# Biography

Yasuhiro Iijima has worked for over 15 years at Novartis Pharma K.K. as a statistical programmer. He has experience working for eData submissions on his work. He belongs to CDISC Japan User Group ADaM Team which provides recommendations on the eData submission process.

Takashi Kitahara has been working for Novartis Pharma K.K. since October 2014 as statistical programmer. Previously he worked at domestic CRO in Japan for 6.5 years.

He has also been joining CDISC Japan User Group ADaM team over 9 years. He has made several presentation at domestic and global conference about eData submission.

# Electronic Data Submission to PMDA

## – our experiences and matters of concern –

Yasuhiro Iijima, Novartis Pharma K.K.
Takashi Kitahara, Novartis Pharma K.K.

# Disclaimer

- The opinions expressed in this presentation and on the following slides are solely those of the presenters and not necessarily those of Novartis. Novartis does not guarantee the accuracy or reliability of the information provided herein.

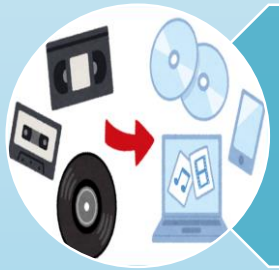
# Outline

- Key message
- Our activities in Novartis
- Overall timeline
- Plan – Identification of data/studies and analyses
- Do – FDA vs PMDA
- Do – Legacy data conversion
- Check/Action – Ideal timeline around NDA
- Check/Action – Process around Gateway
- Lessons Learned
- Key Takeaways

# Our key considerations



Timeline



Legacy data conversion




PMDA specific requirement

# Overview of our activities

Here!

2015 2016 2017 2018 2019 2020

Start accepting eData submission (1st Oct 2016–)

Transitional period (3.5 years)

Mandatory Phase (1st Apr 2020–)

Consecutive discussion with internal task force in Japan

Consecutive discussion with standard team

Consecutive presentation on external conference

Pilot study

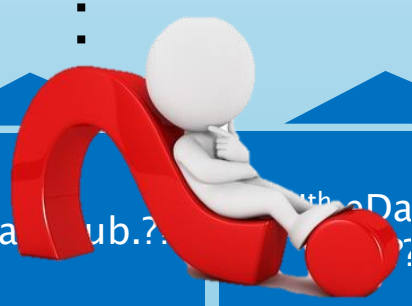
1st eData sub.

2nd eData sub.

3rd eData sub.

4th eDa ub.??

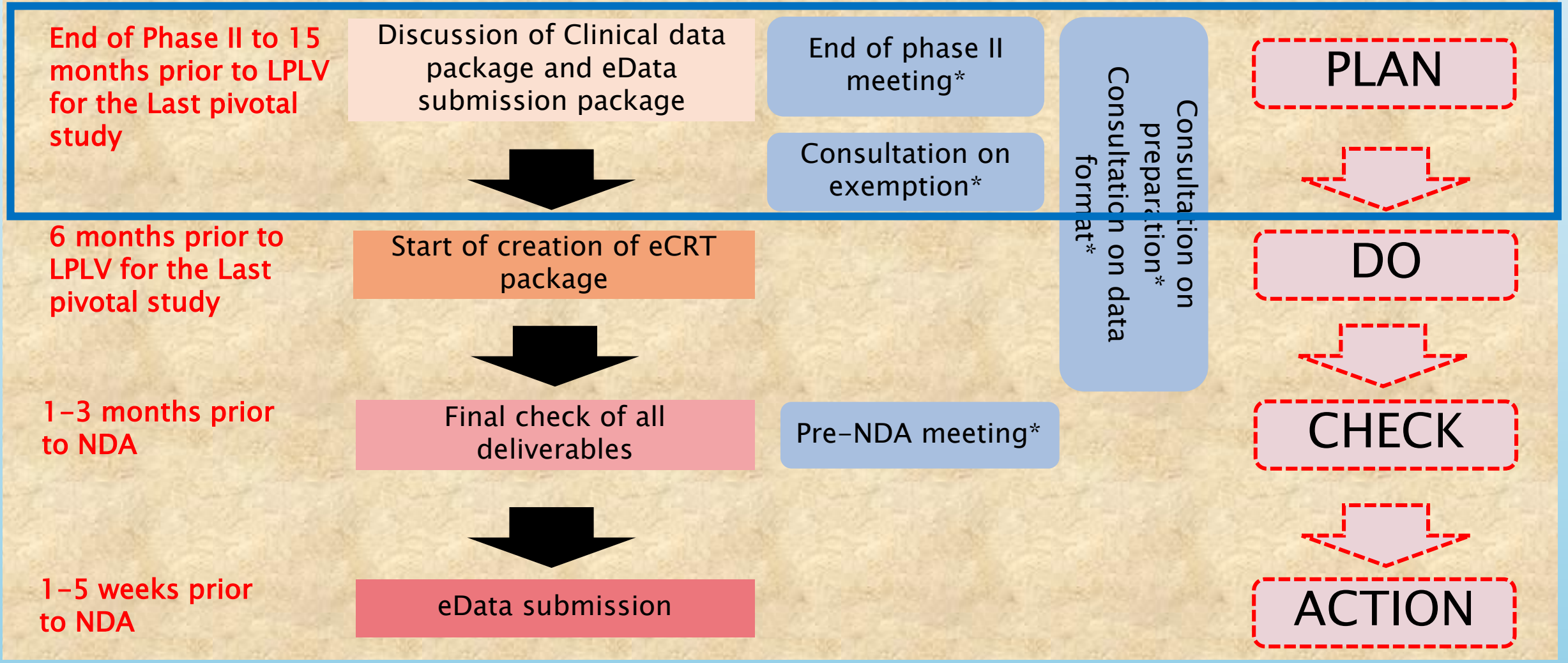
Xth eData sub.??



