Experience of electronic data submission via Gateway to PMDA

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ABSTRACT

PMDA started accepting the submission of electronic study data of clinical trials for new drug applications (NDA) on October 1st, 2016. In this poster, our preparation for the electronic data submission and experience of PMDA consultations for ADaM, SDTM and Define.XML, including how to explain the errors in Appendix 8, will be shown.

In addition, the experience of submission via Gateway system will also be shown. In Gateway system, it is difficult for the sponsor to input descriptions for each item of study data by clicking every single file. To avoid that, a TSV file is provided from Gateway system to edit and update information outside the system. However, this TSV file can only be provided after the advance notice of the application (1-5 weeks before NDA) to PMDA. To prepare in advance, creating the TSV file using a SAS program will also be shown.

INTRODUCTION

PMDA started accepting the submission of electronic study data for new drug applications on October 1st, 2016. Therefore a cross functional task force team was established, consisting of a Biostatistician, Statistical programmer and Regulatory Affairs. This task team discussed gap analysis, a road map until the mandatory period, whether a pilot study should be conducted, pros/cons of pilot study and researched electronic study data submission. After discussion, the task team got approval from the project team. So this paper explains the experience of PMDA consultation for electronic study data, how to explain Reject messages and Error messages to PMDA and how to create the Appendix 8. After three consultations, future tasks such as the selection of participants, what PMDA requests and how to explain the validation errors were understood.

In addition, the electronic study data needs to be submitted via Gateway system. In Gateway system, it is difficult for the sponsor to input descriptions for each item of study data by clicking every single file. To avoid that, a TSV file is provided from Gateway system to edit and update information outside the system. However, this TSV file can only be provided after the advance notice of the application (that is 5 weeks to 1 week before NDA) to PMDA. After 1st submission, the task team discussed how to prepare in advance a TSV file using SAS programming. Then it could be submitted successfully at the time of re-submission. The SAS program will be shown.

EXPERIENCE FROM CONSULTATION

As pilot study, two selected studies (a global pivotal study and a Japanese study) of the planned clinical data package were submitted for electronic study data submission. The overall timeline is from 1st PMDA consultation for electronic data to NDA shown in Figure 1. The sponsor should complete the consultation for electronic data before the meeting prior to pre-NDA consultation. However, as there were some additional errors due to data updates, preparation time was tight to have the 3rd consultation before the meeting prior to pre-NDA consultation. Also, explanation of validation error provided to PMDA in validation report and appendix 8 will be shown.
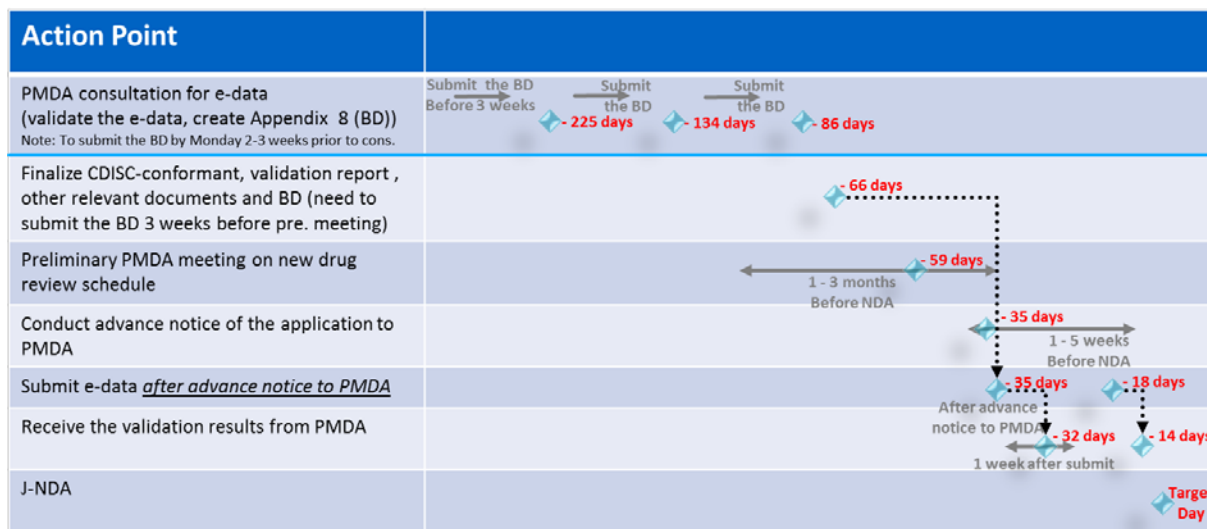
Figure 1. Actual timeline/date with standard timeline from PMDA guidance

