Drug Development and e-Submission for PMDA filing

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Japan CTD

- Highlights
- Specific requirements
- Examples

Highlights (1)

- ICH-CTD format is applied.
- e-CTD is preferable, but not mandatory
  - **Sanofi Japan submits NDA with e-CTD in principle**
- Number of studies to be included
  - **Japan CTD = global CTD + Japan studies**
- Language
  - **Module 1 and 2: Japanese**
    - Tables and Figures can be in English
  - **Module 3 to 5: English is acceptable**
    - Module 5.3.7 is Japan specific requirements

Highlights (2)

- Global Module 2 is not simply used for J-NDA.
  - **Contents is described in more detail**
    - But, ISE and ISS are not necessary for Japan
  - **Additional description on Japan study is necessary**
  - **Optimal dose and safety in Japanese population are keys**
- Both Japanese and English are needed for Module 2
  - **Japanese: for submission purpose**
  - **English: for global team's review purpose**
  - **About TLG, English only except AE terms**
    - AE summary tables and listings in Japanese should be submitted

Specific Requirements (1)

- The recommended format for preparing CTD
  - **To reduce total review time**
- Module 2.7.4
  - **If results from a multi-regional study(ies) including Japanese subjects are presented as the Evaluation Data, then tables etc. should be prepared to enable comparison of the AE profile between Japanese and non-Japanese subjects. If many Asian subjects other than Japanese are included in the study, ensure that comparison of AEs between Japanese and non-Japanese Asian population can be made.**
  - **All AE terms should be preferably written in Japanese.**
  - **The tables presented in section 2.7.4 may contain only AEs with an incidence of greater than a certain threshold value.**
    - "2% or higher" (certain disease areas with lower incidence of AEs)
    - "10% or higher" (certain disease areas with higher incidence of AEs)

Specific Requirements (2)

Module 2.7.4.3 AEs summary in long-term trial(s)

- **The AEs should be grouped according to the time of onset post the start of drug administration. Generally, these groups will partition the data into periods of 3 months in duration.**
- **The day of onset should be identified as, in principle, the time point when the AE was first observed in a subject.**

AEs observed at an incidence of 2.0% or higher in the entire study period

		The investigational product				
Day of onset	Total	To Month 3	Month 4 to 6	Month 7 to 9	Month 10 to 12	Month 13 or later
Number of subjects evaluated	100	100	92	85	80	76
All AEs	xx (xx%)	xx	xx	xx	xx	xx
Number of deaths	xx (xx%)	xx	xx	xx	xx	xx
Number of subjects with SAEs other than deaths	xx (xx%)	xx	xx	xx	xx	xx
Number of subjects who discontinued	xx (xx%)	xx	xx	xx	xx	xx
Nasopharyngitis	xx (xx%)	xx	xx	xx	xx	xx
Headache	xx (xx%)	xx	xx	xx	xx	xx
.....						
.....						

Specific Requirements (3)

- Module 2.7.6 Example of descriptions of AEs
  - **Summarize all AEs occurring in the studies to be submitted as the evaluation data regardless of the threshold percentage above, in the tables of "all AEs" and "treatment-related AEs", unless agreed in advance with the review team.**

Table xx Number of subjects with AEs (%) (Study xxxx)

	All-causality AEs			Treatment-related AEs		
	Group A (n=150)	Group B (n=148)	Group C (n=151)	Group A (n=150)	Group B (n=148)	Group C (n=151)
Number of subjects with AEs (%)	132 (88.0)	135 (91.2)	140 (92.7)			
Infections and infestations	32 (21.3)	40 (27.0)	50 (33.1)			
Nasopharyngitis	23 (15.3)	25 (16.9)	30 (19.9)			
.....						
.....						
Upper respiratory tract infection	0 (0)	3 (2.0)	4 (2.6)			
Dizziness postural	1 (0.6)	2 (1.3)	0 (0)			
....						

Adverse event terms: MedDRA/J ver xx.0

Causality assessment: Causal relationship is assessed using the following six-degree scale: "not related," "probably not related," "possibly related," "probably related," "related," and "unknown." If an AE is assessed as "possibly related," "probably related," "related" or "unknown," it was summarized as a treatment-related AE.