# Japan statistical programmers in Novartis cover…

- Lead whole eData submission to PMDA
  - Close communication with related functions and PMDA
- Discussion with global standard team
  - Timely information sharing of PMDA requirements
  - Have frequent Lessons & Learned sessions
- Lead implementation of internal process
  - Discuss internal process and Release internal guidances

# Ideal timeline for eData submission to PMDA in internal guidance




* Please refer to the PMDA website about the purpose of the consultations
https://www.pmda.go.jp/files/000229469.pdf

# Identification of data/studies and analyses

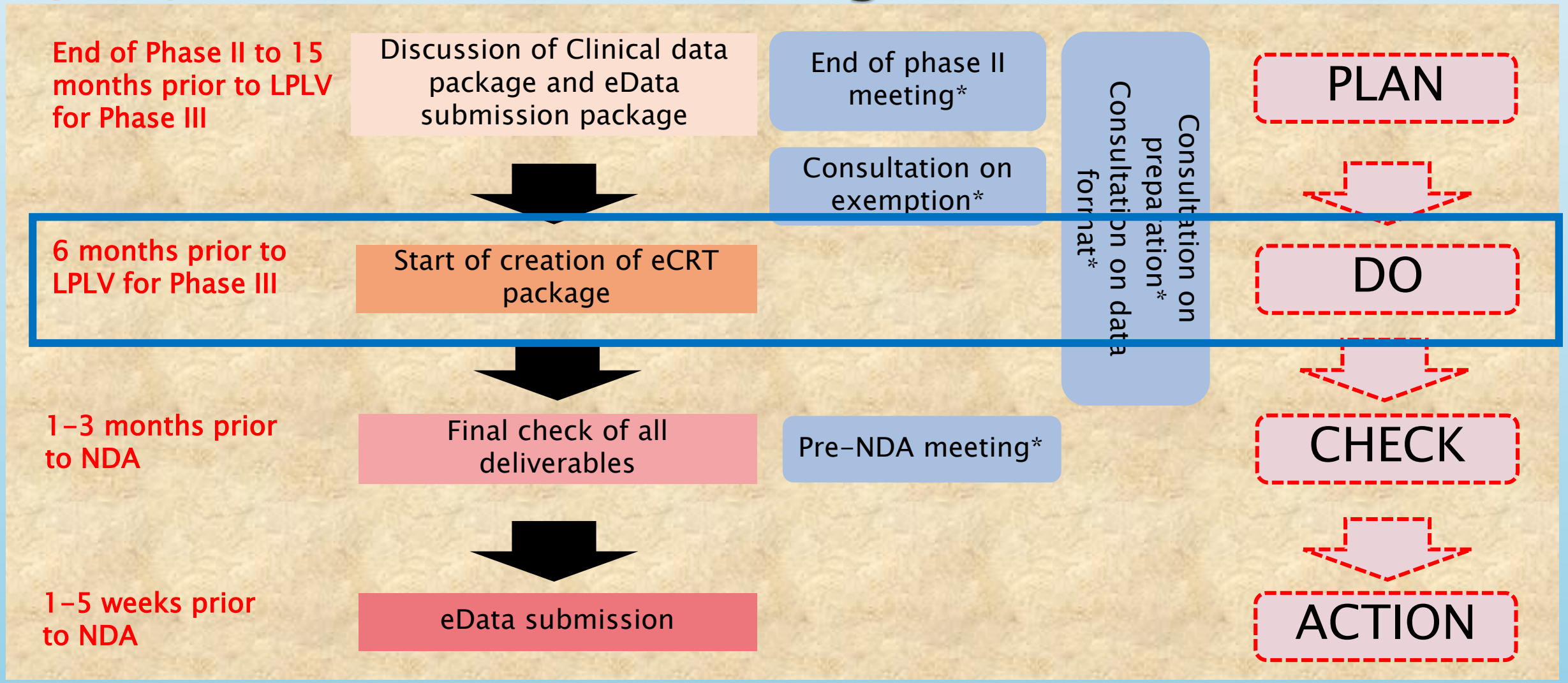
Which Study we need to submit?

Which ADaM(Analysis) we need to submit?

Clinical consultation

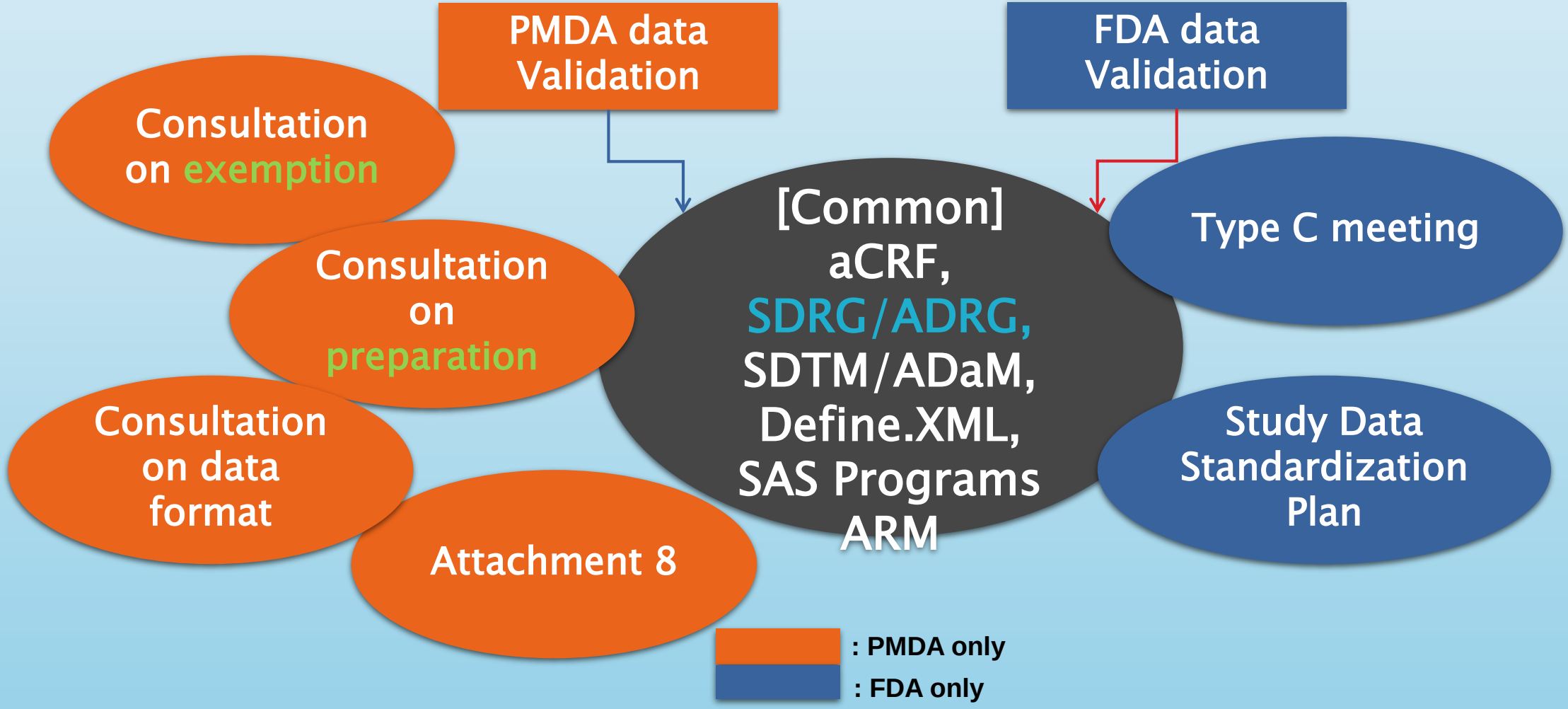
(End of Phase 2 Meeting)

