

**From:** [Giordano, Erica](#)  
**To:** [Patel, Manisha](#)  
**Cc:** [Patel, Manisha](#)  
**Subject:** RE: BL 125646 Validation Errors for Studies 2202 and 2205  
**Date:** Friday, March 10, 2017, 11:06:54 AM  
**Attachments:** [image001.png](#)  
[image002.png](#)  
[image003.png](#)  
[image004.png](#)  
**Sensitivity:** Confidential

It seems all of the issues have been resolved, we can cancel the noon telecon.

Thanks  
Erica

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**From:** Patel, Manisha [<mailto:manisha.patel@novartis.com>]  
**Sent:** Friday, March 10, 2017, 9:20 AM  
**To:** Giordano, Erica  
**Cc:** Ahmed, Natin  
**Subject:** RE: BL 125646 Validation Errors for Studies 2202 and 2205  
**Sensitivity:** Confidential

Hi Erica, have you heard back from the CDISC team whether this works? I'm just wondering if we should still plan for a call at noon.

Thank you

Kind regards  
Manisha

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**From:** Giordano, Erica [<mailto:Erica.Giordano@fda.hhs.gov>]  
**Sent:** Thursday, March 09, 2017, 3:46 PM  
**To:** Patel, Manisha  
**Cc:** Ahmed, Natin; Riggins, Cindy  
**Subject:** RE: BL 125646 Validation Errors for Studies 2202 and 2205  
**Sensitivity:** Confidential

Thanks very much. I have passed the instructions along to the team and I will let you know the results.

Thanks  
Erica

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**From:** Patel, Manisha [[mailto:manisha\\_atel@noartis.com](mailto:manisha_atel@noartis.com)]  
**Sent:** Thursday, March 09, 2017, 3:42 PM  
**To:** Giordano, Erica  
**Cc:** Ahmed, Natin; Riggins, Cindy  
**Subject:** RE: BL 125646 Validation Errors for Studies 2202 and 2205  
**Sensitivity:** Confidential

Hi Erica

Since we last spoke, my statistics colleagues managed to get in touch with JMP technical support to better understand why errors may be arising when FDA is viewing the SAS datasets in JMP. Please see attached "instructions" and accompanying test files and let me know if this resolves the issue.

I propose we maintain the TC for tomorrow if the attached does not resolve the issue.

Thanks

Kind regards  
Manisha

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**From:** Giordano, Erica [<mailto:Erica.Giordano@fda.hhs.gov>]  
**Sent:** Wednesday, March 08, 2017, 7:54 PM  
**To:** Patel, Manisha  
**Subject:** RE: BL 125646 Validation Errors for Studies 2202 and 2205  
**Sensitivity:** Confidential

Thank you for confirming the time and providing the call-in information.

Erica

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**From:** Patel, Manisha [[mailto:manisha\\_atel@noartis.com](mailto:manisha_atel@noartis.com)]  
**Sent:** Wednesday, March 08, 2017, 4:38 PM  
**To:** Giordano, Erica  
**Subject:** RE: BL 125646 Validation Errors for Studies 2202 and 2205  
**Sensitivity:** Confidential

Hi Erica, thank you. I confirm Friday 12:00 PM – 12:30 PM is acceptable.

US/Canada Toll Free 1 866 755 6294  
Participant Passcode: **324 113 8817#**

Kind regards  
Manisha

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**From:** Giordano, Erica [<mailto:Erica.Giordano@fda.hhs.gov>]  
**Sent:** Wednesday, March 08, 2017, 2:57 PM  
**To:** Patel, Manisha  
**Subject:** RE: BL 125646 Validation Errors for Studies 2202 and 2205  
**Sensitivity:** Confidential

Manisha,

Please confirm if you and your team are available for a brief call on Friday March 10<sup>th</sup> from 12pm to 12.30pm ET. If so please provide a call-in # and passcode.