Source: Clinical Study Report - Table 20 (5.3.5.1.1)

Specific Requirements (4)

- Module 5.3.7
  - **Listings of patients in main studies to decide dosage and main studies to verify efficacy**
  - **Listings of patients with adverse drug reactions in all studies**
  - **Listings of patients with serious adverse events in all studies**
  - **Listings of patients with laboratory test abnormal values in all studies**
  - **Figures of change in laboratory test values in all studies**

Examples (1) Efficacy Table

Global CTD

Phase 3 study Treatment group	n	Baseline Mean	Month 6 endpoint (LOCF) Mean	Change from baseline to Month 6 endpoint (LOCF)[a] LS Mean (SE)[b]	LS Mean Difference (SE) vs. Lantus[b]	95% CI[b]
T1DM - US001						
HOE901-U300	999	9.99	9.99	-9.99 (9.999)	9.99 (9.999)	(9.999 to 9.999)
Lantus	999	9.99	9.99	-9.99 (9.999)		
T2DM - US002						
HOE901-U300						
Lantus						
T2DM - US003						
HOE901-U300						

Japan CTD

Study	HOE901-U300 N	HOE901-U300 Mean at Baseline	HOE901-U300 LSmean change[ab] (SE)	Lantus N	Lantus Mean at Baseline	Lantus LSmean change[ab] (SE)	LS mean difference[ab] (95%CI)
T1DM - JP001	999	9.99	-9.99 (9.999)	999	9.99	-9.99 (9.999)	9.99
T1DM - US001	999	9.99	-9.99 (9.999)	999	9.99	-9.99 (9.999)	9.99
T1DM - US001 JP	999	9.99	-9.99 (9.999)	999	9.99	-9.99 (9.999)	9.99
T2DM - JP002	999	9.99	-9.99 (9.999)	999	9.99	-9.99 (9.999)	9.99

Examples (2) Safety Table

Global CTD

n (%)	T1DM HOE901-U300 N= (999)	T1DM Lantus N= (999)	T2DM HOE901-U300 N= (999)	T2DM Lantus N= (999)
Patients with any TEAE				
Patients with any treatment emergent SAE				
Patients with any TEAE leading to death[a]				
Patients with an				

Japan CTD

	T1DM study pool HOE901-U300 (N=999)	T1DM study pool Lantus (N=999)	T1DM Japanese patient pool HOE901-U300 (N=999)	T1DM Japanese patient pool Lantus (N=999)
Patients with any TEAE				
Patients with any treatment emergent SAE				
Patients with any TEAE leading to death				

	T2DM study pool HOE901-U300 (N=999)	T2DM study pool Lantus (N=999)	T2DM Japanese patient pool HOE901-U300 (N=999)	T2DM Japanese patient pool Lantus (N=999)
Patients with any TEAE				
Patients with any treatment emergent SAE				
Patients with any TEAE leading to death				

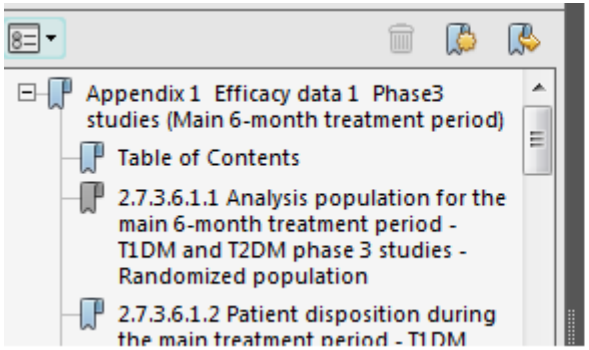
Examples (3) Summary Tables

Primary System Organ Class HLT: High Level Term PrefeRR:ed Term n(%)	T1DM study pool HOE901-U300 (N=999)	 Lantus (N=999)	T1DM Japanese patient pool HOE901-U300 (N=999)	 Lantus (N=999)
Any class				
感染症および寄生虫症				
HLT: 腹部および消化管感染				
胃腸炎				
HLT: ヘルペスウイルス感染				
単純ヘルペス				
ヘルペスウイルス感染				

