB	Days to Anti-GCB Antibody Positive	363	1
	1	1	DY2HGBRP	Days to HGB Response	14	0
	1	1	DY2GCBAB	Days to Anti-GCB Antibody Positive	363	1
	1	1	DY2HGBRP	Days to HGB Response	253	0
	1	1	DY2GCBAB	Days to Anti-GCB Antibody Positive	365	1
	2	2	DY2HGBRP	Days to HGB Response	99	0
	2	2	DY2GCBAB	Days to Anti-GCB Antibody Positive	365	1
	2	2	DY2HGBRP	Days to HGB Response	99	0
	2	2	DY2GCBAB	Days to Anti-GCB Antibody Positive	365	1
	1	1	DY2HGBRP	Days to HGB Response	85	0
	1	1	DY2GCBAB	Days to Anti-GCB Antibody Positive	365	1
	1	1	DY2HGBRP	Days to HGB Response	42	0
	1	1	DY2GCBAB	Days to Anti-GCB Antibody Positive	364	1
	2	2	DY2HGBRP	Days to HGB Response	183	0
	2	2	DY2GCBAB	Days to Anti-GCB Antibody Positive	365	1
	1	1	DY2HGBRP	Days to HGB Response	44	0
	1	1	DY2GCBAB	Days to Anti-GCB Antibody Positive	366	1
	1	1	DY2HGBRP	Days to HGB Response	56	0
	1	1	DY2GCBAB	Days to Anti-GCB Antibody Positive	364	1
	2	2	DY2HGBRP	Days to HGB Response	57	0
	2	2	DY2GCBAB	Days to Anti-GCB Antibody Positive	365	1
	2	2	DY2HGBRP	Days to HGB Response	42	0
	2	2	DY2GCBAB	Days to Anti-GCB Antibody Positive	364	1
	1	1	DY2HGBRP	Days to HGB Response	40	0
	1	1	DY2GCBAB	Days to Anti-GCB Antibody Positive	362	1
	1	1	DY2HGBRP	Days to HGB Response	46	0
	1	1	DY2GCBAB	Days to Anti-GCB Antibody Positive	371	1