Thanks  
Erica

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**From:** Patel, Manisha [<mailto:manisha.patel@novartis.com>]  
**Sent:** Wednesday, March 08, 2017, 2:06 PM  
**To:** Giordano, Erica  
**Subject:** RE: BL 125646 Validation Errors for Studies 2202 and 2205  
**Sensitivity:** Confidential

Hi Erica, it would be helpful for us to speak with the statistical reviewer and CDISC team.

Kind regards  
Manisha

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**From:** Giordano, Erica [<mailto:Erica.Giordano@fda.hhs.gov>]  
**Sent:** Wednesday, March 08, 2017, 1:08 PM  
**To:** Patel, Manisha  
**Subject:** RE: BL 125646 Validation Errors for Studies 2202 and 2205  
**Sensitivity:** Confidential

Manisha,

Below is an example of ADAE domain (yellow highlight part) among many other ADaM domains. The Variables of TRTSDT (Date of First Exposure to Treatment), TRTSDTM (Datetime of First Exposure to Treatment), TRTEDT (Date of Last Exposure to Treatment), TREEDTM (Datetime of Last Exposure to Treatment), AENDT (Analysis End Date), ASTDT (Analysis Start date) are populated as SAS code. The variables should be populated as ISO8601 format in order to be understandable by Medical officers, Chemists and Microbiologists. That is why they are detected by validator as errors:

(b) (6)

Please let me know if the figure above helps to clarify the issues.

You did the right thing in some of the domains of the figure you included below.

If you need further clarification please let me know and I will setup a call.

Erica

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**From:** Patel, Manisha [[mailto:manisha\\_atel@noartis.com](mailto:manisha_atel@noartis.com)]  
**Sent:** Wednesday, March 08, 2017 12:15 PM  
**To:** Giordano, Erica  
**Subject:** RE: BL 125646 Validation Errors for Studies 2202 and 2205  
**Sensitivity:** Confidential

Thank you

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**From:** Giordano, Erica [<mailto:Erica.Giordano@fda.hhs.gov>]  
**Sent:** Wednesday, March 08, 2017 12:14 PM  
**To:** Patel, Manisha  
**Cc:** Ahmed, Narin; Riggins, Cindy  
**Subject:** RE: BL 125646 Validation Errors for Studies 2202 and 2205  
**Sensitivity:** Confidential

I am following up with the review team and will let you know when we can arrange a call.

Erica

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**From:** Patel, Manisha [[mailto:manisha\\_atel@noartis.com](mailto:manisha_atel@noartis.com)]  
**Sent:** Wednesday, March 08, 2017 12:11 PM  
**To:** Giordano, Erica  
**Cc:** Ahmed, Narin; Riggins, Cindy  
**Subject:** RE: BL 125646 Validation Errors for Studies 2202 and 2205  
**Sensitivity:** Confidential

Hi Erica

Would it be possible to arrange a short call with the statistical review lead and CDISC team so that we can discuss?

The date format Novartis submitted was in SAS ISO 8601 format as requested by FDA and in accordance with the required format for CDISC submissions. From our view, the date format should be human-readable in SAS (see screenshot below).

Is there a version of JMP used by FDA which is able to read SAS ISO 8601 date format? From testing the datasets in JMP version 13, we noticed that JMP and SAS have different numeric conversions. We are concerned that forcing conversion will result in error when analyzed in SAS.

(b) (6)

Kind regards  
Manisha

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**From:** Giordano, Erica [<mailto:Erica.Giordano@fda.hhs.gov>]  
**Sent:** Monday, March 06, 2017 8:01 PM  
**To:** Patel, Manisha  
**Subject:** RE: BL 125646 Validation Errors for Studies 2202 and 2205  
**Sensitivity:** Confidential

Hi Manisha,

I have followed up with the CDISC team and they have provided the following feedback.