REJECT MESSAGE

In this electronic data submission, a Reject message was detected due to missing data in required variables in DS domain. However electronic study data was locked before 2016. This pilot study was conducted during the transition period, so the important point of the 1st consultation was whether this data was acceptable or not by PMDA in this period. Regarding this issue, PMDA commented that the Reject message in validation report is not acceptable and the sponsor should fix these violations.

ERROR MESSAGE

Regarding Error message, PMDA commented that the explanation for errors provided in the Appendix 8 is generally acceptable but as written in the PMDA's Technical Conformance Guide, *if violated, the applicant should consult the PMDA before the application about the reason for the violation and the reason why it is not possible to correct it. These rules must also be explained in the data guide*. And then PMDA commented to try to reduce the number of errors as much as possible for future electronic study data submissions. PMDA requested more detailed explanation and reason of why these issues could not be fixed than FDA. For sponsors who have to submit to both FDA and PMDA, further discussion is needed.

This paper shows some explanation and reasons for why errors cannot be fixed. In this list, there is 'No impact for statistical analysis.'. However PMDA commented sponsor should add further detail to explain why this issue is judged to have no impact for analysis. So there is an additional explanation in this list.

Rule ID	Diagnostic Message	Explanation of error	Why cannot fix this error
SD0003	Invalid ISO 8601 value for BEDTC variable	ISO 8601 dates using UTC and/or time offsets from UTC were used for some records	ISO 8601 value applied for this variable correctly. However the error were detected when the data have 'time'.
SD0036	Missing value for LBSTRESC, when LBORRES is provided	No unit was collected for reticulocytes or number of cells. One lab did not provide units for hematocrit.	It is unfeasible without obtaining the data from lab.
AD0154	Multiple baseline records exist for a	One subject had two measurements on vital sign with	No impact for statistical analysis

	unique USUBJID, PARAMCD, BASETYPE	missing collection time on the same date, but site confirm the data issue can't be resolved, therefore both records presented in the data as baseline records. (additional explanation) The one with the highest VSSEQ is used as BASE value in CHG and PCHG calculation when multiple results are flagged as baseline.	
AD0059	*TM is not a numeric variable	PCELTM is not a clock time or a date time variable.	No impact for statistical analysis
DD0060	Define.xml/CDISC variable Label mismatch	RSMETHOD is permissible for addition to domains based on the Findings General Observation Class. The SDTM label is represented since an SDTM-IG label is not defined.	This message appears to be a false positive finding; the sponsor aligned with the SDTM label for --METHOD and the validation used a different value.
DD0033	Unknown NCI Code value for Codelist 'PKUNIT'	C85494 is the Codelist Code for the PKUNIT Codelist in CDISC CT version 2015-03-27.	This Unknown NCI Code error appears to be a false positive finding.
DD0039	Variable is in wrong order within Dataset 'XX'	A unique itemdef is defined for each distinct combination of attributes for a variable. For example, if Length or Comment variess across domains for a variable, in the XML, it is suffixed with a value (eg, .V1, .V2) to uniquely identify the different combinations. Note: The variables are presented in the correct order in the SDTM datasets and SDTM define.xml. The below is sample define code.	This message appears to be a false positive finding.
`<ItemDef OID=" IT.USUBJID.V1" Name="USUBJID" DataType="text" Length="15">...</ItemDef>`			
`<ItemDef OID=" IT.USUBJID.V2" Name="USUBJID" DataType="text" Length="20">...</ItemDef>`			

Table 1. List of Error messages

APPENDIX 8

In Appendix 8 (The following is image for in-house, because original Appendix 8 is only Japanese) for the column 'If submit, check the box (⊠) of most relevant.', PMDA commented to check any of the boxes for the domains with checkmark.

Figure 2. PMDA requested to check any of the boxes for the domains with checkmark

In this case, it was necessary to modify the SDRG to make consistent with Appendix 8.


