Streamlining e-Data submission process with evolving PMDA regulations

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Meet the Speakers

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Title: Principal Statistician / Statistical Analyst

Organization: Eli Lilly Japan K.K.

Koichi has been working in pharmaceutical industry for more than two decades as a statistical analyst. He has been active in internal/external activities related to CDISC and eData submission, including a country lead role for PHUSE Japan, and CDISC ADaM team and CDISC Japan User Group (ADaM).

Tomohiko Funai (船井 友彦)

Title: Senior Statistician / Statistical Analyst

Organization: Eli Lilly Japan K.K.

Tomohiko Funai has over 10 years of experience in pharmaceutical industry as a statistician. One of his roles include Subject Matter Expert for eData submission work in Japan. He is also serving as a member of the eData submission working group for PHUSE Japan.

Disclaimer and Disclosures

- *The views and opinions expressed in this presentation are those of the author(s) and do not necessarily reflect the official policy or position of CDISC or Eli Lilly.*

- *The author(s) have no real or apparent conflicts of interest to report.*

Agenda

1. PMDA e-data submission requirements history
2. Changes to E-data submission process in Lilly
3. Summary

PMDA e-data submission requirements history 2014~2024

PMDA e-data submission history (simplified)

2014
Pilot
submissions

2016~
Voluntary
submission

2020~
Mandatory
Submission

2022~24
Requirements
major revisions

PMDA has implemented strict rules for e-data

Before 2022 April, Sponsor had to

- Have a Consultation Meeting with PMDA before Japan NDA
- Must explain all the “Errors” (otherwise the NDA cannot be filed)

Therefore, there were a few challenges for sponsors, such as

- A timeline risk to NDA due to incomplete e-data (regardless of impact to analyses)
- A hurdle to achieve “simultaneous” submission due to Japan-specific requirements regarding e-data

Recent Changes to the PMDA requirements

- Form A (Description of Electronic Study Data) requirements
- Study Data Validation Rule Applicability (Expansion)
- Explanation of Conformance Issues
- Requirements of CDISC compliant data for older Ph1/CP studies

Form A (Description of Electronic Study Data) (1)

- **Change**: No need to submit Form A before Japan NDA.

Explanation of Electronic Study Data (Form A and Form B)

- Explanation of Electronic Study Data (Form A) [501KB]
- Explanation of Electronic Study Data (Form B) [450KB]

From October 1, 2023 (application date), PMDA does not require to submit "Explanation of Electronic Study Data (Form A)" and "Explanation of Electronic Study Data (Form B)", that describe the contents of electronic study data planned to be submitted to the PMDA, before electronic study data submission for the new drug application.

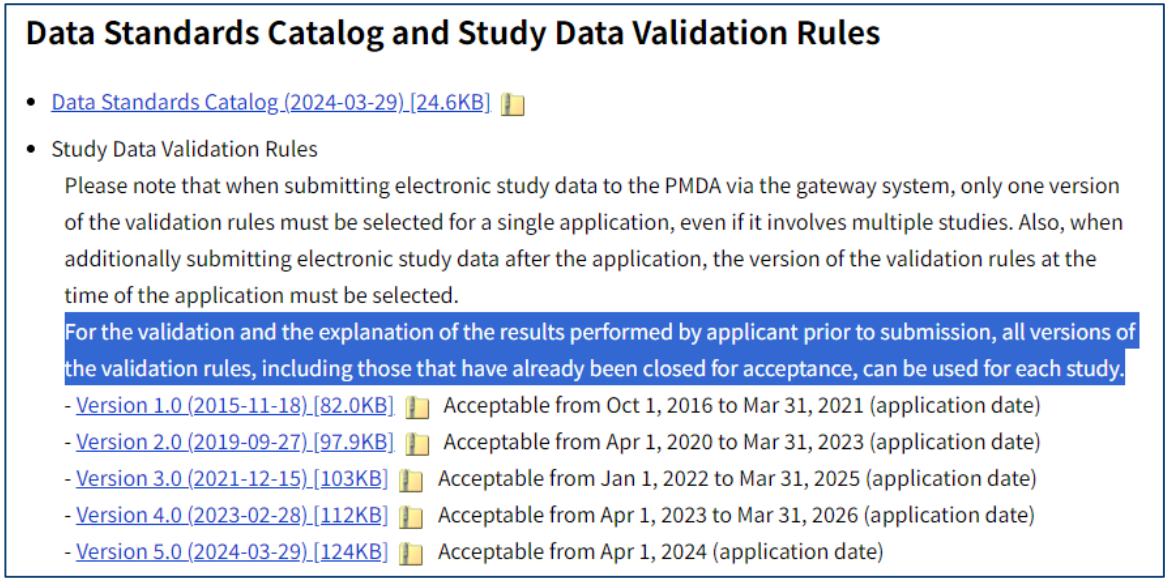
Please note that Form A and Form B still must be submitted to the PMDA for consultations related to submission of electronic study data for new drug applications.