# Ideal timeline for eData submission to PMDA in internal guidance




* Please refer to the PMDA website about the purpose of the consultations
https://www.pmda.go.jp/files/000229469.pdf

# eData Submission: FDA Vs PMDA



# One common eData submission package for both FDA and PMDA

- Validation rule

| FDA | PMDA |
|---|---|
| • Rejection rule<br>  • Based on FDA technical rejection criteria<br>• ERROR<br>  • Should be documented and explained in the Reviewer's Guide<br>• WARNING<br>  • Should be documented and explained in the Reviewer's Guide | • **REJECT**<br>  • Will cause the review to be suspepnded until corrections have been made<br>  • **MUST** be eliminated<br>• **ERROR**<br>  • Will cause the review to be suspended until corrections have been made **without any prior explanation at a consultation**<br>• **WARNING**<br>  • Will not necessarily require any explanation |

- When submitting simultaneously to both FDA/PMDA, Pinnacle 21 validation should be run as early as possible
- REJECT issue have to be eliminated
- ERROR/WARNING should be resolved as possible as you can

# One common eData submission package for both FDA and PMDA

- Study data reviewer's guide

**FDA**
- Legacy data conversion plan & report
- Conformance summary
- Etc…

**PMDA**
- Conversion factor for Parameters to SI
- Character set/ Encoding
- Conformance summary
- Etc…

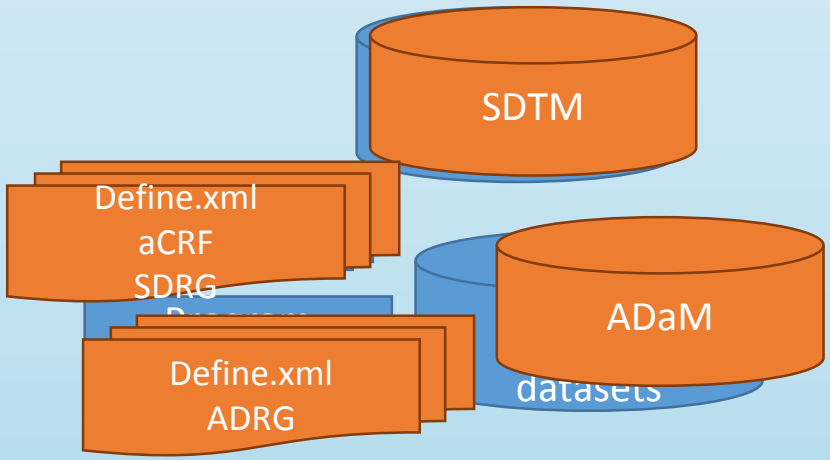
## Template in Novartis

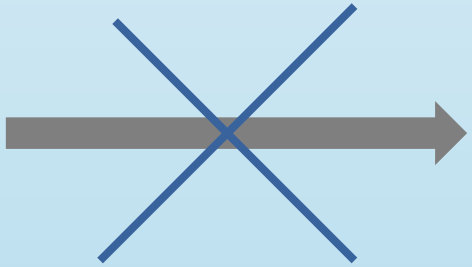
| Table 5-2 | <domain name, e.g. LB> Conversion Factors for Parameters to SI unit | | |
|---|---|---|---|
| <LB>TEST | Original Unit | Conversion Factor | SI unit |
| <Albumin> | <G/DL> | <10> | <g/L> |

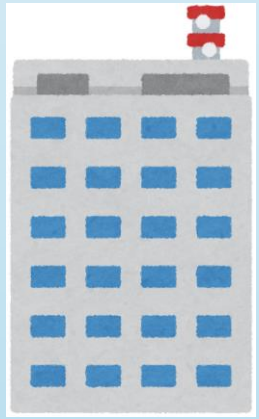
| Standard or Dictionary | Versions Used |
|---|---|
| SDTM | SDTM v[1.2]/SDTM IG v[3.1.3] |
| Toxicity Grading Dictionary | CTCAE v[4.0.3] |
| Characters Set | UTF-8 |
| Encoding | Latin1(Western ISO 8859-1) |
| FDA – Study Data | FDA – Study Data Technical Conformance Guide v[3.2] |

| Table 4-1 | Pinnacle 21 Validator Issue Summary | | | | |
|---|---|---|---|---|---|
| Dataset(s) | Pinnacle 21 diagnostic message ID | Pinnacle 21 diagnostic Message | FDA Severity | PMDA Severity | Description\Explanation |
| <AE, DM> | < [Pinnacle 21 diagnostic message ID]> | <Pinnacle 21 diagnostic message text> | <Error / Warning> | <Reject/ Error / Warning> | <Description\Explanation text outlining issues and why not corrected> |