Figure 3. Consistency of SDRG and Appendix 8

SUBMIT VIA GATEWAY SYSTEM

The electronic study data can be submitted after the advance notice that is 5 weeks before NDA. The sponsor has to do this advance notice in PMDA's portal site and enter the contents of the electronic study data. The contents are file path and name under m5 folder, study ID, file ID, operation, type of study data, analysis type, description for file (if PK analysis is included), controlled terminology of SDTM and ADaM and Japanese character code. As there are multiple studies in one filing, it is difficult for sponsor to input descriptions for each item of study data by clicking every single file. In addition, if Regulatory Affairs member submit these data, it is challenging for them to understand all of the study data and files. QC also needs a lot of time. At the earliest, sponsor can submit electronic study data 5 weeks before NDA. Within the 5 weeks before NDA, there is validation by PMDA and re-submission due to any problems or any system troubles. For that reason, electronic data submission should be completed as early as possible.

In this pilot study, only Regulatory Affairs members had an access to PMDA Gateway system, so they entered all information with the statistician and programmer as support for confirmation of study data and an IS member as support for IT trouble. The study data was 850 MB (500 files). The advanced notice was completed in 30 minutes. After study contents under m5 folder was uploaded via Gateway, a TSV file was provided from Gateway system. Although a TSV file can be created or updated using Excel according to the PMDA's manual, the TSV file updated using Excel couldn't be submitted. Team tried to use the text editor or to enter the manually in Gateway system for the description for each item of study data. It was challenging because many participants were waiting for this submission. However, it is important to try various ways in this time because Gateway system is closed after submission. By these two methods, this pilot study could be submitted successfully by the end of the day.

Display 1 is screen capture.
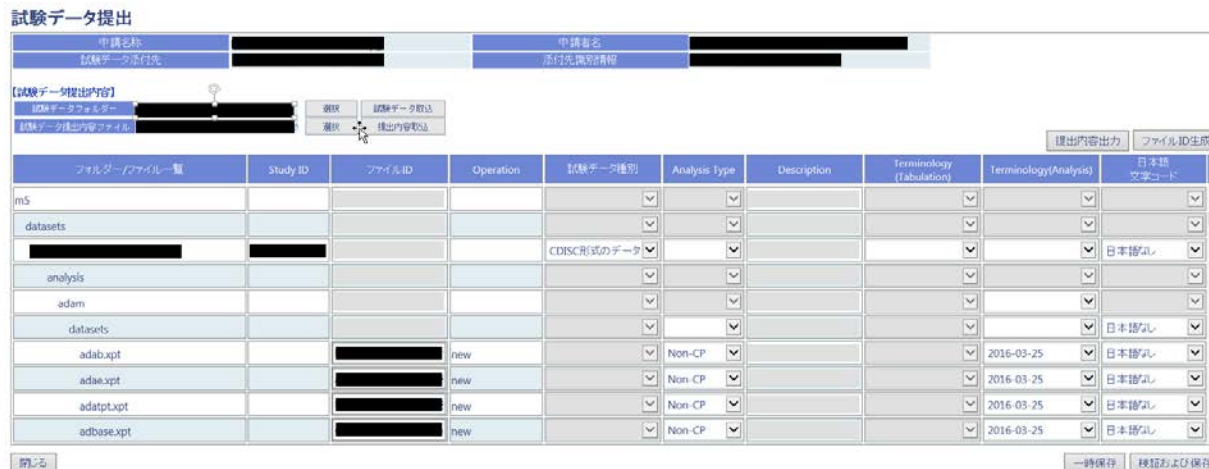
Display 1. Gateway system for electronic study data submission

After the 1st submission, the electronic study data needed to be resubmitted due to a Reviewer's guide update. Since it was only one update, the submission was supposed to be completed immediately. However, there was a reading error and the electronic study data couldn't be resubmitted. The Regulatory Affairs member contacted PMDA and received an answer 4 days later. The cause was a Gateway system error in re-submission phase. After the 2nd submission, PMDA accepted all electronic study data.

TSV FILE USING SAS PROGRAM

After the 1st submission, task team discussed whether a TSV file could be created before the advance notice and why a TSV file updated in Excel couldn't be submitted. As one solution, the task team prepared a SAS program to generate TSV file. The 2nd submission was completed successfully with a TSV file which was generated by SAS programming. SAS programming code will be shown as a method of preparing TSV file in advance.