- 1) The validator detected that SAS codes as values in the timing variables in ADaM datasets. This implied that there are something wrong.
- 2) ADaMIG v. 1.1 required numeric dates, times and datetimes should be formatted, so as to be human-readable shown as figures below from ADaMIG v. 1.1 p15 and p17 and ADaM v. 2.1, page 19

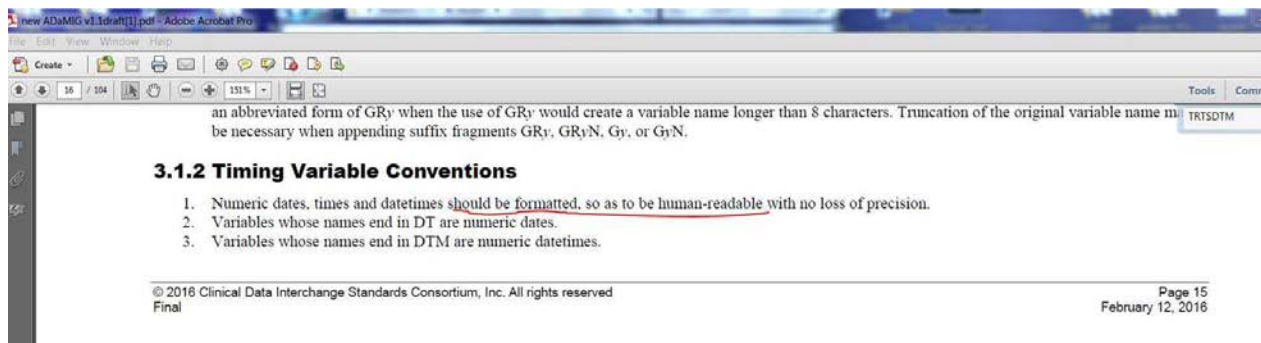


Table 3.1.3.1 Some Examples of Setting of Date Imputation Flag

Missing Elements	SDTM --DTC String	ADaM Date Value ("DT Variable") <sup>[1,2]</sup> (## indicates imputed portion)	Imputation flag ("DIF variable")
None	YYYY-MM-DD	YYYY-MM-DD	Blank
Day	YYYY-MM	YYYY-MM-##	D
Month	YYYY--DD	YYYY-##-DD	M
Month and Day	YYYY	YYYY-##-##	M
Year	--MM-DD	####-MM-DD	Y
Year and Month	----DD	####-##-DD	Y
Year and Month and Day		####-##-##	Y

[1] The ISO formats used in the ADaM Date Value column are for the purposes of illustration, and are not intended to imply any type of display standard or requirement. The DT variable is numeric and the producer will determine the appropriate display format.

[2] The indication of imputed values is not intended to imply an imputation rule or standard. For example, if the month is missing, imputation rules might specify that the collected day value be ignored so that both month and day are imputed.

Dataset Name	Parameter Identifier	Variable Name	Variable Label	Variable Type	Display Format	Codelist / Controlled Terms	Source / Derivation
ADQSADAS	*ALL*	ITTRFL	Intent-to-Treat Record-Level Flag	text	\$1	Y	If the observed data are eligible for analysis (i.e., QS.VISITNUM in 3,8,10,12,201) and if QS.VISIT = the name of the visit window containing ADQSADAS.ADY and if ADQSADAS.ITTRFL="Y" then ITTRFL="Y"; ITTRFL blank otherwise
ADQSADAS	*DEFAULT*	DTYPE	Derivation Type	text	\$4		Not applicable, therefore blank
ADQSADAS	ACTOT11	DTYPE	Derivation Type	text	\$4	LOCF	DTYPE = "LOCF" when the value of ADQSADAS.AVAL (and thus the entire record) has been imputed using the LOCF algorithm, blank otherwise.
ADQSADAS	*ALL*	ONTRTFL	On Treatment Record Flag	text	\$1	Y	If ADQSADAS.TRSDT <= ADQSADAS.ADT <= ADQSADAS.TRTEDT then ONTRTFL="Y". ONTRTFL blank otherwise
ADQSADAS	*ALL*	TRSDT	Date of First Exposure to Treatment	integer	yymmdd10.		ADSL.TRSDT
ADQSADAS	*ALL*	TRTEDT	Date of Last Exposure to Treatment	integer	yymmdd10.		ADSL.TRTEDT
ADQSADAS	*ALL*	VISITDY	Planned Study Day of Visit	integer	3.0		QS.VISITDY
ADQSADAS	*ALL*	VISITNUM	Visit Number	float	4.1		QS.VISITNUM
ADQSADAS	*ALL*	ADT	Analysis Date	integer	yymmdd10.		QS.QSDTC associated with AVAL, converted to SAS date

3) What is ISO8601?