# Legacy data conversion





*PMDA*

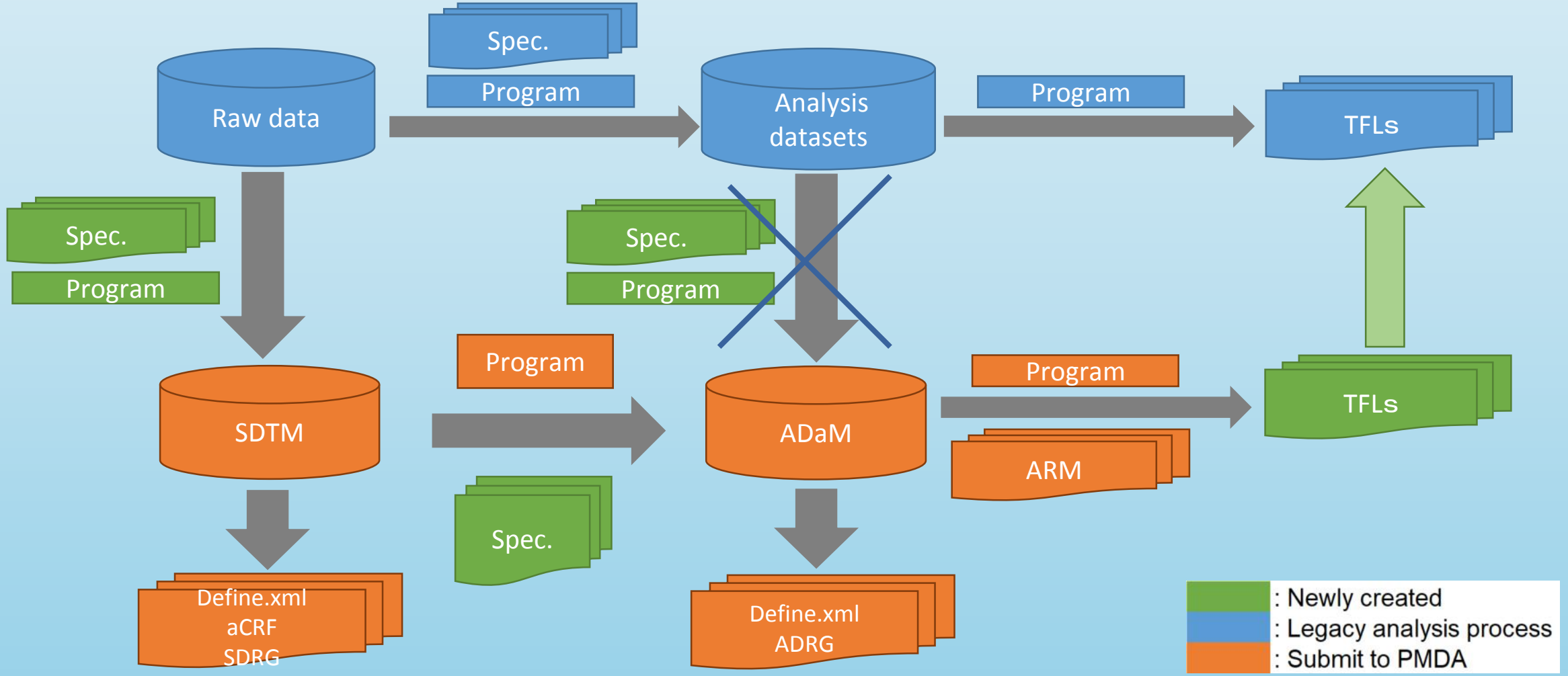
***FDA***

- Studies starting at/after 17-Dec-2016

***PMDA***

- Studies submitted at/after 01-Apr-2020

# Legacy data conversion – flow diagram



# Legacy data conversion – at first

| Study name | CABC999X1101 | CABC999X2201 |
|---|---|---|
| SDTM IG version | 3.1.2 | 3.1.3 |
| Controlled Terminology version | 2015/03/27 | 2016/09/30 |
| MedDRA version | 17.1 | 18.1 |
| WHO-DD version | XXXX2016 | XXXX2016 |
| Pinnacle 21 version | Community 2.1.3 PMDA configuration | Community 2.1.3 PMDA configuration |
| Priority SDTM domains (Optional) | DM/AE/... | DM/AE/... |
| Contact person | Statistician: XXX<br>Data manager: XXX<br>Statistical Programmer: XXX | Statistician: XXX<br>Data manager: XXX<br>Statistical Programmer: XXX |
| Unique Blank CRF | G:/projects/CABC999X/CABC999X1101/ZZZ | G:/projects/CABC999X/CABC999X2201 |
| Legacy aCRF | G:/projects/CABC999X/CABC999X1101/AAA | G:/projects/CABC999X/CABC999X2201 |
| Target data | /vob/CABC999X/CABC999X1101/report/data_s | /vob/CABC999X/CABC999X2201/report |
| Working area | /vob/CABC999X/CABC999X1101/report/XXX | /vob/CABC999X/CABC999X2201/report |
| Trial Design Domain | /vob/CABC999X/CABC999X1101/util | /vob/CABC999X/CABC999X2201/util |
| Reference study | /vob/CABC999X/CABC999X2101/csr_1 | /vob/CABC999X/CABC999X2101/csr_1 |
| Protocol | G:/projects/CABC999X/CABC999X1101/XXX | G:/projects/CABC999X/CABC999X2201 |
| SAP | G:/projects/CABC999X/CABC999X1101/YYY | G:/projects/CABC999X/CABC999X2201 |
| Data Transfer Specidication (DTS) | G:/projects/CABC999X/CABC999X1101/BBB | G:/projects/CABC999X/CABC999X2201 |

