Experience & Differences on Transition from Legacy Submissions to CDISC Submissions

8/20/14

Agenda

- CDISC Standards
- In-Licensing related Challenges & how standards could make it better..?
- Recommendations to support Integrated collection → Analysis/Reporting → Submission
- Where are we moving with standards..?

Presenters

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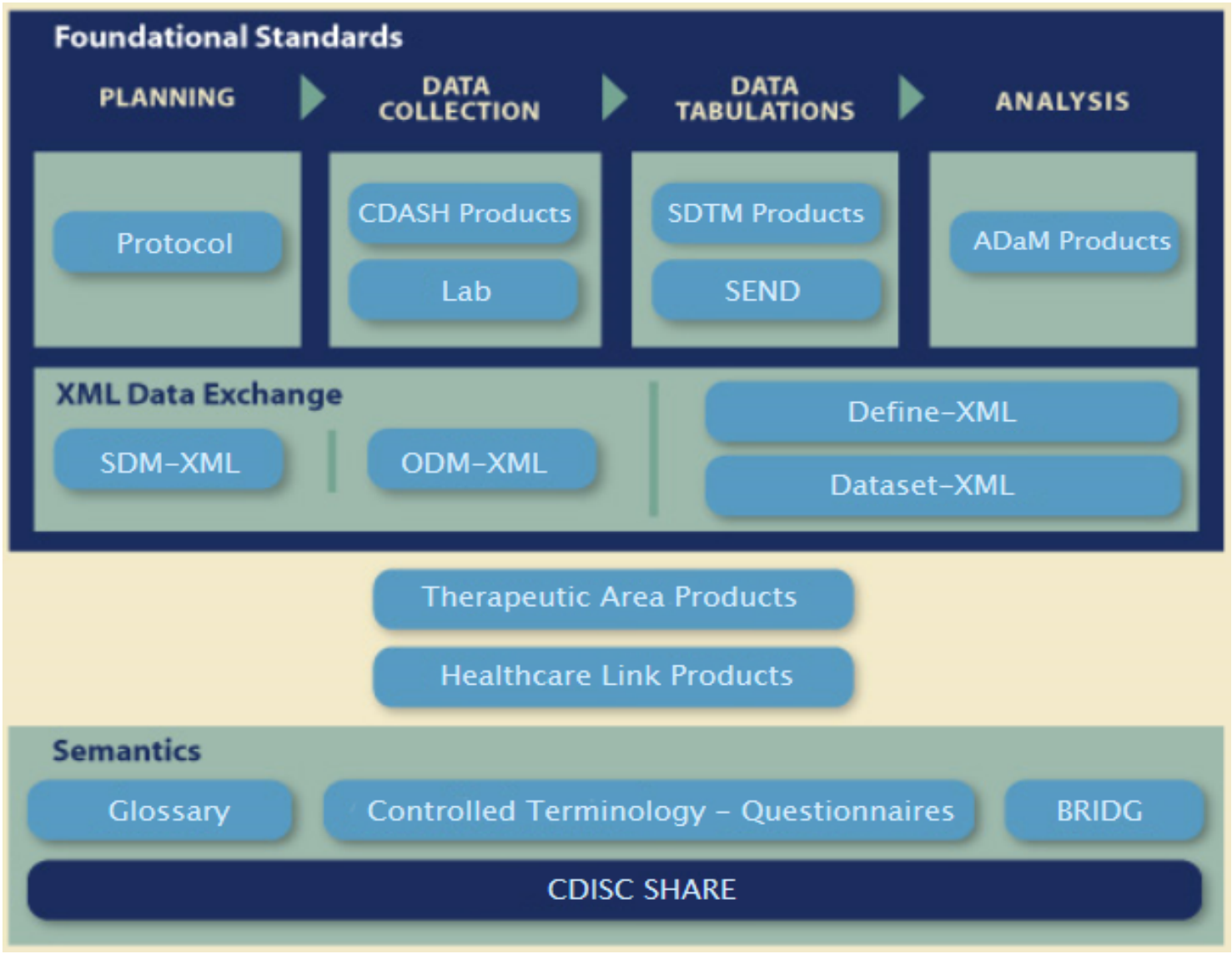
CDISC Standards



Benefits of Standards Implementation

- Improve Data Quality
- Improve Data Exchange
- Meet regulatory requirements
- Minimize legacy conversion
- Supports speedy approval by agencies

Someone Else's Legacy

- Major Pharma have in recent years, externalized more R&D to increase the number of drug projects and thus the chances of getting a major new product to market. In fact, over half of late-stage pipeline compounds are now externally sourced (Exhibit 1).
- This situation is giving rise to an explosion of licensing deals and development partnerships.

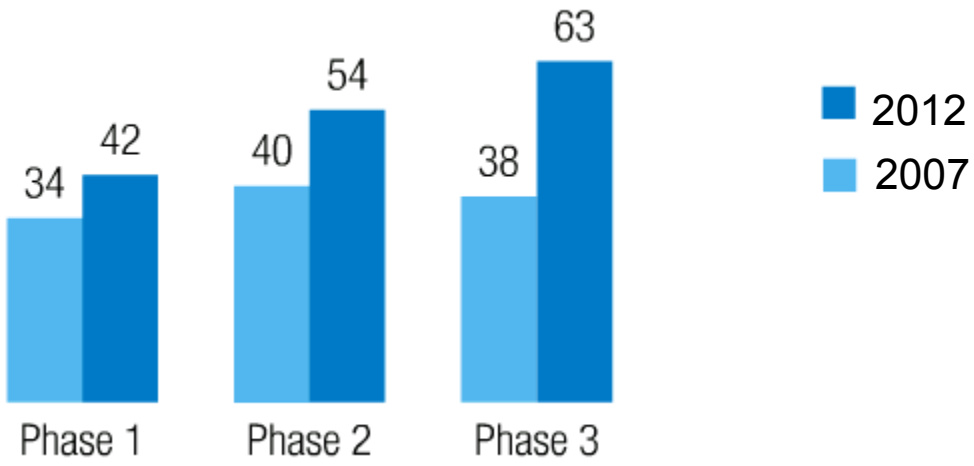
*From Datamonitor: Licensing Strategies: Trends in the top 20 pharmaceutical companies' activity

% of R&D Not “Home Grown”

Outside in

Over half of late-stage pipeline compounds are now externally sourced.

% of reported pipeline compounds originated externally



2012 Source: EvaluatePharma database.

Why CDISC Matters in Licensing

CDISC is the logical “common data language” of R&D Partnerships.

Typical Challenge

- Typical* licensed product will include 10-15 studies from Phase I up to and including Phase III. Studies may encompass multiple formulations, doses and indications.
- It's not unusual for more than one R&D Company to have been involved in the compounds research history and…
  - Multiple CRO, Lab and diagnostic vendors were likely to be involved during the development lifecycle.

* In truth, no two legacy conversion projects are alike and have ranged from 3 studies to over 30

First: Excavate

- During the “due diligence” phase…. when you were negotiating to license the compound, your evaluation team excavated and examined the older clinical study data structures…Correct?
- You have everything and it is in perfect shape. Right?

Legacy Data Check List

1. The Protocol (Final version please!) plus “all” amendments.
2. Final CRFs.
   a) Blank and Annotated (Annotated with DM system or raw SAS dataset variables)
3. Final raw clinical datasets which match the annotated CRFs in #2
   a) (In SAS Format and in English preferably).
   b) Sometimes old study archives contain pipe or tab-delimited ASCII files, Excel Spreadsheets, Access.mdb, Data Listings in PDFs, JMP, SPSS, S-Plus datasets, and occasionally a MS-SQL or Oracle.bin database with little or no documentation.

Legacy Data Check List Cont…

4. All diagnostic data
   a) (ECG, LAB, PK, eDiary, ePRO, etc.)
5. Analysis datasets which were used for the Clinical Study Report (CSR)
6. SAS programs and Macros for CSR TFLs (if available.. Some CROs, Sponsors feel that SAS programs are worthy of copyright status)
7. The Final Clinical Study Report
8. Other study related documents (Don’t discount their importance!!)