ADaM Evaluation

Dataset Check - ADAE

USUBJID	AESQ	AETERM	AEBODSYS	AEDECOD	AESV	AESR	AEACN	AEREL	AABOUT
		1 (BONE) PAIN IN LEGS	Musculoskeletal and connective tissue disorders	Bone pain	MILD	N	DOSE UNCHANGED	NOT RELATED	NOT YET RESOLVED
	3	FEELING COLD AFTER INFUSION	General disorders and administration site conditions	Feeling cold	MILD	N	DOSE UNCHANGED	POSSIBLY RELATED	RESOLVED WITHOUT SEQUELAE
	2	SHIVERING AFTER INFUSION	General disorders and administration site conditions	Chills	MILD	N	DOSE UNCHANGED	POSSIBLY RELATED	RESOLVED WITHOUT SEQUELAE
	4	OTITIS MEDIA	Infections and infestations	Otitis media	MILD	N	DOSE UNCHANGED	NOT RELATED	RESOLVED WITHOUT SEQUELAE
	5	SMALL, CRUSTY LESIONS ON FACE AND FOREARM AND A FEW ELSEWHERE	Skin and subcutaneous tissue disorders	Skin lesion	MILD	N	DOSE UNCHANGED	NOT RELATED	RESOLVED WITHOUT SEQUELAE
	6	TENDERNESS AROUND KIDNEY AREA - BILATERAL	Musculoskeletal and connective tissue disorders	Flank pain	MILD	N	DOSE UNCHANGED	NOT RELATED	RESOLVED WITHOUT SEQUELAE
	7	COLD/FLU	Infections and infestations	Influenza	MILD	N	DOSE UNCHANGED	NOT RELATED	RESOLVED WITHOUT SEQUELAE
	1	FELT COLD	General disorders and administration site conditions	Feeling cold	MILD	N	DOSE UNCHANGED	POSSIBLY RELATED	RESOLVED WITHOUT SEQUELAE
	2	WORSENING OF PAIN IN RIGHT LEG	Musculoskeletal and connective tissue disorders	Pain in extremity	MILD	N	DOSE UNCHANGED	NOT RELATED	RESOLVED WITH SEQUELAE
	3	FLU (CHILLS, FEVER, LASSITUDE)	Infections and infestations	Influenza	MILD	N	DOSE UNCHANGED	NOT RELATED	RESOLVED WITHOUT SEQUELAE
	4	SLIGHT WORSENING OF BONE (HIP) PAIN	Musculoskeletal and connective tissue disorders	Bone pain	MILD	N	DOSE UNCHANGED	NOT RELATED	RESOLVED WITH SEQUELAE
	5	PINK SPOT ON BACK	Skin and subcutaneous tissue disorders	Rash	MILD	N	DOSE UNCHANGED	NOT RELATED	RESOLVED WITHOUT SEQUELAE
	6	MUSCLE SPASMS IN ENTIRE BODY	Musculoskeletal and connective tissue disorders	Muscle spasms	MILD	N	DOSE UNCHANGED	NOT RELATED	RESOLVED WITHOUT SEQUELAE
	7	FAINTING	Nervous system disorders	Syncope	SEVERE	N	DOSE UNCHANGED	NOT RELATED	RESOLVED WITHOUT SEQUELAE
	8	FEVER	General disorders and administration site conditions	Pyrexia	MILD	N	DOSE UNCHANGED	NOT RELATED	RESOLVED WITHOUT SEQUELAE
	9	NO APPETITE	Metabolism and nutrition disorders	Anorexia	MILD	N	DOSE UNCHANGED	NOT RELATED	RESOLVED WITHOUT SEQUELAE
	10	WEAKNESS	General disorders and administration site conditions	Asthenia	MODERATE	N	DOSE UNCHANGED	NOT RELATED	RESOLVED WITHOUT SEQUELAE
	11	VOMITING (ONE TIME)	Gastrointestinal disorders	Vomiting	MILD	N	DOSE UNCHANGED	NOT RELATED	RESOLVED WITHOUT SEQUELAE
	12	WORSENING OF PAIN IN RIGHT HIP	Musculoskeletal and connective tissue disorders	Arthralgia	MODERATE	N	DOSE UNCHANGED	NOT RELATED	NOT YET RESOLVED
	1	(BONE) PAIN IN LEGS AND FEET	Musculoskeletal and connective tissue disorders	Bone pain	MILD	N	DOSE UNCHANGED	NOT RELATED	NOT YET RESOLVED
	3	ITCH OF RIGHT ARM	Skin and subcutaneous tissue disorders	Pruritus	MILD	N	DOSE UNCHANGED	NOT RELATED	RESOLVED WITHOUT SEQUELAE
	2	REDNESS OF RIGHT ARM	Skin and subcutaneous tissue disorders	Erythema	MILD	N	DOSE UNCHANGED	NOT RELATED	RESOLVED WITHOUT SEQUELAE
	4	(MUSCULOSKELETAL) PAIN IN LEFT ARM FROM ELBOW TO SHOULDER	Musculoskeletal and connective tissue disorders	Musculoskeletal pain	MILD	N	DOSE UNCHANGED	NOT RELATED	NOT YET RESOLVED
	5	CLINICALLY SIGNIFICANT LOW IRON LEVELS (TOTAL IRON = 7.3 FROM 8.8 AT BASELINE)	Investigations	Blood iron decreased	MILD	N	DOSE UNCHANGED	NOT RELATED	RESOLVED WITHOUT SEQUELAE
	6	PAIN IN HIP JOINTS WHEN BENDING	Musculoskeletal and connective tissue disorders	Arthralgia	MILD	N	DOSE UNCHANGED	NOT RELATED	NOT YET RESOLVED
	7	ABNORMALLY ELEVATED CRP (7.47MG/L)	Investigations	C-reactive protein increased	MILD	N	DOSE UNCHANGED	NOT RELATED	RESOLVED WITHOUT SEQUELAE
	1	COMMON COLD	Infections and infestations	Nasopharyngitis	MILD	N	DOSE UNCHANGED	NOT RELATED	RESOLVED WITHOUT SEQUELAE
	2	PAIN IN RIGHT GROIN AREA	Musculoskeletal and connective tissue disorders	Groin pain	MILD	N	DOSE UNCHANGED	NOT RELATED	RESOLVED WITHOUT SEQUELAE
	3	PELVIC PAIN	Reproductive system and breast disorders	Pelvic pain	MILD	N	DOSE UNCHANGED	NOT RELATED	RESOLVED WITHOUT SEQUELAE
	4	FATIGUE	General disorders and administration site conditions	Fatigue	MILD	N	DOSE UNCHANGED	NOT RELATED	RESOLVED WITHOUT SEQUELAE
	5	PAIN IN RIGHT TOE	Musculoskeletal and connective tissue disorders	Pain in extremity	MILD	N	DOSE UNCHANGED	NOT RELATED	NOT YET RESOLVED