Form A (Description of Electronic Study Data) (2)

- **Change**: No need to submit Form A before Japan NDA.
- **Implication**:
  - Japan NDA timeline shortened
  - Redundant work (creation of Form A by copying information from the sources) eliminated
  - Some new information, such as a list of Trial Design domains and information of analysis software/environment, needs to be documented in Reviewer's Guide

Study Data Validation Rules (1)

- **Change**:
  - Any versions of PMDA validation rules can be used among studies/analyses in a submission



Data Standards Catalog and Study Data Validation Rules

- Data Standards Catalog (2024-03-29) [24.6KB]
- Study Data Validation Rules

  Please note that when submitting electronic study data to the PMDA via the gateway system, only one version of the validation rules must be selected for a single application, even if it involves multiple studies. Also, when additionally submitting electronic study data after the application, the version of the validation rules at the time of the application must be selected.

  For the validation and the explanation of the results performed by applicant prior to submission, all versions of the validation rules, including those that have already been closed for acceptance, can be used for each study.

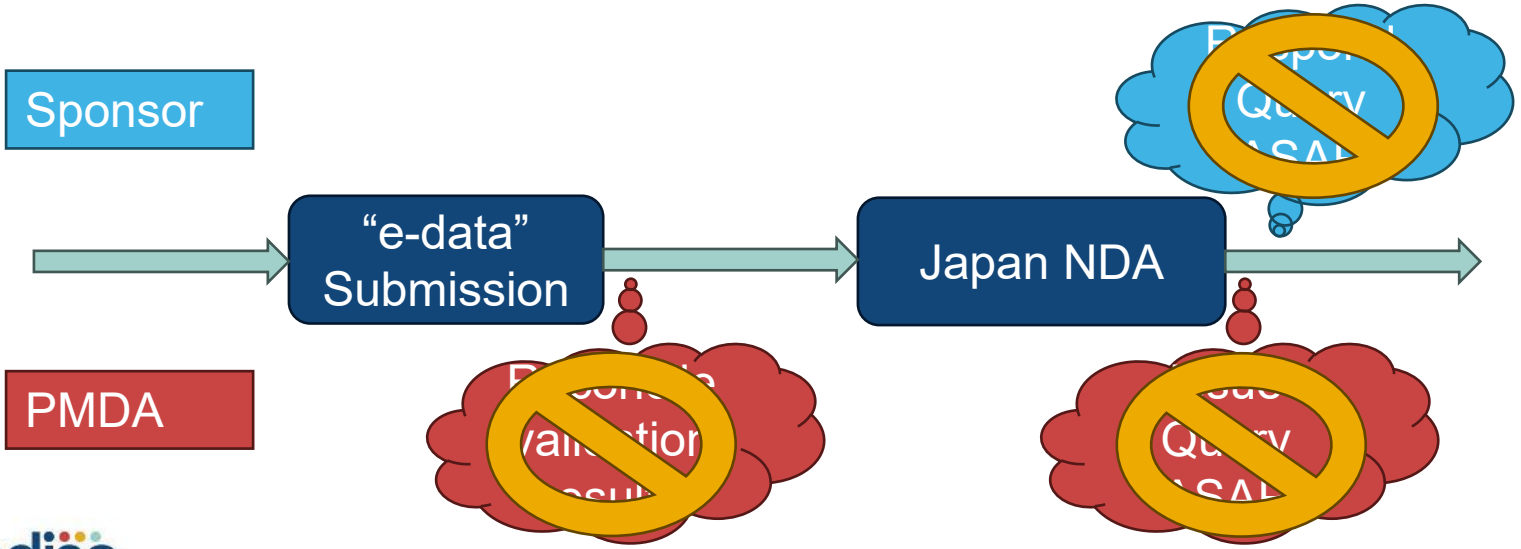
  - Version 1.0 (2015-11-18) [82.0KB] Acceptable from Oct 1, 2016 to Mar 31, 2021 (application date)
  - Version 2.0 (2019-09-27) [97.9KB] Acceptable from Apr 1, 2020 to Mar 31, 2023 (application date)
  - Version 3.0 (2021-12-15) [103KB] Acceptable from Jan 1, 2022 to Mar 31, 2025 (application date)
  - Version 4.0 (2023-02-28) [112KB] Acceptable from Apr 1, 2023 to Mar 31, 2026 (application date)
  - Version 5.0 (2024-03-29) [124KB] Acceptable from Apr 1, 2024 (application date)