Other Related Documents

- Not necessarily “essential” for CDISC conversion… but are invaluable for uncovering the “what and why” of old studies.
  - Data Management Plan
  - Edit Check Specifications
  - Statistical Analysis Plan
  - Analysis Dataset Specifications
  - Coding dictionary versions used
  - Coding synonym lists
  - Laboratory ranges, units, etc…

Legacy Data Considerations

1. Are you able to open and view all of the archived files? (Don't assume you can!.. Watch out for old protected .zip files)
2. Do you have a SDTM conversion project leader with authority and ability to access senior management for tough decisions?
3. Do you have access to someone who can answer questions for each study as to why certain things were done a certain way (i.e., study team contact list)?..are they still available, accessible or even alive?

Legacy Conversion Team

- The Project Manager.
  - Preferably with experience in large and complex clinical data management or statistical programming projects.
    - Manages resources, timelines and budget.
    - Keeps project on track and manages risks for project success
    - Point person for all communications with project stake holders, team members, resources, vendors.

Legacy Conversion Team Cont..

- The Lead CDISC Standards Analyst
  - Very Strong Clinical Data Experience
    - Thoroughly trained and “understands” the CDISC implementation guides.
    - Manages CRF annotation team and reviews, arbitrates all legacy study CRF annotations to enforce SDTM mapping consistency across multiple studies. (5 analysts can have 5 “slightly to greatly” different interpretations of the SDTM implementation guide) Need an experienced leader to referee the annotations and mappings
    - Prepares SDTM conversion specifications using the original CRF’s raw database annotations, and the new SDTM annotations for conversion programming team.

Legacy Conversion Team Cont..

- SDTM Programming Team Leader
  - Seasoned SAS programmer
    - Ideally, someone who has seen it all, The “good, The bad and the ugly” of SAS programs and datasets
    - Responsible for managing the team producing SDTM Datasets from conversion specifications provided by SDTM Analysts
    - Responsible for reviewing (or developing) SDTM validations and along with the Lead SDTM Analyst, communicating, remediating and documenting inconsistencies found from the SDTM validation effort

Legacy Conversion Team Cont..

- The Statistician
  - Must be familiar with the Statistical Analysis Plans (SAPs) for each legacy study to be converted.
  - Responsible for developing SAPs for the integrated summaries of Safety and Efficacy
    - Should review and be very familiar with the legacy study conversion specifications. (Familiarity with the SDTM and ADaM domains and variables is very important for the ISS and ISE data integration plan)

Legacy Conversion Team Cont..

- The Clinical Lead
  - Must have a thorough understanding of the compound, protocol designs, assessments, and results (CSRs) of each legacy study.
  - Will typically be very focused on the pivotal study outcomes but must be aware of how the older legacy data will support the pivotal data.. And where it may not…
  - They are necessary for the really tough decisions that in ***every*** project, must be made.

Examples of Difficult Legacy Conversion Projects

- Due to the mature nature of this content, this portion of the presentation has received a R rating for Really Bad Legacy

Lab Data Collection CRF "Of What Not To Do"

TABLE = LB

LABORATORY STUDIES (Study Entry)

SAMDT (C,10)
DSAMDT (N,DATE)
Date specimen obtained: ____/____/____ *(mm/dd/yy)*

Time obtained *(24-hr clock)* SAMTM (N,TIME) ____:____

TABLE = LBLB

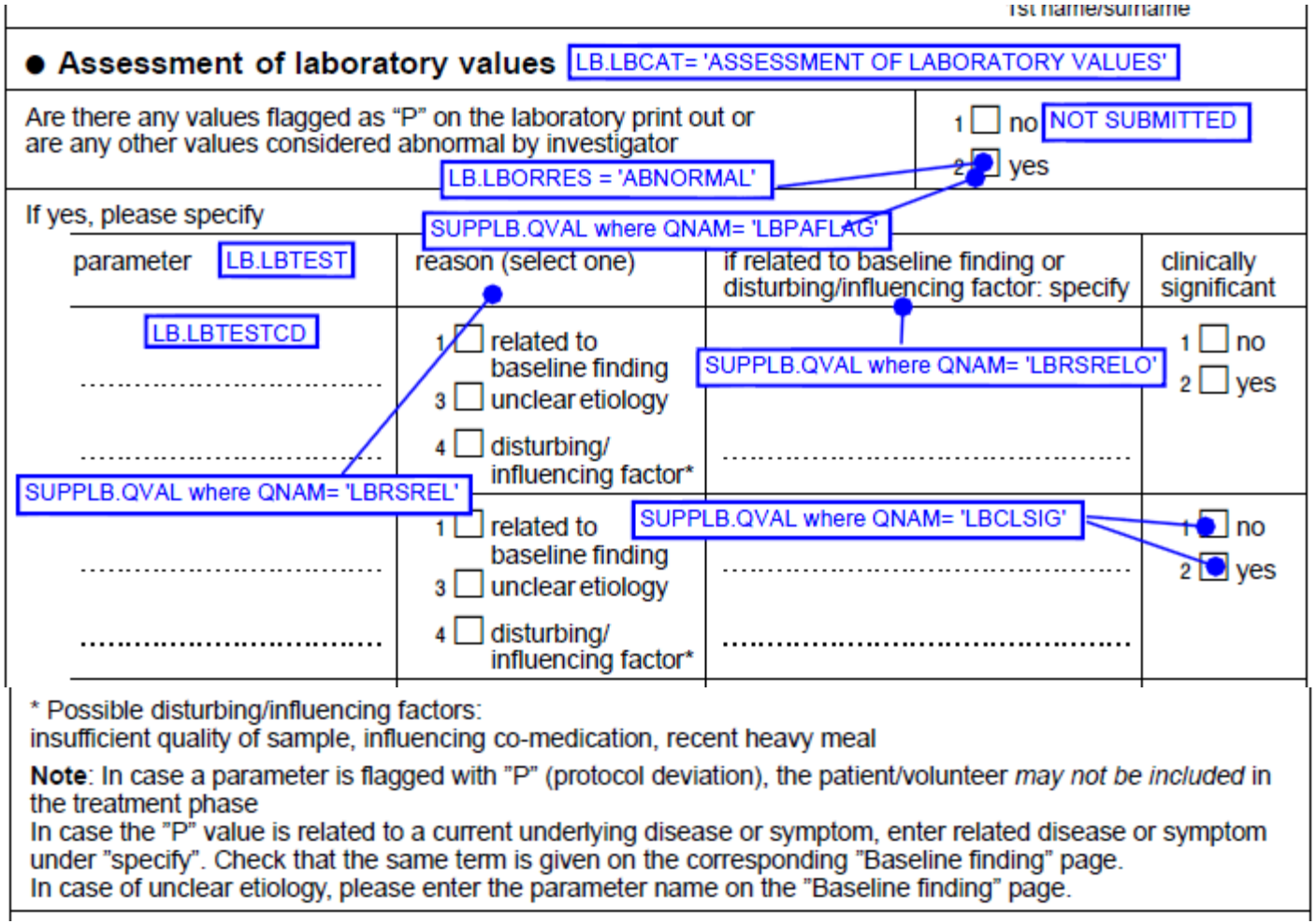
Parameter (TEATSN (N,8) TEST (C,100))	Not assessed[1] (NA (C,$NOTASS))	Value	Units: Conventional	Units: Systeme International	Normal	Abnormal[3] (LABABN (C,2) LABABN_D (C,50))	Not detectable[1]	Comments (COM (C,200))
WBC	☐(99)	____ ____ ____.____	☐(01) µ/l	☐(02) xA9/L	☐(01)	☐(02)	☐(03)	
Hgb	☐(99)	LVALUEN (N,8.2) ____ ____.____	☐(01) g/dL	☐(02) g/L	☐(01)	☐(02)	☐(03)	
Platelets	☐(99)	LVALUE (C,24) ____ ____ ____ ____	☐(01) k/µl	☐(02) xA9/L	☐(01)	☐(02)	☐(03)	
BUN	☐(99)	LVALSTD (N,8.2) ____ ____ ____.____	☐(01) mg/dL	☐(02) mmol/L	☐(01)	☐(02)	☐(03)	
Serum creatinine	☐(99)	____ ____ ____.____	☐(01) mg/dL	☐(02) µmol/L	☐(01)	☐(02)	☐(03)	
Urine creatinine	☐(99)	____ ____ ____ ____.____	☐(01) mg/dL	☐(02) µmol/L	☐(01)	☐(02)	☐(03)	
Total bilirubin	☐(99)	____ ____ ____.____	☐(01) mg/dL	☐(02) µmol/L	☐(01)	☐(02)	☐(03)	
Direct bilirubin	☐(99)	____ ____ ____.____	☐(01) mg/dL	☐(02) µmol/L	☐(01)	☐(02)	☐(03)	
PT ---OR--- INR	☐(99)	____ ____ ____.____ ____.____ ____	sec UNITS (C,10)		☐(01)	☐(02)	☐(03)	
PTT	☐(99)	____ ____ ____.____	sec		☐(01)	☐(02)	☐(03)	
Fibrinogen	☐(99)	____ ____ ____ ____	☐(01) mg/dL	☐(02) µmol/L	☐(01)	☐(02)	☐(03)	
HCT	☐(99)	____ ____.____	%		☐(01)	☐(02)	☐(03)	
Serum Na	☐(99)	____ ____ ____	mmol/L		☐(01)	☐(02)	☐(03)	
Urine Na	☐(99)	____ ____ ____	mmol/L		☐(01)	☐(02)	☐(03)	
Fractionated Excretion of Sodium[2]	☐(99)	____ ____ . ____ ____			☐(01)	☐(02)	☐(03)	