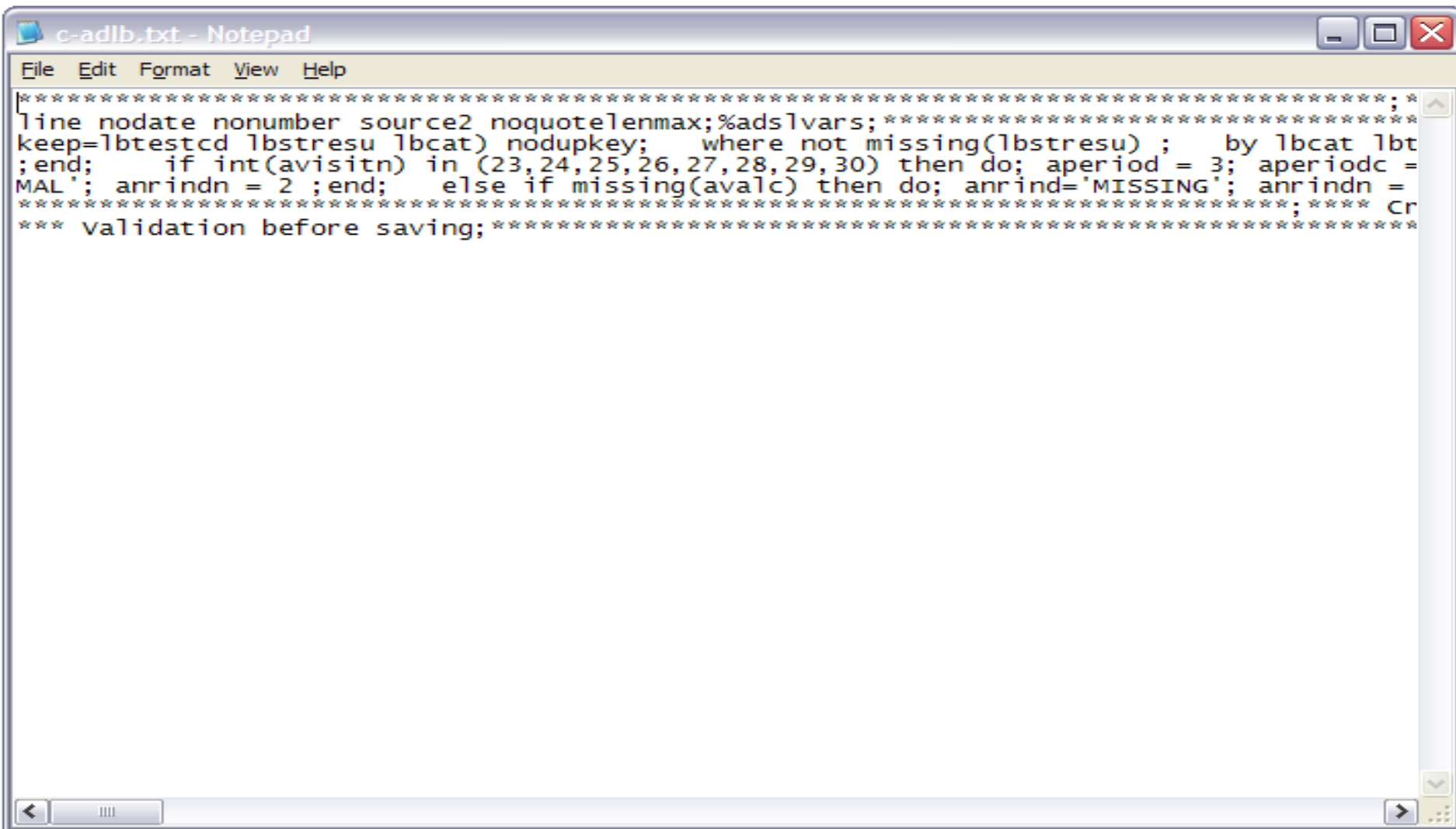
ADaM Evaluation

We have ADaM “Compliance”!