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# What is ISO 8601?

ISO 8601 describes an internationally accepted way to represent dates and times using numbers.

When dates are represented with numbers they can be interpreted in different ways. For example, 01/05/12 could mean January 5, 2012, or May 1, 2012. On an individual level this uncertainty can be very frustrating, in a business context it can be very expensive. Organizing meetings and deliveries, writing contracts and buying airplane tickets can be very difficult when the date is unclear.

ISO 8601 tackles this uncertainty by setting out an internationally agreed way to represent dates:

YYYY-MM-DD

For example, September 27, 2012 is represented as 2012-09-27.

Again, SAS code and format for timing variable are understandable for Biostatisticians but they are not understandable for Medical officers, Chemists and Microbiologists. That is why they are detected as errors.

Please let me know if this helps or if you have any other questions.

Thanks  
Erica

From: Patel Manisha [mailto:manisha.patel@novartis.com]  
Sent: Monday, March 06, 2017, 9:49 AM  
To: Giordano Erica  
Subject: RE: BL 125646 Validation Errors for Studies 2202 and 2205  
Sensitivity: Confidential

Hi Erica

Regarding the comment on readability of SAS date format of time and day, my stats colleagues have confirmed that per CDISC requirement, all dates in ADaM datasets are reported in ISO 8601 format and are expressed as IS8601 (screenshot is provided below). Can you confirm which JMP software version is being used by FDA?

#	Variable	Type	Length	Format	Inform	Label
1	STUDYID	Character	10	\$10	\$10	Study Identifier
2	USUBJID	Character	35	\$35	\$35	Unique Subject Identifier
3	SUBJID	Character	10	\$10	\$10	Subject Identifier for the Study
4	SITEID	Character	10	\$10	\$10	Study Site Identifier
5	SCRNPL	Character	2	\$2		Screening Population Flag
6	ENRFL	Character	2	\$2		Enrolled Population Flag
7	IEASFL	Character	2	\$2		Interim Efficacy Analysis Pop. Flag
8	EASFL	Character	2	\$2		Efficacy Analysis Population Flag
9	FASFL	Character	2	\$2		Full Analysis Set Population Flag
10	SAFFL	Character	2	\$2		Safety Population Flag
11	TRTP	Character	200	\$200		Planned Treatment
12	TRTA	Character	200	\$200		Actual Treatment
13	TRTSDT	Numeric	8	ISO8601DA		Date of First Exposure to Treatment
14	TRTSDTM	Numeric	8	ISO8601DT		Datetime of First Exposure to Treatment
15	TRTEDT	Numeric	8	ISO8601DA		Date of Last Exposure to Treatment
16	TRTEDTM	Numeric	8	ISO8601DT		Datetime of Last Exposure to Treatment

Please see below response regarding the comment on AE domain and let me know if the reviewers have any further question on this topic. I will also formally submit a response through the gateway.

The Full Analysis Set Population Flag (FASFL) and Safety Population Flag (SAFFL) are used to identify patients in the Full analysis set and Safety set respectively. Both analysis sets are defined to include only patients who have received CTL019 infusion (as per screenshot below from define XML). Therefore, by definition, patients who have not received CTL019 infusion have "N" as the value for both flags FASFL and SAFFL.

FASFL	Full Analysis Set Population Flag	text	NO/YES	DA/ADSL	Set to "Y" for patients who received at least one infusion who is not lost to follow-up (SAFFL is not blank and is not after ADTCUTPOINT). Set to "N" otherwise.
SAFFL	Safety Population Flag	text	NO/YES	ADSL	Set to FASFL.

As a result, Datetime of First Exposure to Treatment (TRTSDTM) and Datetime of Last Exposure to Treatment (TRTEDTM) are missing if and only if FASFL and SAFFL equals to "N" (i.e. patient is not treated).