Patient ID/Country	Age(yrs)/ Sex[a]/ Race/ Strata	Primary SOC/ Preferred term/ Reported term	Onset date/ Study day[b]/ AE duration/ AE status[c]	Duration of exposure (Days)	Intensity/ Corr. Treatment[d]/ Action taken with IMP[e]	Relationship to study medication/ Outcome/ Date of death if any	Seriousness/ Seriousness criteria[f]
276003007/ Germany		心臓障害 / 心筋梗塞 / POSSIBLE CAUSE OF DEATH IS MYOCARDIAL INFARCTION					
276008001/ Germany		一般・全身障害および投与部位の状態 / 心突然死 / SUDDEN DEATH DUE TO CORONARY ARTERY DISEASE					

Examples (4) English and Japanese Titles

English title



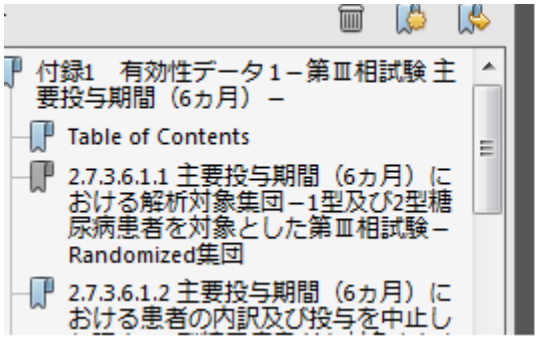
JCTD-Module 2.7.3-2.7.3.6.1-EN

Project Code / Study Number / Analysis: HOE901 / OVERALL / CTD_2013_JP

2.7.3.6.1.1 Analysis population for the main 6-month treatment period - T1DM and T2DM phase 3 studies -

Phase 3 study Treatment group	Randomized	mITT
T1DM - EFC12449		
HOE901-U300		
Lantus		
T1DM - EFC12456		
HOE901-U300		

Japanese title



JCTD-Module 2.7.3-2.7.3.6.1-EN

Project Code / Study Number / Analysis: HOE901 / OVERALL / CTD_2013_JP

2.7.3.6.1.1 主要投与期間（6ヵ月）における解析対象集団－1型及び2型糖尿病患者を対象とした第Ⅲ相試験－Rando

Phase 3 study Treatment group	Randomized	mITT
T1DM - EFC12449		
HOE901-U300		
Lantus		
T1DM - EFC12456		
HOE901-U300		

Audit and Inspection

- Outline
- Commonly-checked points
- Examples
- Another point to be considered

Outline

- Compliance review by Japan authority
  - **Reliability standard => Raw data check**
    - To check if the studies were performed in accordance with GCP/ GLP and study reports are made based on the raw data
    - Subject listings in Module5.3.7 used to check the consistencies among
      - CRF
      - Database
      - Analysis data (derived data)
      - Analysis results

Commonly-checked Points

- Process
  - **How to get raw/external/global data**
  - **How to integrate TLGs into CSR**
  - **How to conduct QC of B&P deliverables**
- Consistencies between documents/data
  - **CTP ⇔SAP⇔define/specs⇔ADS/TLGs⇔CSR**
  - **raw data⇔ADS⇔Listing⇔Table/Graph**
- If documentation is adequate
  - **Validation plan**
  - **Tracking doc**
  - **Define file and specifications**
  - **Program header**

Example (1) Observations in Audit

35. Any modifications to the Validation Plan should be clearly identified in the tracking document.

- "There was differences in QC type between Validation Plan and Tracking doc but no description"
  - → **We have to write which points were changed along with why if applicable.**

VALIDATION PLAN FOR ADS					
ADS/SDS Name	**ADS/SDS Label**	**Variable**	**Priority (Recommended)**	**Risk Assessment**	**Quality Control type**
ADDM	*Demographies*	*ALL VARIABLES*		*H/l*	*Basic, O*
ADEX	*Exposure*	*AESTCDY*		*H/h*	*Basic, R*