# Legacy data conversion– in case unexpected issue is found

Unexpected issue is found…

Team discussion

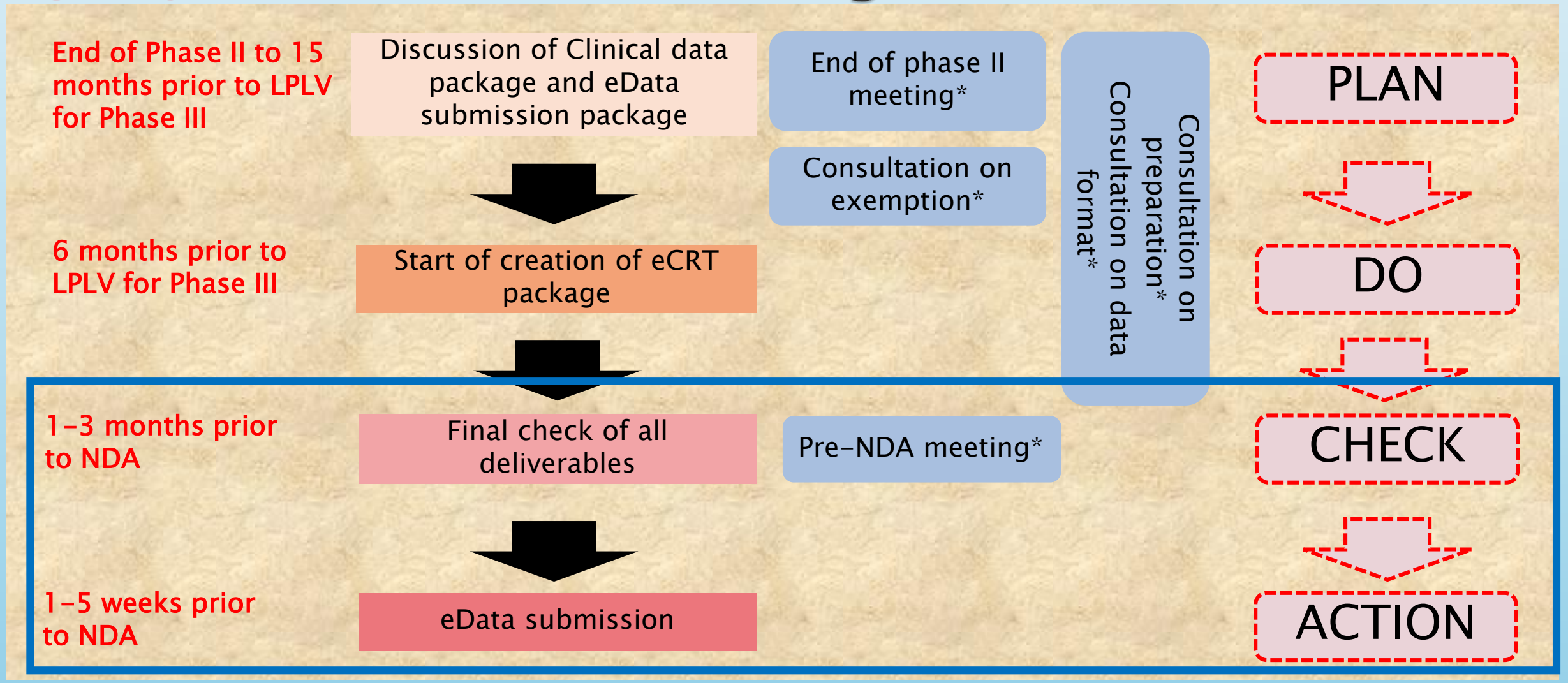
Consultation on preparation

# Exemptions of Legacy data conversion

## Exemption is applied in following four conditions

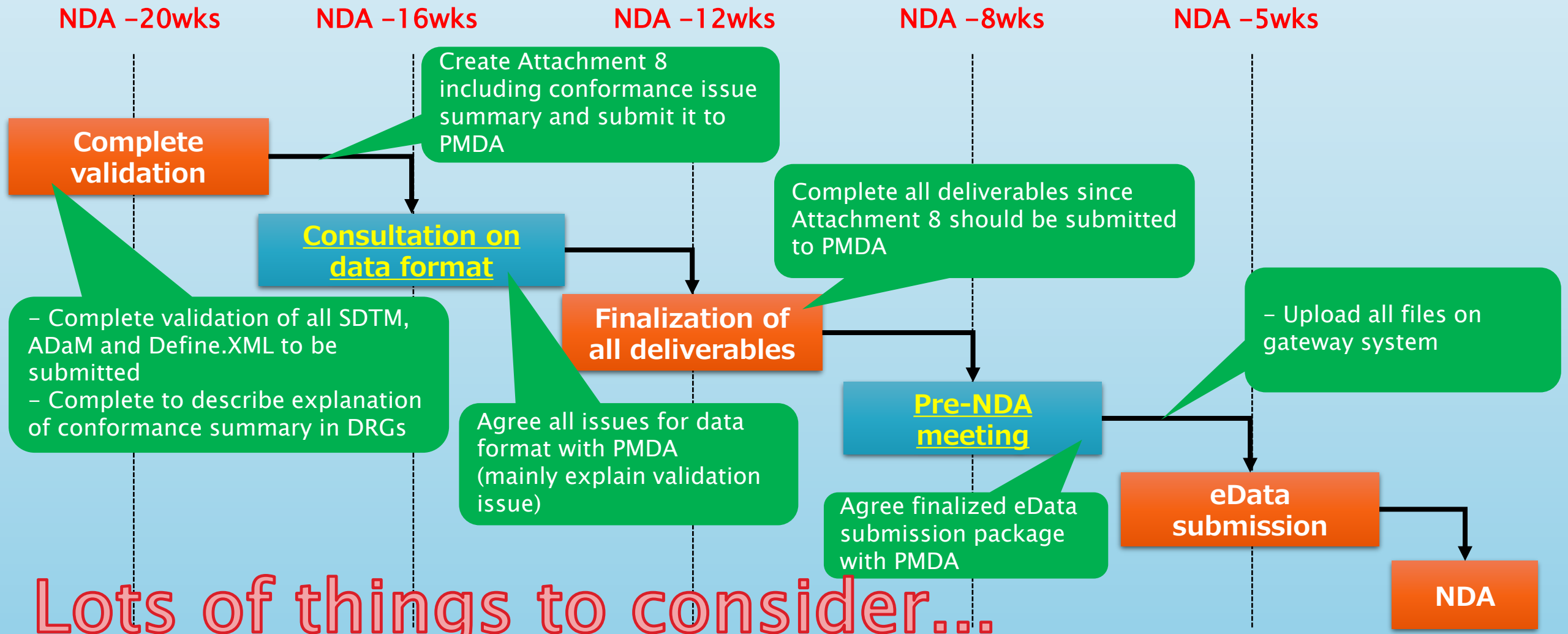
| | |
|---|---|
| Orphan drug | • Studies in orphan drug designation that started before Jun 20, 2014(the date of "Basic Principles on Electronic Submission of Study Data for New Drug Application" released) |
| Anti-HIV drugs | • Anti-HIV drugs which are eligible for prior assessment based on the Pharmaceutical and Medical Safety Bureau (PMSB)/ELD Notification No. 1015 (dated November 12, 1998) , and the data was legacy format. |
| Public knowledge-based application | • Studies in "public knowledge-based application" |