Study Data Validation Rules (2)

- **Change**:
  - Any versions of PMDA validation rules can be used among studies/analyses in a submission
- **Implication**:
  - No need to “re-validate” old studies using the single “submission version” of the validation rule
    - SDTM and ADaM in a study may be validated with different version of validation rules
  - Preparation of Study Data can be completed at the time of study closure (not at the submission)

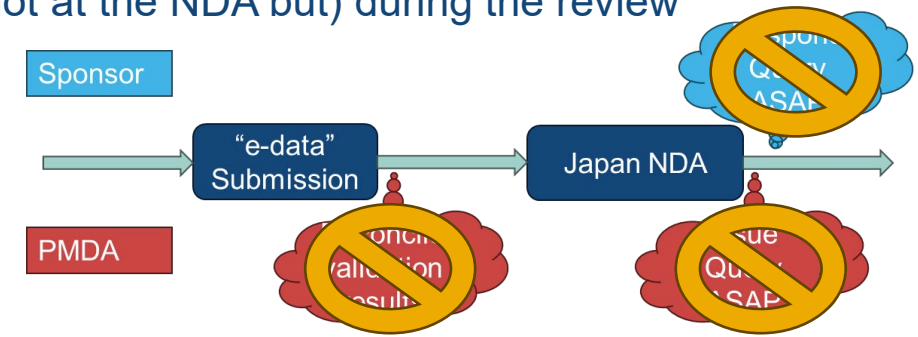
Explanation of Conformance Issues (1)

- **Change**:
  - Explanation for “Missing” Errors are not queried at the time of Japan NDA
  - “Insufficient” explanation of Errors are not queried at the time of Japan NDA



Explanation of Conformance Issues (2)

- **Change**:
  - Explanation for “Missing” Errors are not queried at the time of Japan NDA
  - “Insufficient” explanation of Errors are not queried at the time of Japan NDA
- **Implication**:
  - No review timeline risk due to “Missing/Insufficient” explanation for Errors
  - Could potentially shorten the time leading between gateway submission and Japan NDA (e.g. 5 weeks to 1~2 weeks)
  - (Unlikely but) query may be issued (not at the NDA but) during the review



Non-CDISC data for old Ph1/CP study (1)

- **Change**:
  - For Non-Oncology Ph1/CP studies, format other than SDTM/ADaM are allowed for studies with a start date (the day when the first subject was enrolled) before April 1, 2020

Table: Types and submission formats of documents subject to electronic submission