TRACKING DOCUMENT FOR ADS

ADS/SDS	Variable	Priority (Optional)	Quality Control Type	Programmer name	Program Name	Date Ready for QC	Internal Reviewer Name	QC program Name	Modification Requester	Modification against validation plan	Comments of findings of QC	Date of final QC
ADDM	ALL VARIABLES		Basic,O									
ADEX	AESTCDY		Basic					NA		Remove		
	AEAELTM		Basic					NA		New variable		
	AEDURCDV		Basic,O							QC level changed from X to Y		

Example (2) Observations in Audit

32. The QC of individual deliverables (ADS/TLGs and SDTM datasets if applicable) is performed according to analysis datasets specifications and table shells defined based on SAP or any other additional requirements.

- "About the ADS specifications, ADS name was not displayed on some of the printed specifications and we (auditors) could not identify which ADS were associated with which specifications"
  - → **We have to demonstrate that programming and QC were performed according to the specifications appropriately**
  - → **Therefore, the specifications should be clearly mentioned to enable anybody understand it well**

Example (3) What were Checked in Inspection

③ 解析業務に関する調査
□ 解析の実施過程
解析計画書完成日：平成　年　月　日
解析計画書改訂日（該当する場合）：平成　年　月　日
解析報告書承認日（該当する場合）：平成　年　月　日

- Checklist from PMDA
- We were asked dates for Randomization list, TLG completion and etc other than the checklist
- Check consistencies between eCRF and subject listings in Module5.3.7
- “Please explain how to conduct QC”

→ “Please show the validation plan and tracking document”

Example (4) Remark in Inspection

- Q: “How did you calculate the actual dose (mg/m2)?”
  - **PMDA calculate it by themselves and their result was different from one Sanofi provided**
    - Not big differences, but small differences
  - **We explained the formula and how to round the resulted value along with the example data**

Another Point to be Considered

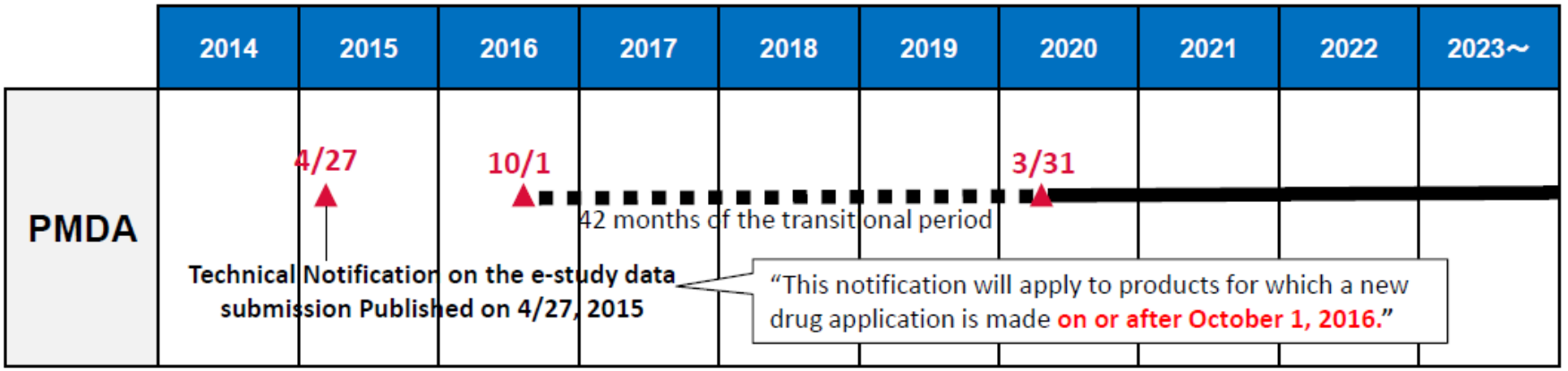
- Program should be readable and executable
  - **We have to explain how to derive the value in program whenever we are asked**
  - **We have to conduct additional analysis (e.g. subgroup analysis) if requested by authority**

e-Submission

- Timeline
- Notifications and guide released for industry
- Differences between FDA's requirements and PMDA's requirements
- Considerations

Timeline

- **The initiation date** of submission of e-study data is **October 1, 2016**.
- There is a **transitional period of 42 months from October 1, 2016** to March 31, 2020.