| No electronic legacy data | • Old studies that considered extremely difficult to convert to CDISC format (e.g. studies have no electronic legacy data) |

# Ideal timeline for eData submission to PMDA in internal guidance



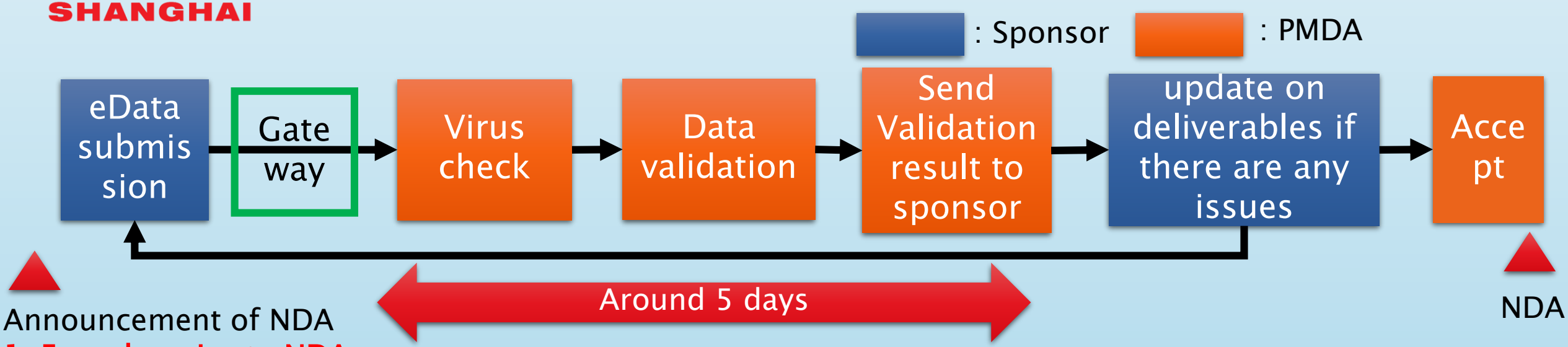

* Please refer to the PMDA website about the purpose of the consultations
https://www.pmda.go.jp/files/000229469.pdf

# Ideal timeline from completion of all validation to NDA



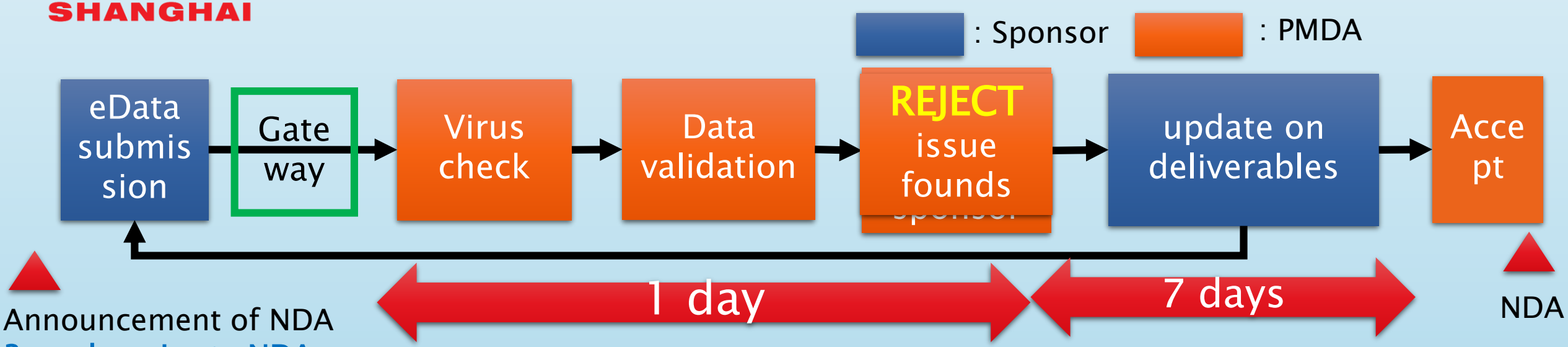

Lots of things to consider…

# eData submission via gateway




- Test loading can be conducted from 8 weeks before NDA
  - Only virus check is done. Pinnacle21 validation is not run.
- PMDA run Pinnacle 21 validation and check the validation results
  - Sponsor may receive inquiry when the Pinnacle21 result is different from the issue summary agreed on attachment 8

# eData submission via gateway




- REJECT issue was detected
- It took 7 days to resolve the issue.