Macro parameter	Description
PATH	Directory of files under m5 folder
STDCnt	Count of study
STUDYIDx	e.g. 00000123
ANLTYPEx	1: single study (CDISC), 2: Integrated study (CDISC), 3: Non-CDISC
STUDYCTx	new, replace, delete
PK_TYPEx	STS: standard two stage approach, POP: population approach, PBPK: physiologically-based pharmacokinetic model analysis, Other: other analysis
SDTM_CTx	YYYY-MM-DD: Controlled Terminology for SDTM
ADaM_CTx	YYYY-MM-DD: Controlled Terminology for ADaM

```
* Get the all file name and directory from m5 folder *;
option NOXWAIT;
x "cd &PATH.\m5"; x "dir /b /s &PATH.\m5\*.* > &PATH.\TSV_m5.txt " ;

DATA work.filenm ;
  infile "&PATH.\m5\TSV_m5.txt" DSD MISSOVER DLM = '09'x ;
  length filename $ 1000 ;
  input  filename $ ;
run ;

* Study information *;
DATA work.Study_info (drop=i) ;
  length COL1 - COL3 $ 160 ;
```

```sas
    do i = 1 to &STDCnt ;
      COL1 = "S" ; * 'S'tudy information *;
      COL2 = symget( "STUDYID" || strip( put( i , 8. ) ) ) ;
      COL3 = symget( "ANLTYPE" || strip( put( i , 8. ) ) ) ;
      output ;
    end ;
  run ;

  * File information *;
  DATA work.File_info ;
    length COL1 - COL10 $ 160 ;
    set work.filenm ;
     COL1 = "F" ; * 'F'ile information *;
     COL2 = substr( filename , length( "&Path" ) + 2 ) ;
     COL3 = uuidgen() ;
    do i = 1 to &STDCnt ;
      STUDYID = symget( "STUDYID" || strip( put( i , 8. ) ) ) ;
      if scan( COL2 , 3 , "\" ) = STUDYID then do ;
        COL4 = symget( "STUDYCT" || strip( put( i , 8. ) ) ) ; COL5 = "" ;
        COL6 = symget( "PK_TYPE" || strip( put( i , 8. ) ) ) ;
        if COL6 = "STS" then COL7 = "-" ;
        if index( COL2 , "\sdtm" ) then
          COL8 = symget( "SDTM_CT" || strip( put( i , 8. ) ) ) ;
        if index( COL2 , "\adam" ) then
          COL9 = symget( "ADaM_CT" || strip( put( i , 8. ) ) ) ;
      end ;
    end ;
    if index( COL2 , ".xpt" ) then COL10 = "日本語なし" ;
    Srt_val1 = scan( COL2 , -1 , "\" ) ;
    Srt_val2 = substr( COL2 , 1 , length( COL2 ) - length( Srt_val1 ) ) ;
  proc sort ;
    by Srt_val2 Srt_val1 ;
  run ;

  DATA work.TSV (keep = COL:);
    set work.Study_info work.File_info  ;
    if COL1 = "S" or find( COL2 , "." ) ; * Remove the folder path*;
  run ;

  * Output the TSV file *;
  filename OUT "&PATH.\TSV_file.txt" ENCODING = 'UTF-8' ;
  DATA _NULL_ ;
    set  work.TSV ;
    file OUT DLM = "09"x DSD ;
    put COL1 - COL10 ;
  run ;

  *-- end of program --*;
```