Section in notification on electronic study data	Content		Individual clinical study data	Analysis dataset	
				Concerning efficacy and safety analysis	Concerning PK or PK/PD analysis
2 (1) b (a)	Data on results from all phase II and phase III studies (including long-term studies) that are generally regarded to be a major evidence for evaluation of efficacy, safety, and dose and administration		SDTM	ADaM	
2 (1) b (b)	Data on result from phase I studies and clinical pharmacology studies listed right	Phase I studies of oncology drugs	SDTM	ADaM	
		Phase I studies that have been conducted in both Japanese and non-Japanese subjects (e.g.; in case of a strategy of global clinical trials and bridging studies)	SDTM*1	ADaM*2	In principle, ADaM*2, but other formats may be acceptable in certain cases
		QT/QTc studies based on the ICH E14 guideline			ADaM*2
2 (1) b (c)	Other Phase I studies and clinical pharmacology studies,	Clinical studies where standard pharmacokinetic analysis was performed	SDTM*1	ADaM*2	ADaM is preferable, but other formats are acceptable

*1: Format other than SDTM are allowed for studies with a start date (the day when the first subject was enrolled) before April 1, 2020

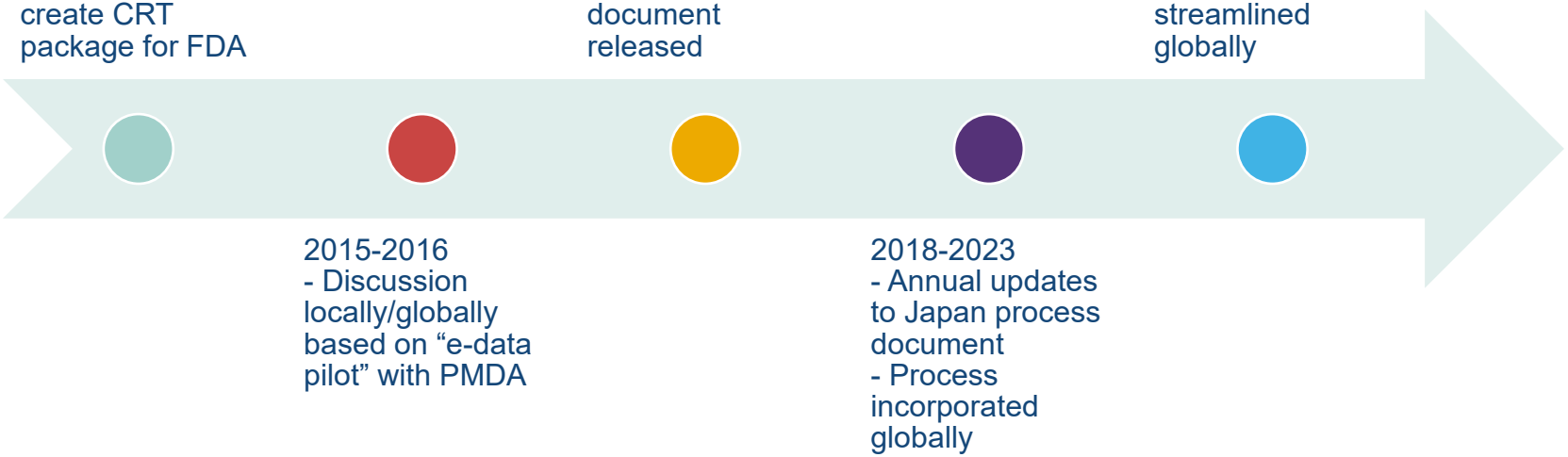
*2: Formats other than ADaM are allowed for studies with a start date (the day when the first subject was enrolled) before April 1, 2020

Non-CDISC data for old Ph1/CP study (2)

- **Change**:
  - For Non-Oncology Ph1/CP studies, format other than SDTM/ADaM are allowed for studies with a start date (the day when the first subject was enrolled) before April 1, 2020
- **Implication**:
  - “Legacy Data Conversion” is no longer required for these studies
  - SDTM-like/ADaM-like data would be acceptable for these studies (without formal CDISC-compliant documentation)