For More detail, please refer the presentation:
https://www.google.com/url?sa=t&rct=j&q=&esrc=s&source=web&cd=2&ved=2ahUKEwiP4OmLx97jAhVyxYsBHZltBngQFjABegQICBAC&url=https%3A%2F%2Fwww.pharmasug.org%2Fproceedings%2F2017%2FSS%2FPharmaSUG-2017-SS06.pdf&usg=AOvVaw2vISWW_B3HFRJ2zjJE0Gvl

# Attachment 8

| Describe the data which are used in submitted: |
|---|

| Standards and those versions used for cre<br>If the version used at the time of datase<br>please enter the version used at the tim | |
|---|---|
| Standard | Version |
| SDTM<br>SDTM IG | |
| ADaM<br>ADaM IG | |
| Define-XML | SDTM :<br>ADaM : |
| Controlled Terminology | SDTM :<br>ADaM : |
| MedDRA | |
| WHODD | |
| (Others) | |

| The dataset planned to be submitted as electronic data (SDTM) | | | | | | |
|---|---|---|---|---|---|---|
| Definition file | ☐Define-XML | | | | | |
| Data guide | ☐Study Data Reviewer's Guide | | | | | |
| Data set | Submission<br>Please tick for domains to be submitted. Please do not change the order or delete the domains which are not be submitted. | | | | | |
| TA | ☐ | | | | | |
| TD | ☐ | | | | | |
| TE | ☐ | | | | | |
| TV | ☐ | | | | | |
| TI | ☐ | | | | | |
| TS | ☐ | | | | | |
| Data set | Please tick the most suitable one if the domain is planned to be submitted | | | Please tick the corresponding one | | RELREC |
| | Efficacy | Safety | Other | SUPP | Including Japanese | Related dataset |
| CO | ☐ | ☐ | ☐ | ☐ | ☐ | |
| DM | ☐ | ☐ | ☐ | ☐ | ☐ | |
| SE | ☐ | ☐ | ☐ | ☐ | ☐ | |
| SV | ☐ | ☐ | ☐ | ☐ | ☐ | |

# SDRG and ADRG

## SDRG

### 3.3 SDTM Subject Domains

| Dataset – Dataset Label | Efficacy | Safety | Other | SUPP- | Related Using RELREC | Observation Class |
|---|---|---|---|---|---|---|
| AE – Adverse Events | | X | | | ZA | Events |
| CM – Concomitant Medications | X | X | | | | Interventions |
| CO – Comments | | | X | | | Special Purpose |
| DM – Demographics | | | X | | | Special Purpose |

### 1.2 Study Data Standards and Dictionary Inventory

| Standard or Dictionary | Versions Used |
|---|---|
| SDTM | SDTM v1.2/SDTM IG v3.1.2 including SDTM Amendment 1 |
| Controlled Terminology | 2011-07-22 |
| Data Definitions | define.xml v1.0 |
| Medications Dictionary | Proprietary medication dictionary |
| Medical Events Dictionary | MedDRA v14.1 |

## ADRG

### 5.2 Analysis Datasets

| Dataset Dataset Label | Class | Efficacy | Safety | Baseline or other subject characteristics | PK/PD | Primary Objective | Structure |
|---|---|---|---|---|---|---|---|
| ADSL Subject Level Analysis Dataset | ADSL | | | X | | | One observation per subject |
| | | | | | | | |

### 1.3 Study Data Standards and Dictionary Inventory

| Standard or Dictionary | Versions Used |
|---|---|
| SDTM | SDTM v1.2/SDTM IG v3.1.2 (with amendment 1) |
| ADaM | ADaM Model Document 2.0<br>ADaM Implementation Guide v1.0<br>ADaM Data Structure for Adverse Event Analysis v1.0<br>ADAM Basic Data Structure for Time-to-Event Analysis v1.0 |
| Data Definitions | define.xml v1.0 |

# Keep consistency

SDRG

ADRG

### 3.3 SDTM Subject Domains

| Dataset – Dataset Label | Efficacy | Safety | Other | SUPP- | Related Using RELREC | Observation Class |
|---|---|---|---|---|---|---|
| AE – Adverse Events | | X | | | ZA | Events |
| CM – Concomitant Medications | X | X | | | | Interventions |
| CO – Comments | | | X | | | Special Purpose |
| DM – Demographics | | | X | | | Special Purpose |

### 1.2 Study Data Standards and Dictionary I

| Standard or Dictionary | Versions Used |
|---|---|
| SDTM | SDTM v1.2/SI |
| Controlled Terminology | 2011-07-22 |
| Data Definitions | define.xml v1.( |
| Medications Dictionary | Proprietary me |
| Medical Events Dictionary | MedDRA v14. |

### 1.3 Study Data Standards and Dictionary Inventory

| Standard or Dictionary | Versions Used |
|---|---|
| SDTM | SDTM v1.2/SDTM IG v3.1.2 (with amendment 1) |
| ADaM | ADaM Model Document 2.0<br>ADaM Implementation Guide v1.0<br>ADaM Data Structure for Adverse Event Analysis v1.0<br>ADAM Basic Data Structure for Time-to-Event Analysis v1.0 |
| Data Definitions | define.xml v1.0 |

Attachment 8

| Data set | Please tick the most suitable one if the domain is planned to be submitted | | | Please tick the corresponding one | | RELREC |
|---|---|---|---|---|---|---|
| | Efficacy | Safety | Other | SUPP | Including Japanese | Related dataset |
| CO | ☐ | ☐ | ☐ | ☐ | ☐ | |
| DM | ☐ | ☐ | ☐ | ☐ | ☐ | |
| SE | ☐ | ☐ | ☐ | ☐ | ☐ | |
| SV | ☐ | ☐ | ☐ | ☐ | ☐ | |

| Standard | Version |
|---|---|
| SDTM<br>SDTM IG | |
| ADaM<br>ADaM IG | |
| Define-XML | SDTM :<br>ADaM : |
| Controlled Terminology | SDTM :<br>ADaM : |
| MedDRA | |
| WHODD | |

# Key Takeaways

- The timing of the Consultation on data format meeting is Key
- Validation result from PMDA after Gateway eData submission

## Timeline



- We should start Legacy data conversion activities early

## Legacy data conversion



- Learn the difference between FDA/PMDA and standardize from where we can.