S	00000123		1					**Study information**
S	00000456		1					
F	m5¥datasets¥00000123¥analysis¥adam¥datasets¥adrg.doc	d3a4a91a-7f2d-4a17-98d3-e8acbddd7cdc	new	Non-CP			2016-03-25	
F	m5¥datasets¥00000123¥analysis¥adam¥datasets¥adrg.pdf	6eafb528-f181-44e2-a77d-2de588083aa5	new	Non-CP			2016-03-25	
F	m5¥datasets¥00000123¥analysis¥adam¥datasets¥define.pdf	6e420bfb-12cb-4739-86eb-12272bb09a92	new	Non-CP			2016-03-25	
F	m5¥datasets¥00000123¥analysis¥adam¥datasets¥adab.xpt	245a8c26-ba49-4ff0-8aba-28dc11550685	new	Non-CP			2016-03-25	日本語なし
F	m5¥datasets¥00000123¥analysis¥adam¥datasets¥adae.xpt	94014b3a-96df-491d-bd50-e0943466e113	new	Non-CP			2016-03-25	日本語なし
F	m5¥datasets¥00000123¥analysis¥adam¥programs¥adab.sas	c87a8ae5-b0ea-449c-8947-39ce65d53c5b	new	Non-CP			2016-03-25	
F	m5¥datasets¥00000123¥analysis¥adam¥programs¥adae.sas	6d5f02b1-aa38-4a04-a4fe-0d576bf02bb8	new	Non-CP			2016-03-25	
F	m5¥datasets¥00000123¥analysis¥adam¥programs¥t-ae-sum-pref.sas	44f29be6-03f7-4be2-b99c-b277116fed49	new	Non-CP			2016-03-25	
F	m5¥datasets¥00000123¥tabulations¥sdtm¥sdrg.docx	5e64c3b5-d88d-4aa2-aac0-e948944161ae	new	Non-CP		2015-03-27		
F	m5¥datasets¥00000123¥tabulations¥sdtm¥acrf.pdf	d3c04a4d-185c-46a2-9945-39d3838538b0	new	Non-CP		2015-03-27		
F	m5¥datasets¥00000123¥tabulations¥sdtm¥define.pdf	7d8a5b9f-d9af-4575-a48e-55764d7d848a	new	Non-CP		2015-03-27		
F	m5¥datasets¥00000123¥tabulations¥sdtm¥sdrg.pdf	b68f41df-f4b0-4f29-9c6c-b261c7a4ca07	new	Non-CP		2015-03-27		
F	m5¥datasets¥00000123¥tabulations¥sdtm¥define.xml	dada7aa6-83ce-488c-b7ce-5701fa57f228	new	Non-CP		2015-03-27		
F	m5¥datasets¥00000123¥tabulations¥sdtm¥ab.xpt	927e6229-1a76-45f3-a245-742f9288732b	new	Non-CP		2015-03-27		日本語なし
F	m5¥datasets¥00000123¥tabulations¥sdtm¥ae.xpt	3f77efd1-968f-46f2-a209-2891e3b8b60e	new	Non-CP		2015-03-27		日本語なし
F	m5¥datasets¥00000456¥analysis¥adam¥datasets¥adrg.docx	e5bd0ff9-2955-4855-b7a3-7f553efbbb6e	new	STS	-		2016-03-25	
F	m5¥datasets¥00000456¥analysis¥adam¥datasets¥adrg.pdf	c2061dc9-ac12-4aa7-bc19-d0b47e9c984b	new	STS	-		2016-03-25	
F	m5¥datasets¥00000456¥analysis¥adam¥datasets¥define.pdf	e41c65cf-bc3b-484d-b26e-d3077afb3331	new	STS	-			**File information**
F	m5¥datasets¥00000456¥analysis¥adam¥datasets¥define_adpc.pdf	57cefd0a-fcc2-46b2-85d1-2d8f3b44fd7f	new	STS	-			
F	m5¥datasets¥00000456¥analysis¥adam¥datasets¥adae.xpt	5c5af9ba-c27b-49b9-8157-4a5fc3894cb8	new	STS	-		2016-03-25	日本語なし

Figure 4. Image of TSV file using SAS program

CONCLUSION

This electronic data submission was a big challenge as it was the 1st experience to test whether the error explanation was accepted from PMDA. PMDA requested more detailed explanation and reasons of these issues cannot be fixed than FDA. This submission was 2 studies and members attended consultations were only from the Japan team. In mandatory period, it is difficult to understand all study data and files from DM to Statistical analysis and PK analysis for limited members (i.e. less than 10 members). Therefore, selection of participants and reduction in the number of errors as much as possible for electronic study data submissions are future tasks.

In addition, electronic data submission should be completed as soon as possible after advance notice. Because of validation by PMDA, re-submission due to any problems or any system troubles may be required within 5 weeks before NDA like this pilot study. Finally, why the TSV file which was updated in Excel couldn't be submitted, how to collaborate with clinical pharmacokinetics team if PK analysis is included and how to create TSV files by those who cannot use SAS like Regulatory Affairs member are future challenges.

REFERENCES

PMDA "Technical Conformance Guide on Electronic Study Data Submissions", September 11, 2017. https://www.pmda.go.jp/review-services/drug-reviews/about-reviews/p-drugs/0026.html

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