CRF Design (Contd)

Patient (PT)	Value (num) (LVALUEN)	Units (UNITS)	Date specimen obtained (SAMDT)	Time obtained (SAMTM)	Comments (COM)
01D12	18.6	sec	13JAN2008	6:09	DRAWN @ 17:24 ON 1/13/08
01D12	1.5		13JAN2008	6:09	DRAWN @ 17:24 ON 1/13/08
01D12	59.9	sec	13JAN2008	6:09	DRAWN @ 17:24 ON 1/13/08
01D12	25.9	mg/dL	22JAN2008	2:42	DRAWN @ 6:11 ON 1/22/08
01D12	1.9	mg/dL	22JAN2008	2:42	DRAWN @ 6:11 ON 1/22/08
01D12	36	mg/dL	22JAN2008	2:42	DRAWN @ 6:11 ON 1/22/08
01D12	74	mg/dL	22JAN2008	2:42	DRAWN @ 6:11 ON 1/22/08
01D12	29	mg/dL	07JAN2008	4:42	DRAWN @ 6:23 ON 1/7/08
01D12	7.4	mg/dL	07JAN2008	4:42	DRAWN @ 6:23 ON 1/7/08
01D12	0.9	mg/dL	07JAN2008	4:42	DRAWN @ 6:23 ON 1/7/08
01D12	4.5	mg/dL	07JAN2008	4:42	DRAWN @ 6:23 ON 1/7/08
01D12	18.3	mg/dL	16JAN2008	6:08	DRAWN @ 6:34 ON 1/16/08
01D12	24.5	mg/dL	16JAN2008	6:08	DRAWN @ 6:34 ON 1/16/08
01D12	24	mg/dL	16JAN2008	6:08	DRAWN @ 6:34 ON 1/16/08
01D12	1	mg/dL	16JAN2008	6:08	DRAWN @ 6:34 ON 1/16/08
01D12	10.5	g/dL	29DEC2007	5:35	DRAWN @ 8:02 ON 12/29/07
01D12	31.8	%	29DEC2007	5:35	DRAWN @ 8:02 ON 12/29/07
01D12	45	k/µl	29DEC2007	5:35	DRAWN @ 8:02 ON 12/29/07
01D12	1	mg/dL	29DEC2007	5:35	DRAWN @ 8:02 ON 12/29/07
01D12	25	mg/dL	29DEC2007	5:35	DRAWN @ 8:02 ON 12/29/07
01D12	3.9	mg/dL	29DEC2007	5:35	DRAWN @ 8:02 ON 12/29/07
01D12	2.2	mg/dL	29DEC2007	5:35	DRAWN @ 8:02 ON 12/29/07
01D12	.		21DEC2007	5:31	FIBRINOGEN LAB NOT DONE ON
01D12	13.8	g/dL	06FEB2008	5:34	HGB DRAWN AT 16:41 ON 2/6/
01D12	17.4	mg/dL	14FEB2008	6:33	LAB NORMALS NOT AVAILABLE
01D12	38	mmol/	14FEB2008	6:33	LAB NORMALS NOT AVAILABLE

CRF Sample Collection Date & Time (LBDTC) differs from the actual date/ time of collection in recorded in the Comments Field

SUPP- domains contain unnecessary information (Contd)
Don’t place important data / Key variables/standard variables in SUPPQUAL



SUPP- domains contain unnecessary information (Contd) …

sas7bdat

DOMAIN	USUBJID	LBSEQ	LBGRPID	LBTESTCD	LBTEST	LBCAT	LBORRES	LBSTRESC	LBNAM	LBSPEC
LB	[redacted]20733	75		GGT	Gamma Glutamyl Transferase	ASSESSMENT OF LABORATORY VALUES	ABNORMAL	ABNORMAL	[redacted]	BLOOD
LB	[redacted]20733	76		HDL	HDL Cholesterol	ASSESSMENT OF LABORATORY VALUES	ABNORMAL	ABNORMAL	[redacted]	BLOOD
LB	[redacted]20733	77		SGOT	Aspartate Aminotransferase	ASSESSMENT OF LABORATORY VALUES	ABNORMAL	ABNORMAL	[redacted]	BLOOD
LB	[redacted]20733	78		SGPT	Alanine Aminotransferase	ASSESSMENT OF LABORATORY VALUES	ABNORMAL	ABNORMAL	[redacted]	BLOOD
LB	[redacted]20733	79		TRIG	Triglycerides	ASSESSMENT OF LABORATORY VALUES	ABNORMAL	ABNORMAL	[redacted]	BLOOD

pplb.sas7bdat

RDOMAIN	USUBJID	IDVAR	IDVARVAL	QNAM	QLABEL	QVAL	QORIG	QEVAL
LB	[redacted]20733	LBSEQ	74	LBCLSIG	Lab Result, Clinically Significant	Y	CRF	
LB	[redacted]20733	LBSEQ	74	LBPAFLAG	PD Alert Flag	ALERT	CRF	
LB	[redacted]20733	LBSEQ	74	LBRSREL	Reason for Flagging Lab Value	AE related	CRF	
LB	[redacted]20733	LBSEQ	74	LBRSRELO	Reason for Flagging, Specification	ELEVATED TRANSAMINASES	CRF	
LB	[redacted]20733	LBSEQ	75	LBCLSIG	Lab Result, Clinically Significant	Y	CRF	
LB	[redacted]20733	LBSEQ	75	LBPAFLAG	PD Alert Flag	ALERT	CRF	
LB	[redacted]20733	LBSEQ	75	LBRSREL	Reason for Flagging Lab Value	AE related	CRF	
LB	[redacted]20733	LBSEQ	75	LBRSRELO	Reason for Flagging, Specification	ELEVATED TRANSAMINASES	CRF	

.sas7bdat

DOMAIN	AESEQ	USUBJID	AETERM	AEMODIFY	AECAT	AESEV	AESER	AEACN	AEREL	AEOUT	AE
AE	10	[redacted]20733	DYSMENORRHEA	DYSMENORR	GENERAL	SEVERE	N	DOSE NOT	PROBABLY RELATED	NOT RECOV	200
AE	6	[redacted]20733	ELEVATED TRANSAMINASES - ALAT	ELEVATED	LABORATOR			DRUG WITH	RELATED	RECOVERED	200
AE	8	[redacted]20733	ELEVATED TRANSAMINASES - GAMMA-GT	ELEVATED	LABORATOR			DRUG WITH	RELATED	RECOVERED	200
AE	2	[redacted]20733	ELEVATED TRANSAMINASES ALK. PHOSPHATAS	ELEVATED	LABORATOR			DRUG WITH	RELATED	RECOVERED	200
AE	4	[redacted]20733	ELEVATED TRANSAMINASES ASAT	ELEVATED	LABORATOR			DRUG WITH	RELATED	RECOVERED	200