TRTSDTM	Datetime of First Exposure to Treatment	integer	ISO8601TM	DM	Datetime of first infusion (TRTSDTC). Set it to null if it is after cutoff.
TRTEDTM	Datetime of Last Exposure to Treatment	integer	ISO8601TM	EX	Last infusion datetime (TRTEDTC) if none done (EXOCODE is not missing). Set it to null if time is not collected.

Kind regards  
Manisha

From: Patel Manisha  
Sent: Monday, March 06, 2017, 7:50 AM  
To: Erica Giordano [mailto:Erica.Giordano@fda.hhs.gov]  
Subject: RE: BL 125646 Validation Errors for Studies 2202 and 2205  
Sensitivity: Confidential

Hi Erica, thank you, yes, much more clear.

From: Giordano Erica [mailto:Erica.Giordano@fda.hhs.gov]  
Sent: Sunday, March 05, 2017, 8:35 PM  
To: Patel Manisha  
Subject: RE: BL 125646 Validation Errors for Studies 2202 and 2205  
Sensitivity: Confidential

Does the attached help at all? If not, please let me know and I can see what else I can get from the CDISC team.

Thanks  
Erica

From: Patel Manisha [mailto:manisha.patel@novartis.com]  
Sent: Friday, March 03, 2017, 5:26 PM  
To: Giordano Erica  
Subject: RE: BL 125646 Validation Errors for Studies 2202 and 2205  
Sensitivity: Confidential

Hi Erica, would it be possible to provide a higher resolution image of the screenshot below?  
Kind regards  
Manisha

From: Giordano Erica [mailto:Erica.Giordano@fda.hhs.gov]  
Sent: Friday, March 03, 2017, 3:12 PM  
To: Patel Manisha  
Cc: Ahmed Namin, Riggins, Cindy  
Subject: BL 125646 Validation Errors for Studies 2202 and 2205  
Sensitivity: Confidential

Good afternoon,

After looking through the raw data in several domains, the CDISC team has reported that the SAS date format of time and day are not readable in JMP. For example, the time and day and variable labels expressed in TRTSDT (Analysis End Date), TRTSDTM (Analysis End Date), TRTEDT (Analysis End Date), and TRTEDTM (Analysis End Date) are not understandable.

Please convert SAS date values into ISO8601 date and time format for the following

Study 2202 ADaM and domains: AE, AEERISK, ADB2A, ADB2B, ADCE, ADCM, ADDS, ADDV, ADEFIRC1, ADEFLOC, ADEX, ADGROW, ADLB, ADM1, ADM2, ADM3, ADMH, ADPC, ADPPF, ADPPQ, ADPUB, ADQS, ADSL, ADTTEIRC, ADTTELOC, ADVS, ADXG, ADZB, ADZP, ADZR, ADZT, ADZH

Study 2205 ADaM and domains: AE, AEERISK, ADB1, ADB2A, ADB2B, ADCE, ADCM, ADDS, ADDV, ADEFIRC1, ADEFLOC1, ADEX, ADGROW, ADLB, ADM1, ADM2, ADM3, ADMH, ADPC, ADPP, ADPUB, ADQS, ADSL, ADTTEIRC, ADTTELOC, ADVS, ADXG, ADZB, ADZP, ADZR, AND ADZT

For the AE domain, the missing data is because the values of SAFFL and FASFL are populated as "N". So the subjects are not defined in the statistical analysis plan. The corresponding numeric version ("FN") can be included only if a SAFFL and FASFL

flags are populated as "Y". Therefore, it is acceptable that there are no ASTDT and AENDT values in those records. However, TRTEDTM and TRTSDTM for those subjects should be populated with human readable time and date.

(b) (6)

Please let me know if you have any questions.

Thank you,

**Erica Giordano**

*Regulatory Project Manager*

Center for Biologics Evaluation and Research

Office of Issues and Advanced Therapies

U.S. Food and Drug Administration

Tel: 202-02-8298

[Erica.Giordano@fda.hhs.gov](mailto:Erica.Giordano@fda.hhs.gov)



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