Notifications and Guide Released for Industry

Notifications/Guide	Release Date	Issuer	Overview
Basic Principles on Electronic Submission of Study Data for New Drug Applications ("Basic Principles")	June 20, 2014	Ministry of Health, Labor and Welfare	• The first official announcement that MHLW/PMDA will require electronic study data in NDA.
Technical Notification on the e-data submission* ("Technical Notification")	April 27, 2015	Ministry of Health, Labor and Welfare	• Explains practical issues regarding the introduction of electronic submissions of study data for new drug applications • States the start date of e-study data submission for NDA
Technical Conformance Guide* ("Technical Guide")	April 27, 2015	PMDA	• Explains technical details regarding e-study data submission • Subject to updates based on the accumulated experience and/or the revisions of the data standards

Differences between FDA's Requirements and PMDA's Requirements

- ADaM
- Programs
- Validation rule
- Split dataset
- Resize of variable length

ADaM

- FDA
  - **Non binding recommendation**
- PMDA
  - **Mandatory**
  - **Submit the SDTM datasets and the ADaM datasets used for main analyses, except in the case of data on the results of a phase I study and clinical pharmacology study**
  - **ADaM datasets should be submitted for analyses performed to obtain important results on efficacy and safety and clinical study results that provide the rationales for setting of the dosage and administration, such as primary efficacy analysis and secondary efficacy analyses, primary safety analyses and basic analyses of adverse events, and analyses to investigate the effect of major factors on efficacy and safety.**
  - **If ADS was used for the CSR analysis, we have to create ADaM that can reproduce the CSR analysis results and submit them for J-NDA.**

Programs

- FDA
  - **Non binding recommendation**
  - **Any submitted programs (scripts) generated by an analysis tool should be provided as ASCII text files or PDF files, e.g., adsl.sas should be submitted as either adsl.txt or adsl.pdf.**
- PMDA
  - **Mandatory**
  - **The file name should include the extension attached by the analysis software. If the file name does not contain an extension, an explanation about the file format should be included in the data guide.**
  - **It is mandatory to submit programs for ADaM datasets and analysis program at least for main analysis.**

Validation Rule

- FDA
  - **If applicable, FDA may report important data validation errors to the sponsor for correction.**
- PMDA
  - **The rules used for validation have been classified by the level of importance taking into consideration**
  - **(a) Rules which, if violated, will cause the review to be suspended until corrections have been made. Very basic rules such as the presence/ absence of necessary datasets for each clinical study.**
  - **(b) Rules which, if violated without any prior explanation, will cause the review to be suspended until corrections have been made. 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.**
  - **(c) Rules which, even when violated, will not necessarily require any explanation.**

Split Dataset

- FDA
  - **Non binding recommendation**
  - **Datasets greater than 5 gigabyte (gb) in size should be split into smaller datasets no larger than 5 gb.**
- PMDA
  - **Mandatory**
  - **Consult the PMDA beforehand if the dataset is 5 gigabytes or greater.**
  - **We need two versions of SDRG/ADRG, for FDA and for PMDA because only non-split data should be submitted to PMDA.**

Resize of Variable Length

- FDA
  - **Non binding recommendation**
  - **The allotted length for each column containing character (text) data should be set to the maximum length of the variable used across all datasets in the study.**
- PMDA
  - **PMDA's position is not clear**
  - **If the studies are submitted only to PMDA, we may be able to skip "resize" process.**

Considerations

- We will need additional resource for PMDA specific requirements for e-Data Submission
  - **ADaM (dataset, define, ADRG), Analysis Result Metadata, programs, etc.**
- Collaboration in global teams (BJ, EU, US and JP) is essential
  - **Not only Prog but also Stat**
  - **Please keep JP team in the loop on discussions of e-data submission packages for FDA submission**

Thank you