SUPP- domains contain unnecessary information (Contd)…

● Assessment of laboratory values

Are there any values flagged as "A" on the laboratory print out or are any other values considered abnormal by investigator	1 ☐ no 2 ☐ yes

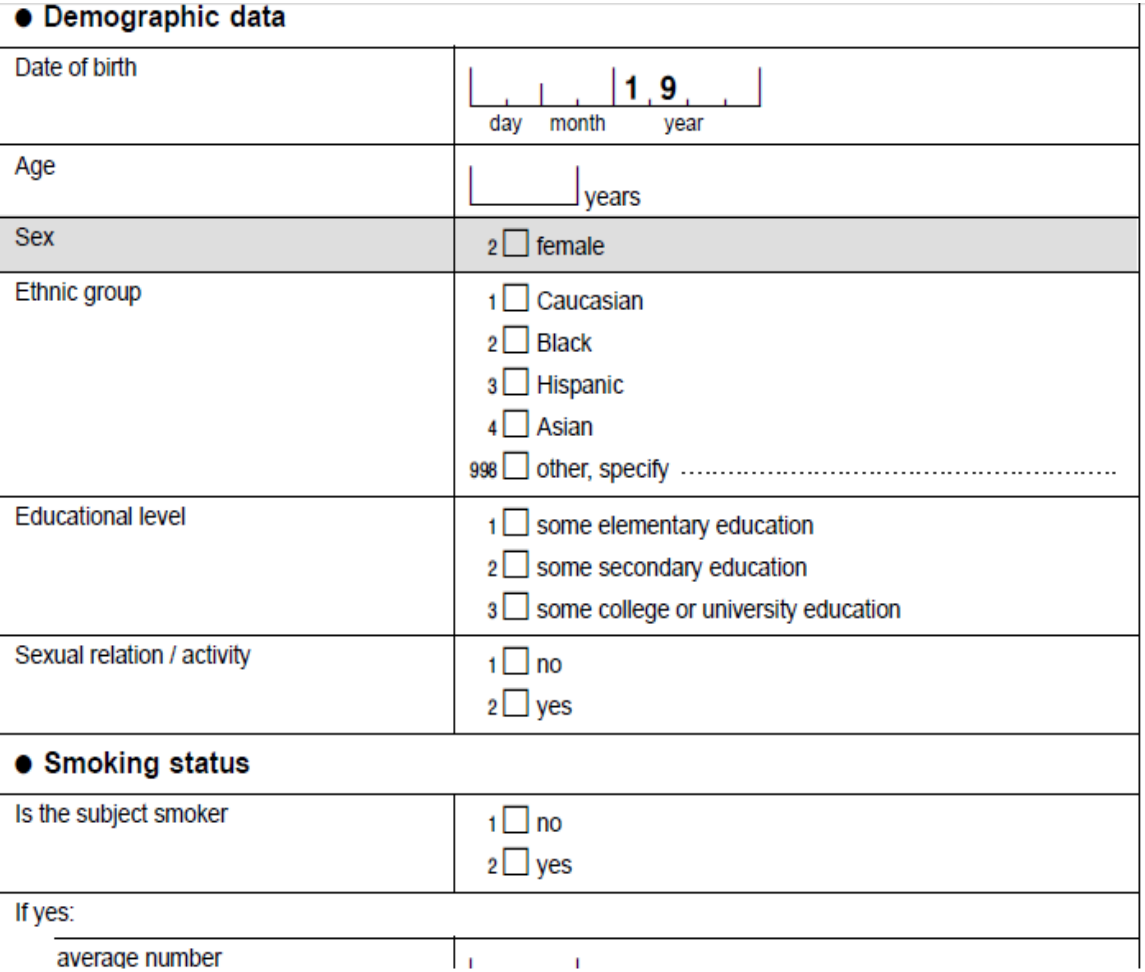
If yes, please specify

parameter	reason (select one)	if related to adverse event or disturbing/influencing factor: specify	clinically significant
…… ……	2 ☐ related to adverse event 3 ☐ unclear etiology 4 ☐ disturbing/ influencing factor*	~~instead of a free text: AE #~~ **should help to relate these records**……	1 ☐ no 2 ☐ yes
…… ……	2 ☐ related to adverse event 3 ☐ unclear etiology 4 ☐ disturbing/ influencing factor*	…… ……	1 ☐ no 2 ☐ yes

* Possible disturbing/influencing factors:
insufficient quality of sample, influencing co-medication, recent heavy meal

Note: In case a parameter is flagged with "A" (alert value), enter related disease or symptom under "specify". Check that the same term is given on the corresponding "Adverse event" page. If the value is of unclear etiology, complete CRF page "Laboratory adverse event".

Collecting data in single source dataset that actually go in to different classes/domains

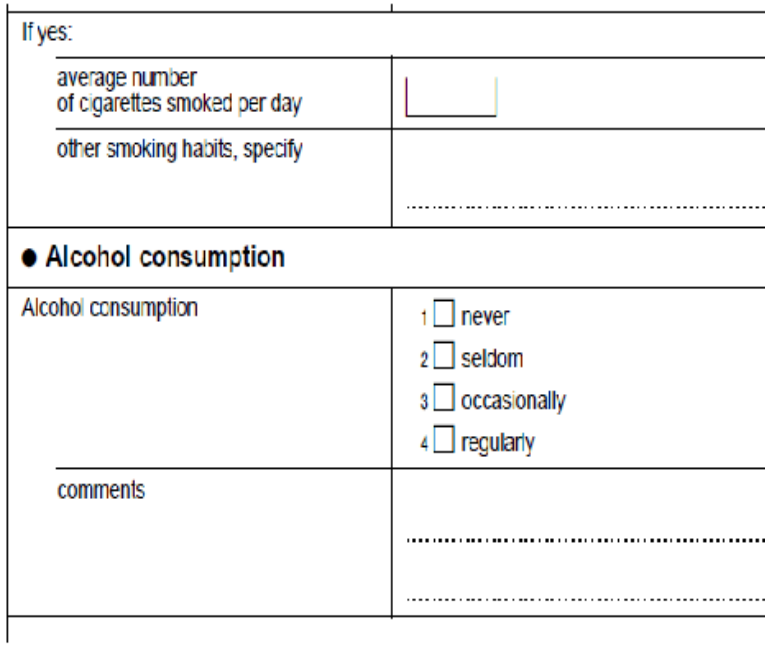


● Demographic data

Date of birth	1 9 (day month year)
Age	____ years
Sex	2 ☐ female
Ethnic group	1 ☐ Caucasian 2 ☐ Black 3 ☐ Hispanic 4 ☐ Asian 998 ☐ other, specify .....
Educational level	1 ☐ some elementary education 2 ☐ some secondary education 3 ☐ some college or university education
Sexual relation / activity	1 ☐ no 2 ☐ yes

● Smoking status

Is the subject smoker	1 ☐ no 2 ☐ yes
If yes:	
average number	



If yes:

average number of cigarettes smoked per day	____
other smoking habits, specify	.....