ADaM Evaluation

- Was this a perfect electronic submission?
 - No...

ADaM Evaluation



The screenshot shows a Notepad window titled "c-adlb.txt - Notepad". The menu bar includes File, Edit, Format, View, and Help. The text area contains the following SAS code:

```
*****; *
line nodate nonumber source2 noquotelenmax;%adslvars;*****; *
keep=lbtestcd lbstresu lbcate) nodupkey; where not missing(lbstresu) ; by lbcate lbt
;end; if int(avisitn) in (23,24,25,26,27,28,29,30) then do; aperiod = 3; aperiodc =
MAL'; anrindn = 2 ;end; else if missing(avalc) then do; anrind='MISSING'; anrindn =
*****; **** Cr
*** validation before saving;*****
```

Usefulness of ADaM for other Statistical Reviewers

Survey of OB statisticians (including myself) who received an ADaM submission on or after January 1, 2012

Usefulness of ADaM for other Statistical Reviewers

- Q1: Did ADaM data help you in your review relative to non-standardized analysis data?
- A1: Yes (unanimous)

Usefulness of ADaM for other Statistical Reviewers

- Q2: What did you most like about ADaM data relative to non-standardized analysis data?
- A2: Various answers
 - Predictable structures
 - Decreased need for data management/programming
 - Predictable variable naming
 - Useful Variables such as '**DTYPE**'
 - Traceability

Usefulness of ADaM for other Statistical Reviewers

- Q3: What didn't you like about ADaM data?
- A3: Various answers
 - Variability in Data Modeling
 - Timing variables in certain circumstances

Usefulness of ADaM for other Statistical Reviewers

Some statistical (and even medical) reviewers at CDER don't like analysis data regardless of whether it's standardized or not.

We've started a grassroots effort to educate!

Usefulness of ADaM for other Statistical Reviewers

- Q4: Which ADaM datasets did you primarily utilize?
- A4: ADSL (unanimous), ADEFF, ADAE, ADLB

Usefulness of ADaM for other Statistical Reviewers

- Q5: Did you receive a Define.XML file?
- A5: Yes (unanimous)
Some asked for, and subsequently received, both Define.XML and Define.PDF

Usefulness of ADaM for other Statistical Reviewers

- So what format do Regulatory Reviewers really want for their metadata files?
 - Define.XML?
 - Define.PDF?
 - Both?
- Define.XML v2.0 is potentially a great upgrade

Usefulness of ADaM for other Statistical Reviewers

- Q6: Did you make any subsequent analysis data requests to the sponsor during the review cycle?
- A6: No (unanimous)

Usefulness of ADaM for other Statistical Reviewers

- Q7: Did the clinical reviewer utilize ADaM in their review? If so, was it useful to them?
- A7: Yes (every reviewer except 3). Yes.

Example Data Request from my Medical Division

- Data needs should be communicated **as early as possible** in the product development lifecycle
- In my medical division, the Division of Gastroenterology and Inborn Errors Products (DGIEP), we request a Full Case Report Tabulation (CRT) for **at least each adequate and well-controlled study** in the application

Example Data Request from my Medical Division

“Please provide the following for each adequate and well-controlled study (per 21 CFR 314.126) you plan to include in your NDA/BLA submission:

1. All clean/locked clinical data presented in electronic datasets, submitted utilizing SAS Version 5 Transport, along with the annotated case report form (aCRF) and a thorough data definition file. We recommend, but do not require, that the electronic datasets, aCRF, and data definition file comply with the latest CDISC/SDTM, CDISC/CDASH, and CDISC/Define.XML standards respectively. Define.PDF is also an acceptable format for the data definition file.

Example Data Request from my Medical Division

2. All corresponding analysis data presented in electronic datasets, submitted utilizing SAS Version 5 Transport, along with a thorough data definition file. We recommend, but do not require, that these electronic datasets incorporate the modeling approaches described by the latest CDISC/ADaM standard along with both the CDER Data Standards Common Issues Document and the Study Data Specifications document (<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.htm>). We recommend, but do not require, that the data definition file comply with the latest CDISC/Define.XML standard, however Define.PDF is also acceptable.

Example Data Request from my Medical Division

3. A well commented and organized software program written for each analysis dataset and efficacy table created.”



Thank You for your Attention

Comments are appreciated

Please send to Behrang.Vali@fda.hhs.gov