Changes to E-data submission process in Lilly

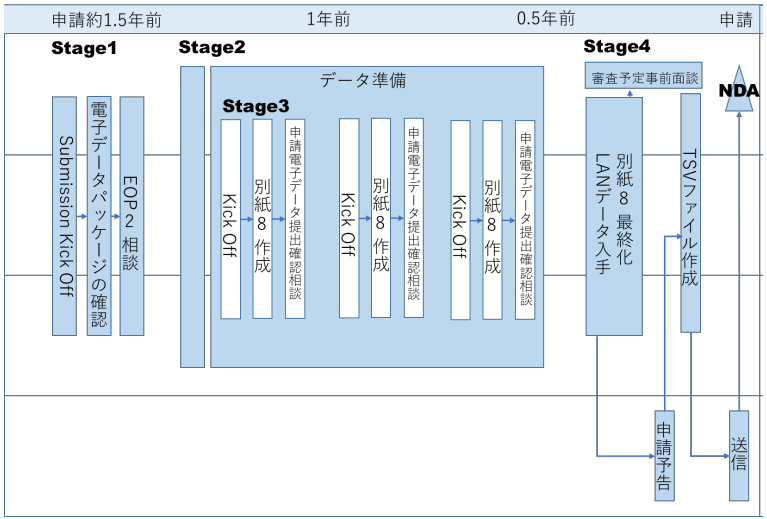
E-data submission process at Lilly



E-data Submission Process (High-level)

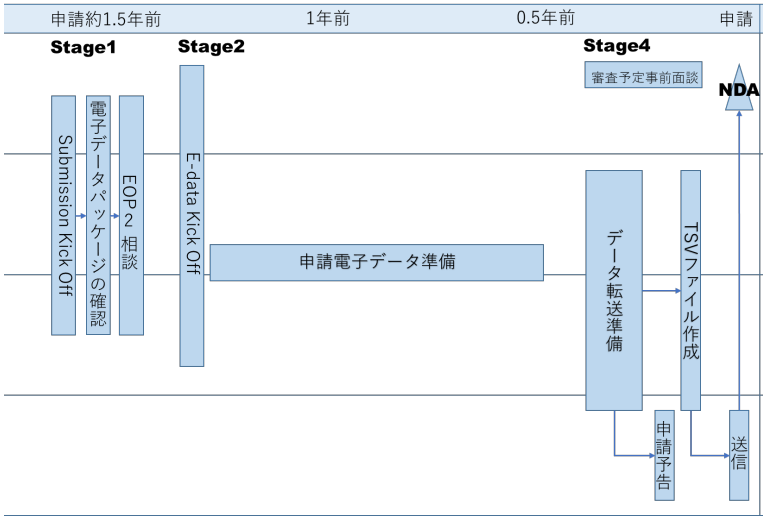
2018

- Staged, including multiple regulatory interactions



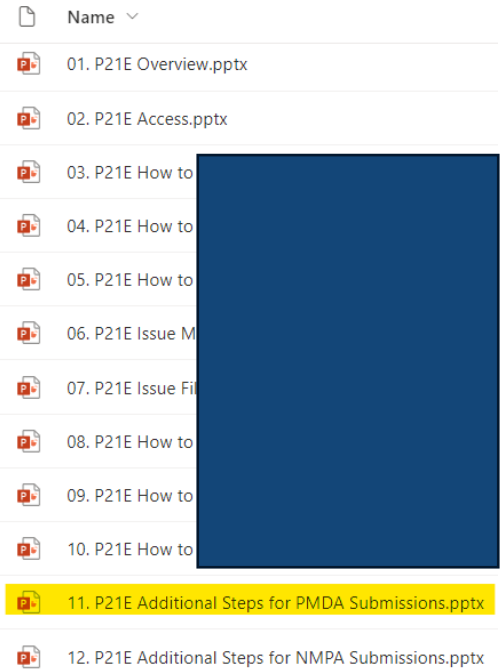
2024

- Simplified, focused.