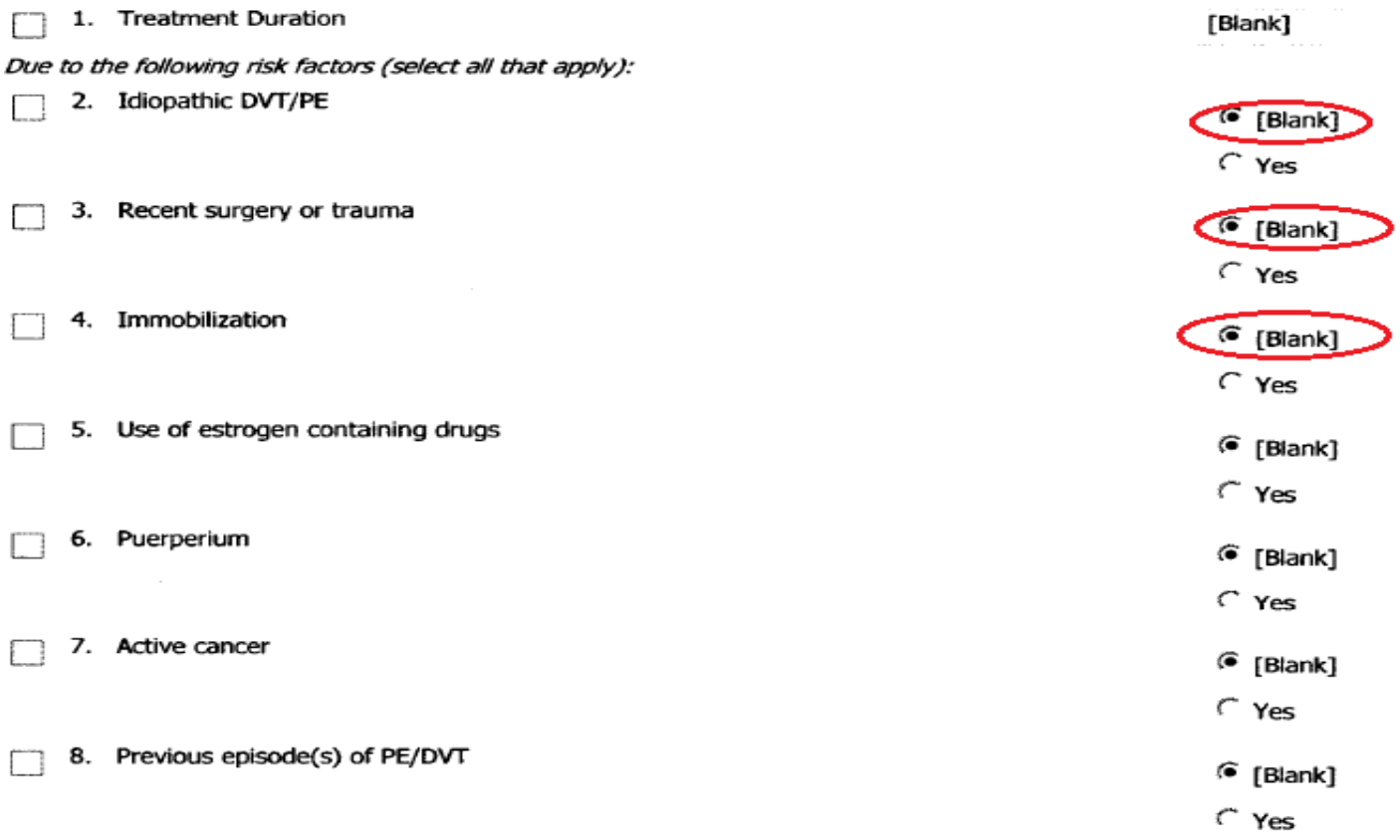
● Alcohol consumption

Alcohol consumption	1 ☐ never 2 ☐ seldom 3 ☐ occasionally 4 ☐ regularly
comments	....

- Avoid collecting all the panel of information in the same CRF page in the same source dataset

Collect Yes/No to obtain response for the questions rather than having blanks in the data

- Use Y/N to obtain responses for questions rather than not having blank values. CDASH Best Practices



Align pick list values as much as to the published controlled terminology.

- Data collected like this not only involves additional mapping efforts but leads to potential errors..

Date of birth	day month 1 9 year
Age	years
Sex	2 ☐ female
Ethnic group	1 ☐ Caucasian 2 ☐ Black 3 ☐ Hispanic 4 ☐ Asian 998 ☐ other, specify ----------

As per submission requirements, RACE & ETHNICITY have to be presented as different elements. Likewise Anatomical location & directionality are different elements

Same subjects rolling over to multiple studies should have the USUBJID Unique across the submission

As per the Study Protocol, this is a cross over study with 7 steps and the same subjects rolling over more than one steps. But, the USUBJID have to be same for all the subjects who are entering different STEPS / Phases…

Dose and Number of Subjects

Investigational Product	[redacted]								
Route of Administration	Oral								
Step	I[1)]		II		III	IV	V	VI	VII
Dose	0.1 mg	0.25 mg	0.5 mg	1 mg	2.5 mg	5 mg	10 mg	20 mg	30 mg
Subjects	A	B	C	D	E	F	E	F	E
Administration Timing	After breakfast								
No. of Subjects	Per treatment group: Active substance: 3 subjects, placebo 1 subject				Per step: Active substance: 6 subjects, placebo 2 subjects				

Same subjects rolling over to multiple studies should have the USUBJID Unique across the submission (Contd)

	STUDYID (STUDYID)	PID (PID)	SEX (SEX)	AGE (AGE)	HEIGHT (HEIGHT)	WEIGHT (WEIGHT)
25	[redacted]	3-E	M	26	171.3	71.5
26	[redacted]	5-E	M	26	171.3	71.5
27	[redacted]	3-F	M	26	170.2	58.7
28	[redacted]	5-F	M	26	170.2	58.7
29	[redacted]	7-F	M	26	170.2	58.7
30	[redacted]	3-G	M	25	166.7	61.9
31	[redacted]	5-G	M	25	166.7	61.9
32	[redacted]	7-G	M	25	166.7	61.9
33	[redacted]	5-H	M	23	179.3	70.3
34	[redacted]	7-H	M	23	179.3	70.3
35	[redacted]	5-D	M	27	175.3	72.9
36	[redacted]	7-A	M	20	171	56.4
37	[redacted]	7-B	M	28	168.3	70.8
38	[redacted]	7-E	M	31	167.7	54.8
39	[redacted]	4-A	M	22	178.7	67.7
40	[redacted]	6-A	M	22	178.7	67.7
41	[redacted]	4-B	M	29	173.3	56.4
42	[redacted]	4-C	M	32	169.7	65
43	[redacted]	6-C	M	32	169.7	65
44	[redacted]	4-D	M	34	167.4	60.4
45	[redacted]	6-D	M	34	167.4	60.4
46	[redacted]	4-E	M	28	177.4	65.4
47	[redacted]	6-E	M	28	177.4	65.4
48	[redacted]	4-G	M	28	176.6	68.1
49	[redacted]	6-G	M	28	176.6	68.1
50	[redacted]	6-F	M	24	168.1	55.8
51	[redacted]	4-F	M	21	169.9	60.5
52	[redacted]	4-H	M	24	177.2	78.3

As per the Protocol design, there should be a max of 32 subjects, but the raw datasets and the demographic subject identifiers created a different Identifiers …