## PMDA specific requirement



# References


PMDA eData submission guidance
https://www.pmda.go.jp/review-services/drug-reviews/about-reviews/p-drugs/0026.html

PMDA "FAQs on Electronic Study Data Submission (Excerpt)"
https://www.pmda.go.jp/english/review-services/reviews/advanced-efforts/0007.html

PhUSE "Website for Study Data Reviewer's Guide"
https://www.phusewiki.org/wiki/index.php?title=Study_Data_Reviewer%27s_Guide

PhUSE "Website for Analysis Data Reviewer's Guide"
https://www.phusewiki.org/wiki/index.php?title=Analysis_Data_Reviewer%27s_Guide

# Thank you!




Yasuhiro Iijima
Novartis Pharma K.K.
Address: Toranomon Hills Mori Tower 23-1,
Toranomon 1-chome Minatoku, Tokyo, 105-6333, Japan
Work Phone: +81-3-6899-8743
Fax: +81-3-6257-3611
Email: yasuhiro.iijima@novartis.com
Web: https://www.novartis.co.jp/
Twitter:

Takashi Kitahara
Novartis Pharma K.K.
Address: Toranomon Hills Mori Tower 23-1,
Toranomon 1-chome Minatoku, Tokyo, 105-6333, Japan
Work Phone: +81-3-6899-7754
Fax: +81-3-6257-3611
Email: takashi.kitahara@novartis.com
Web: https://www.novartis.co.jp/
Twitter:

# Back up slides

| Data Exchange Standard | Supported Version(s) | Implementation Guide Version | Date Support Begins (PMDA) | Date Support Ends (PMDA) | Date Requirement Begins | Data Requirement Ends |
|---|---|---|---|---|---|---|
| SDTM | 1.2 | 3.1.2 | 01OCT2016 | | 17DEC2016 (IND:17DEC2017) | 15MAR2019 (IND:15MAR2020) |
| SDTM | 1.2 | 3.1.2 Amendment1 | 01OCT2016 | | 17DEC2016 (IND:17DEC2017) | 15MAR2019 (IND:15MAR2020) |
| SDTM | 1.3 | 3.1.3 | 01OCT2016 | | 17DEC2016 (IND:17DEC2017) | |
| SDTM | 1.4 | 3.2 | 01OCT2016 | | 15MAR2018 (IND:15MAR2019) | |
| ADaM | 2.1 | 1.0 | 01OCT2016 | | 17DEC2016 (IND:17DEC2017) | 15MAR2019 (IND:15MAR2020) |
| ADaM | 2.1 | 1.1 | 01OCT2016 | | 15MAR2019 (IND:15MAR2020) | |
| Define | 1.0 | - | 01OCT2016 | | 17DEC2016 (IND:17DEC2017) | 15MAR2018 |
| Define | 2.0 | - | 01OCT2016 | | 17DEC2016 (IND:17DEC2017) | |

# Identification of data/studies and analyses

*Target analyses for eData submission on clinical data package*

| Protocol No | Phase | Evaluation/ Reference | eData submission | Notes | Target analyses |
|---|---|---|---|---|---|
| 001 | I | **Evaluation** | **Yes** | To meet condition to be submitted eData for CP study on FAQ (e.g. TQT study, BE study) | **PK, AE, LB** |
| 002 | I | **Evaluation** | **Yes** | | **PK, AE, EG** |
| 003 | I | **Reference** | **Yes** | | **PK, AE** |
| 004 | I | **Reference** | **No** | NOT to meet condition to be submitted eData for CP study on FAQ (e.g. Within the 0.8 - 1.25 range on the geometric mean ratio in Food Effect and DDI studies) | **-** |
| 005 | I | **Reference** | **No** | | **-** |
| 006 | II | **Evaluation** | **Yes** | Studies that are generally regarded to be the major evidence for evaluation of efficacy, safety, and dose and administration | **Key efficacy endpoint, AE, LB, Biomarker** |
| 007 | II | **Evaluation** | **Yes** | | **Key efficacy endpoint, AE, LB, EG** |
| 008 | III | **Evaluation** | **Yes** | | **Key efficacy endpoint, AE, LB** |
| 009 | III | **Evaluation** | **Yes** | | **Key efficacy endpoint, AE, LB, EG** |
| ISS | - | **Evaluation** | **Yes** | Analyses were performed to assess rare adverse events | **AE** |

# Our experiences for eData submission to PMDA during transitional period

| | Project A | Project B | Project C |
|---|---|---|---|
| *NDA date* | Nov. 2016 | Apr. 2017 | Jan. 2018 |
| *Number of studies to be submitted* | 1 | 1 | 1 |
| *Full / Partial** | Full | Partial | Partial |
| *FDA submission planned.* | Yes | No | No |
| *Legacy data conversion considered.* | No | No | No |
| *Number of PMDA consultations on data format*** | F2F mtg: 2 | F2F mtg: 3<br>TC: 1 | TC: 1 |
| *Clinical Pharmacology study included?* | No | No | No |

* Partial: PMDA review is conducted by conventional process (eData won't be used during review)
** Consultation on data format: Currently the consultation has been divided into 2 consultations, consultation on preparation, consultation on data format