E-data Submission Process (Detailed - Validation)

- Pinnacle21 Enterprise “How to”s



- “PMDA Checklist”

General

- ~~Single validation engine version~~

SDTM

- Custom domain documentation
- PP requirements

ADaM

- Validation must include SDTM AE/DM/EX
- ADPC/ADPP requirements

Define.xml

- Validate define.xml w/wo datasets
- Standard versions consistency

RGs

- Rule ID, Issue explanations

E-data Submission Process (Detailed – SDRG/ADRG)

- Instructions for PMDA submission

General Instructions for Use of This Template

Regulatory Expectations	
	[redacted]

- PMDA Submission:
  - Ensure to run the P21E validation on the XPT and DEFINE files with the appropriate PMDA engine. See specifics in Section 4.
  - Only ERROR validation issues that are not resolved must be explained and reported in section 4.2.
  - ~~All the clinical trials in a PMDA submission need to be run with the same PMDA validation engine.~~

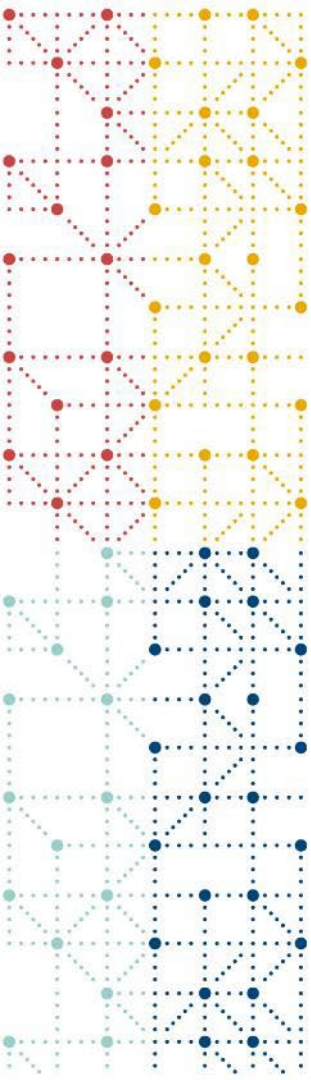
[redacted]

PMDA version specific requirements

- All **REJECT** findings must be resolved.
- Only **ERROR** issues that are not resolved from the summary output are expected to be provided with explanation in this summary table.
- **WARNING** and **NOTICE** issues are not required to be provided in this summary table.
- All the clinical trials in a PMDA submission need to be run with the same PMDA validation engine.