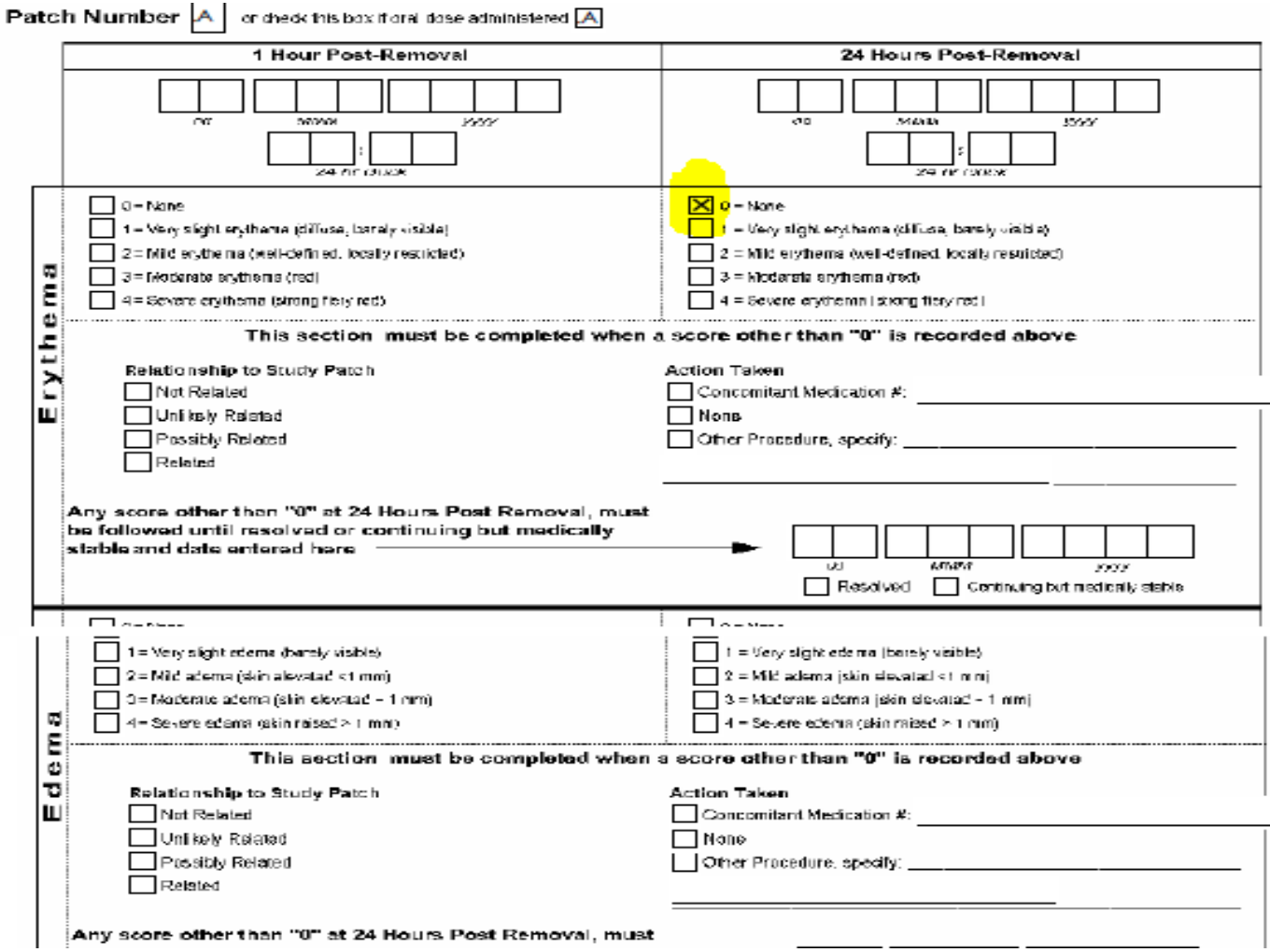
Raw Data should be the source for SDTM and SDTM should then create Analysis/ADaM

- Discrepancy in the count produced from the SDTM & Analysis data produced directly from the RAW data

14.3.1.6.1. Summary of Skin Irritation Assessment: Erythema - SAFETY Population

Statistic	Group 1 (N=10)	Group 2 (N=14) Patch 1 (N=14)	Patch 2 (N=14)	Patch 3 (N=14)	Patch 4 (N=14)	Patch 5 (N=13)	Worst Score* (N=14)
1 hr post-removal							
N	8	14	14	14	13	11	14
Mean (SD)	0.6 (0.74)	0.4 (0.65)	0.6 (0.76)	0.6 (0.65)	0.5 (0.66)	1.2 (0.98)	1.3 (0.91)
Median	0.5	0.0	0.0	0.5	0.0	1.0	1.0
Range (min, max)	(0, 2)	(0, 2)	(0, 2)	(0, 2)	(0, 2)	(0, 3)	(0, 3)
Erythema severity scores, n (%)							
(0) None	4 (40.0)	9 (64.3)	8 (57.1)	7 (50.0)	7 (50.0)	3 (21.4)	3 (21.4)
(1) Very Slight	3 (30.0)	4 (28.6)	4 (28.6)	6 (42.9)	5 (35.7)	4 (28.6)	5 (35.7)
(2) Mild	1 (10.0)	1 (7.1)	2 (14.3)	1 (7.1)	1 (7.1)	3 (21.4)	5 (35.7)
(3) Moderate	0	0	0	0	0	1 (7.1)	1 (7.1)
(4) Severe	0	0	0	0	0	0	0
24 hrs post-removal							
N	8	14	14	14	13	12	14
Mean (SD)	0.4 (0.74)	0.0 (0.00)	0.0 (0.00)	0.0 (0.00)	0.0 (0.00)	0.2 (0.39)	0.1 (0.36)
Median	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Range (min, max)	(0, 2)	(0, 0)	(0, 0)	(0, 0)	(0, 0)	(0, 1)	(0, 1)
Erythema severity scores, n (%)							
(0) None	6 (60.0)	14 (100.0)	14 (100.0)	14 (100.0)	13 (92.9)	10 (71.4)	12 (85.7)
(1) Very Slight	1 (10.0)	0	0	0	0	2 (14.3)	2 (14.3)
(2) Mild	3 (30.0)	0	0	0	0	0	0
(3) Moderate	0	0	0	0	0	0	0
(4) Severe	0	0	0	0	0	0	0

Raw Data should be the source for SDTM and SDTM should then create Analysis/ADaM (Contd.)


Patch Number [A] or check this box if oral dose administered [A]

	1 Hour Post-Removal	24 Hours Post-Removal
Erythema	0 = None 1 = Very slight erythema (diffuse, barely visible) 2 = Mild erythema (well-defined, locally restricted) 3 = Moderate erythema (red) 4 = Severe erythema (strong fiery red)	[X] 0 = None 1 = Very slight erythema (diffuse, barely visible) 2 = Mild erythema (well-defined, locally restricted) 3 = Moderate erythema (red) 4 = Severe erythema (strong fiery red)

This section must be completed when a score other than "0" is recorded above

Relationship to Study Patch
- Not Related
- Unlikely Related
- Possibly Related
- Related

Action Taken
- Concomitant Medication #: _____
- None
- Other Procedure, specify: _____

Any score other than "0" at 24 Hours Post Removal, must be followed until resolved or continuing but medically stable and date entered here → DD MMM YYYY

- Resolved
- Continuing but medically stable

	1 Hour Post-Removal	24 Hours Post-Removal
Edema	1 = Very slight edema (barely visible) 2 = Mild edema (skin elevated < 1 mm) 3 = Moderate edema (skin elevated ~ 1 mm) 4 = Severe edema (skin raised > 1 mm)	1 = Very slight edema (barely visible) 2 = Mild edema (skin elevated < 1 mm) 3 = Moderate edema (skin elevated ~ 1 mm) 4 = Severe edema (skin raised > 1 mm)

This section must be completed when a score other than "0" is recorded above

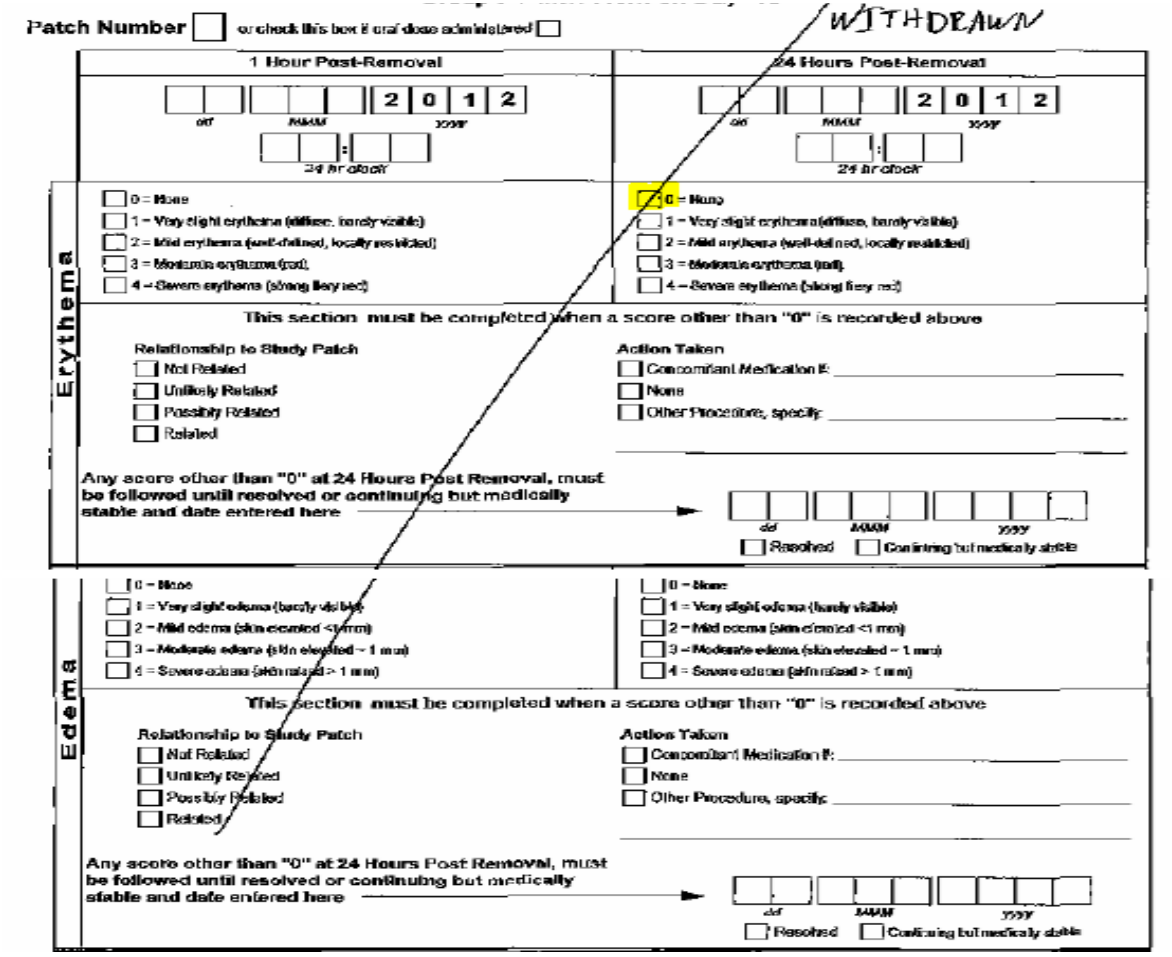
Relationship to Study Patch
- Not Related
- Unlikely Related
- Possibly Related
- Related

Action Taken
- Concomitant Medication #: _____
- None
- Other Procedure, specify: _____

Any score other than "0" at 24 Hours Post Removal, must

SDTM produced with the actual CRF for the subject

Raw Data should be the source for SDTM and SDTM should then create Analysis/ADaM (Contd.)



A strike-through or crossed out line across the CRF page through the NONE checkbox in the CRF page which triggered the DM system to collect it as a value

Recommendations to support Integrated collection → Analysis/Reporting → Submission

- Follow CDASH standards for CRF design; Implement CDASH Best practices
- Don't place important data / Key variables/standard variables in SUPPQUAL
- Data collection must be aligned to published CT as much as possible.
- USUBJID of the subject rolling over to multiple studies should be unique across the submission.
- Raw Data should be the source for SDTM and SDTM should then be used to create Analysis/ADaM datasets.
- Ensure Traceability in to ADaM

Recommendations to support Integrated collection → Analysis/Reporting → Submission

- AE Outcome – Avoid ‘Worsening’ as an outcome for AEs. As per NCI guidelines for investigators on persistent/Recurrent AEs: "If the [AE] grade becomes more severe the AE must be reported again with the new grade."

- Ensure all the REQUIRED/EXPECTED variables are collected. Missing REQUIRED/EXPECTED variables will lead to compliance exceptions and needs to be justified

- Adopt CDASH recommendations at least for all core domains – Ensure that data collection elements are in line with the submission and facilitates creation of Tabulation datasets

Recommendations to support Integrated collection → Analysis/Reporting → Submission

- Eliminate redundancy. Collecting the same information leads to redundancy creating opportunity for discrepancy. Also, leads to data cleaning.

- Collect only data needed to support the protocol/analysis and avoid 'Nice to Haves'. All collected data needs to be accounted in SDTM.

- FDA recognizes the difficulty of legacy data conversion and the potential for errors in the conversion. Better approach is to implement standards upfront, achieve efficiency, avoid delays & errors

Where are moving with Standards..?

- ~ 30% of unique NDAs received by CDER in 2011 submitted CDISC/SDTM data
- ~ 20% of the BLA's received by CBER in 2011 submitted CDISC/SDTM data

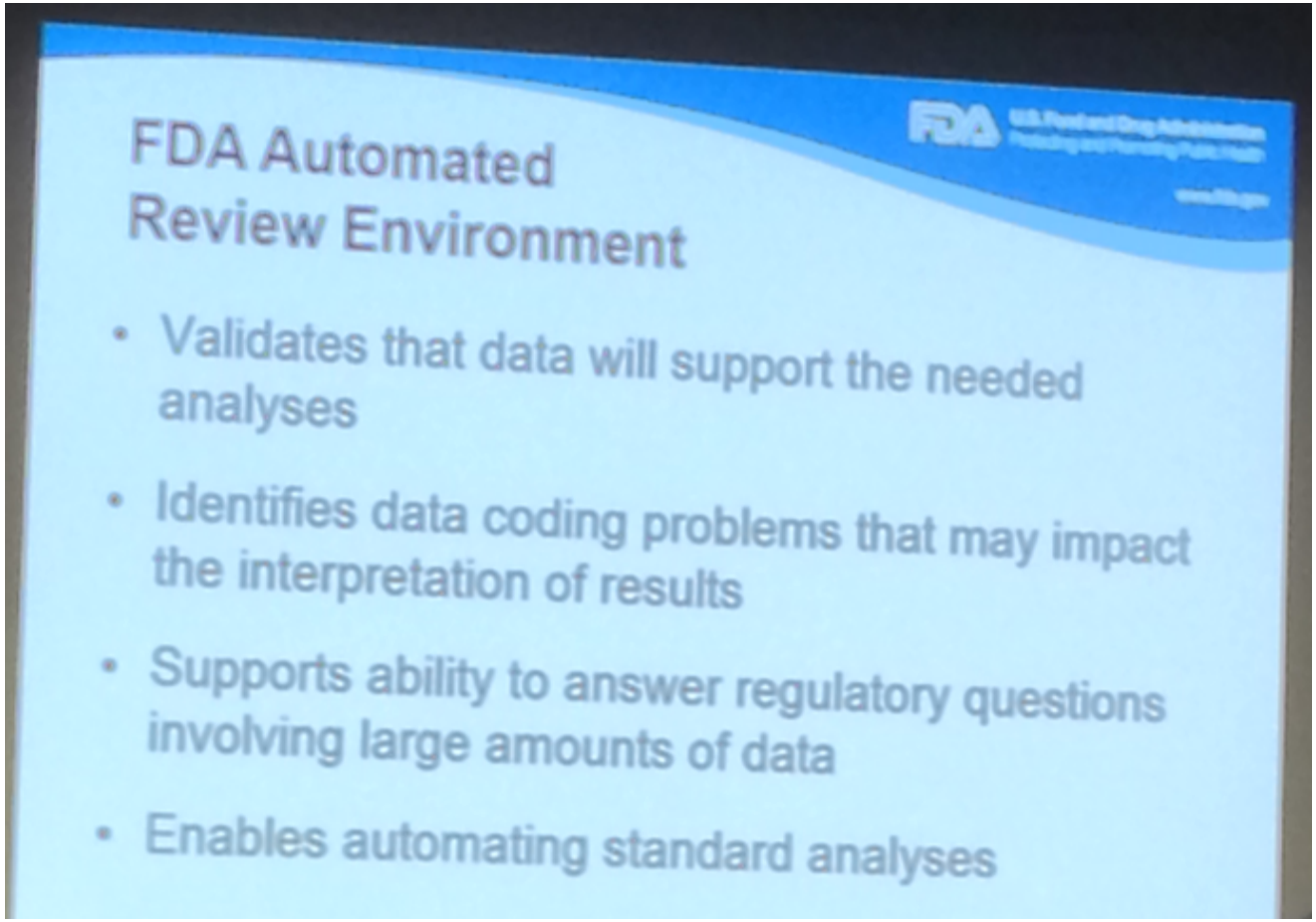
More and more Submissions are embracing SDTM / ADaM Standards

Fiscal Year 2013:
Number and Percent (%) of NDAs with Study Data Submissions in CDISC SDTM

NDAs	# of Submissions	% with CDISC SDTM Data
New Unique NDAs	98	61%
All NDAs	223	50%