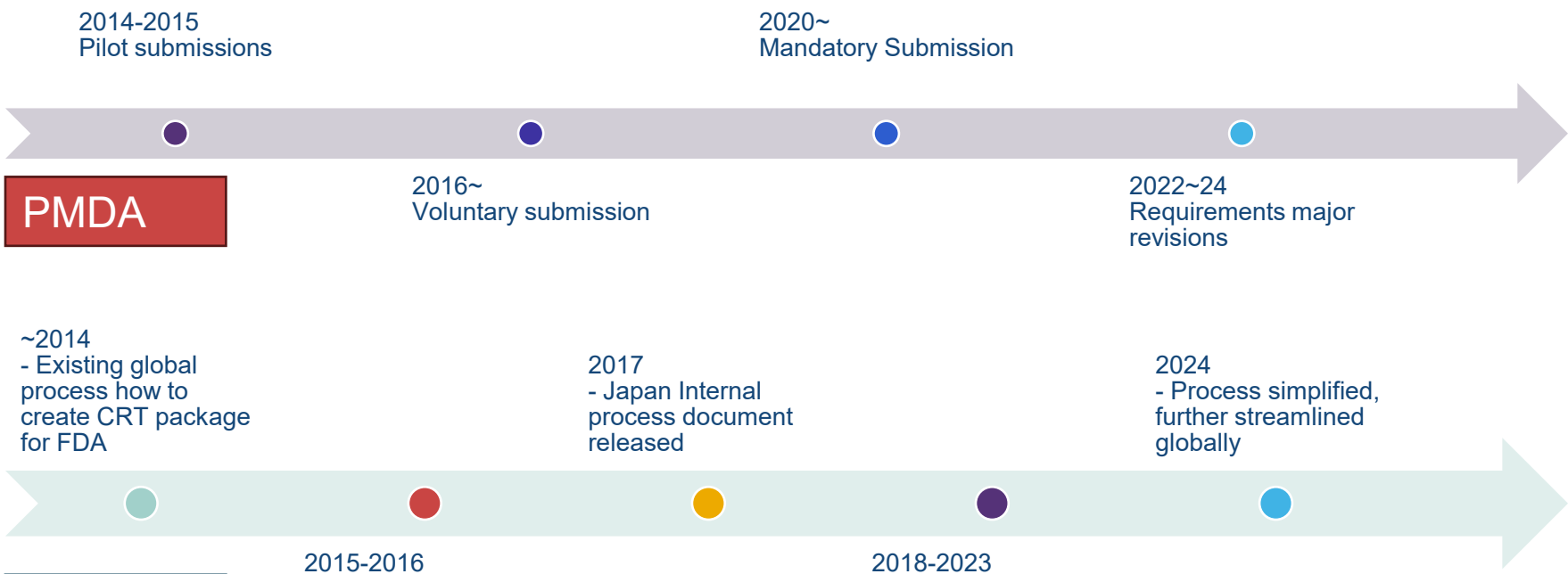
7. Submission of Programs

[redacted] The programs were created using <analyses software name and version number> on the software execution environment (operating system): <operating system name and version number>.



Summary

PMDA and Lilly Timeline



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Summary (1)

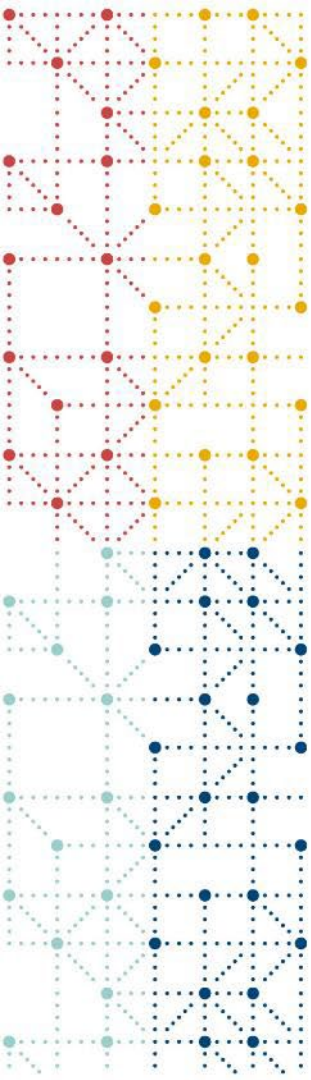
- Recent updates to PMDA's e-data notification/technical conformance guide have **substantial impact to sponsor's submission preparation in a favorable manner**
  - **So-called "PMDA-specific" requirements have decreased significantly**
- Important to **catch up/understand the current requirements, and to update internal process continually** to best allocate resources, while maintaining quality of study data
  - **Some of previous PMDA "requirements" are no longer required, but are still recommended to follow and/or document them for better preparation/use of data both for sponsors and reviewers**

Summary (2)

- Sponsors and Reviewers share the same goal to serve patients by providing effective medication faster, and we should **continue to collaborate and seek the better way how to prepare, submit, and use the e-data to achieve the goal**
  - **“Simultaneous” submission/approval would not be jeopardized anymore**
- It may be good to looking into the future and to **pursue further effective drug development and review process** with proper control, such as
  - **Integrated review platform**, e.g., Accumulus Synergy
  - **Modernization of data format**, e.g., Dataset-JSON
  - **Use of (interactive) visualization of data**, e.g., RShiny

References

- New Drug Review with Electronic Data | Pharmaceuticals and Medical Devices Agency (pmda.go.jp)
  - Revision of Notification on Electronic Study Data
  - Q&A Regarding Notification on Electronic Study Data
  - Notification on Gateway Application
  - Revision of Technical Conformance Guide
  - FAQs on Electronic Study Data Submission
- Efficient Preparation of eData (CRT package) for PMDA Submissions Using PHUSE Templates (PHUSE SDE Tokyo 2022)
- 「申請電子データ提出にかかる通知改正等に関する説明会」| 独立行政法人 医薬品医療機器総合機構 (pmda.go.jp) (Japanese only as of 2024-05-28)



Thank You!

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