As presented in the Europe CDISC Interchange, April 2014

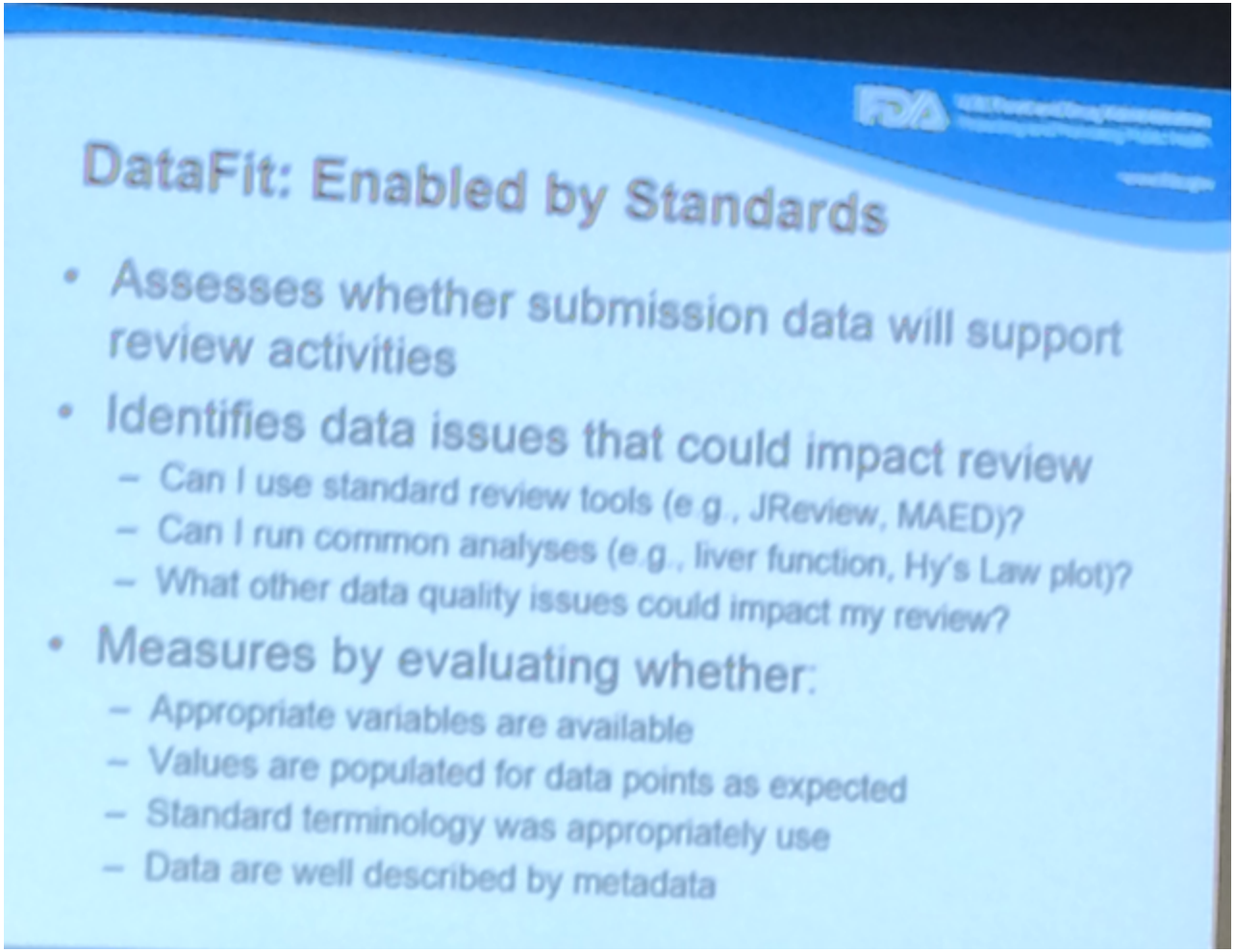
Agency Review Environment



Standards support FDA's Modern Review Environment

- As presented in the Europe CDISC Interchange, April 2014

Data Fitness – enabled by Standardized data Submission



That's why the data submitted must be CDISC SDTM / ADaM compliant

- As presented in the Europe CDISC Interchange, April 2014

PMDA's pilot on Standardized Data Submission

Results of FY2013 pilot project (outline)

- Implementation details
  - Data visualization and analysis were conducted from January to February 2014
  - Around 100 persons in charge
    - About 80 reviewers from new drug review offices, including clinical reviewers, clinical pharmacologists, and statistical reviewers
    - About 20 staff from the Task Force for Advanced Review and Consultation with Electronic Data
  - PMDA introduced and used software for
    - Data visualization/exploratory analysis
    - Analyzing CDISC compliant study data
    - Statistical analysis
    - Pharmacokinetic analysis

PMDA Japan shared the results of the CDISC pilot Project confirming the feasibility of Reviewing & Analyzing actual data from Clinical Trial data submitted in CDISC format

PMDA's pilot on Standardized Data Submission

Results of FY2013 pilot project (outline)

- Confirmation of feasibility
  - There were no problems regarding data storage and management within PMDA.
  - Analysis of actual clinical trial data was confirmed to be feasible by the reviewers who possess a certain level of knowledge regarding datasets and software.
- Future and ongoing tasks
  - Improvement and enhancement of the training for the reviewers
  - Consideration of the new review process with clinical data analysis
  - Preparation of basic and technical notices to keep high level of conformance to the data standards

Data standards = CDISC is the key in handling the clinical study data of a lot of products at the PMDA

Binding + Guidance Documents from FDA

- FDA has issued a series of draft Binding & Guidance documents that mandates the submission of data to the agency as CDISC Standards following the versions, Controlled Terminology as published in the Data Catalogue over a period of time.

eCTD Guidance

- FDA eCTD GUIDANCE FOR INDUSTRY

- Provides the requirements for a valid electronic submission of standardized study data under section 745A(a) of the FD&C Act

- Submissions that are not submitted electronically and electronic submissions that are not in a format that FDA can process, review, and archive will not be filed, unless exempted from the electronic submission requirements

Guidance under Sec 745(a)

- Regulatory Submissions in Electronic Format - Submissions Under Section 745A(a) of the Federal Food, Drug, and Cosmetic Act

- Requires submissions submitted in electronic format specified by the Food and Drug Administration (FDA or the 14 Agency), beginning no earlier than 24 months after FDA issues a final guidance specifying an electronic submission format.

- Guidance describes how FDA interprets and plans to implement the requirements of section 745A(a). Specifically, this guidance discusses
  - Submission types that must be submitted electronically
  - Exemptions from and waivers of the electronic submission requirements,
  - Timetable and process for implementing the requirements.

Study Data Technical Conformance Guide

- STUDY DATA TECHNICAL CONFORMANCE GUIDE

Study Data Technical Conformance Guide (Guide) provides specifications, recommendations, and general considerations on how to submit standardized study data using FDA-supported data standards located in the **Data Standards Catalog** (Standards Catalog) The Guide supplements the guidance for industry *Providing Regulatory Submissions in Electronic Format — Standardized Study Data* (eStudy Data Guidance).

- STANDARDIZED STUDY DATA

When finalized, this guidance will implement the electronic submission requirements of section 745A(a) of the FD&C Act for study data to CDER/ CBER specifying the format for the electronic submission

Submissions that are not submitted electronically and electronic submissions that are not in a format that FDA can process, review, and archive will not be filed, unless exempted from the electronic submission

FDA Standards Catalog & CDER Common Issues Document

- FDA DATA STANDARDS CATALOG

Specifies the Data standards & Standard Terminology supported by FDA.

- CDER Common Data Standards Issues Document

Communicates general CDER preferences and experiences regarding the submission of standardized data to aid sponsors in the creation of standardized datasets for both tabulation datasets and analysis datasets

Discuss with the review division

Communiction: The FDA / Sponsor Data Submission Discussion

= DISASTER

Newby and Wilson, 2009

Why Standards are important from Regulatory perspective

- “The electronic format and standards are critical for FDA…”
- “We cannot improve efficiency or innovate without standards..."
- “We want to improve regulatory decision-making through better access to structured scientific data... Non-standard electronic data limits quality and efficiency during the review process. ….”

Thank You