

# Electronic Data Submission and Utilization in Japan

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# Outline

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- Current situation of e-data submission
- Preparation for the end of the transitional period
- Practical case for utilization of submitted data in review process
- Utilization of accumulated data

# Accumulation and utilization of data

## NDA submission

### e-Submission of data

- ◆ Submission of electronic data from clinical and nonclinical studies

Storage of electronic data in the dedicated server and registration in the database

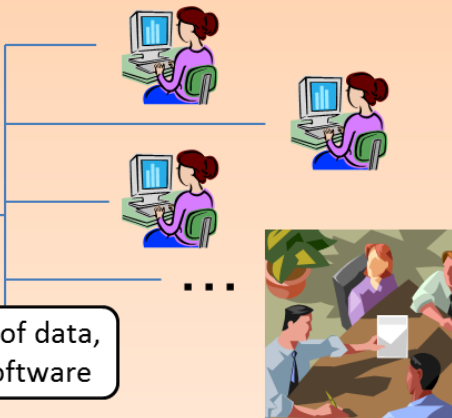


Visualization and analysis of data, supported by browsing software

## Regulatory Review

### Use of electronic data

- ◆ Accessible, visualized electronic data for each reviewer
- ◆ Easy to identify individual clinical case data, drilling down of data
- ◆ Operation of various analyses - simple, subgroup analysis for the present



Scientific discussion and decision making on the basis of internal analysis result

## Utilization of Accumulated Data

### Integration of cross-products information

- ◆ Utilization of exhaustive information by therapeutic category for review/consultation
- ◆ Internal review on particular theme – e.g.) active utilization of M&S
  - Review on pediatric dosage
  - Preparation of disease model
  - Development of evaluation indicator
- ◆ Utilization in preparation of guideline

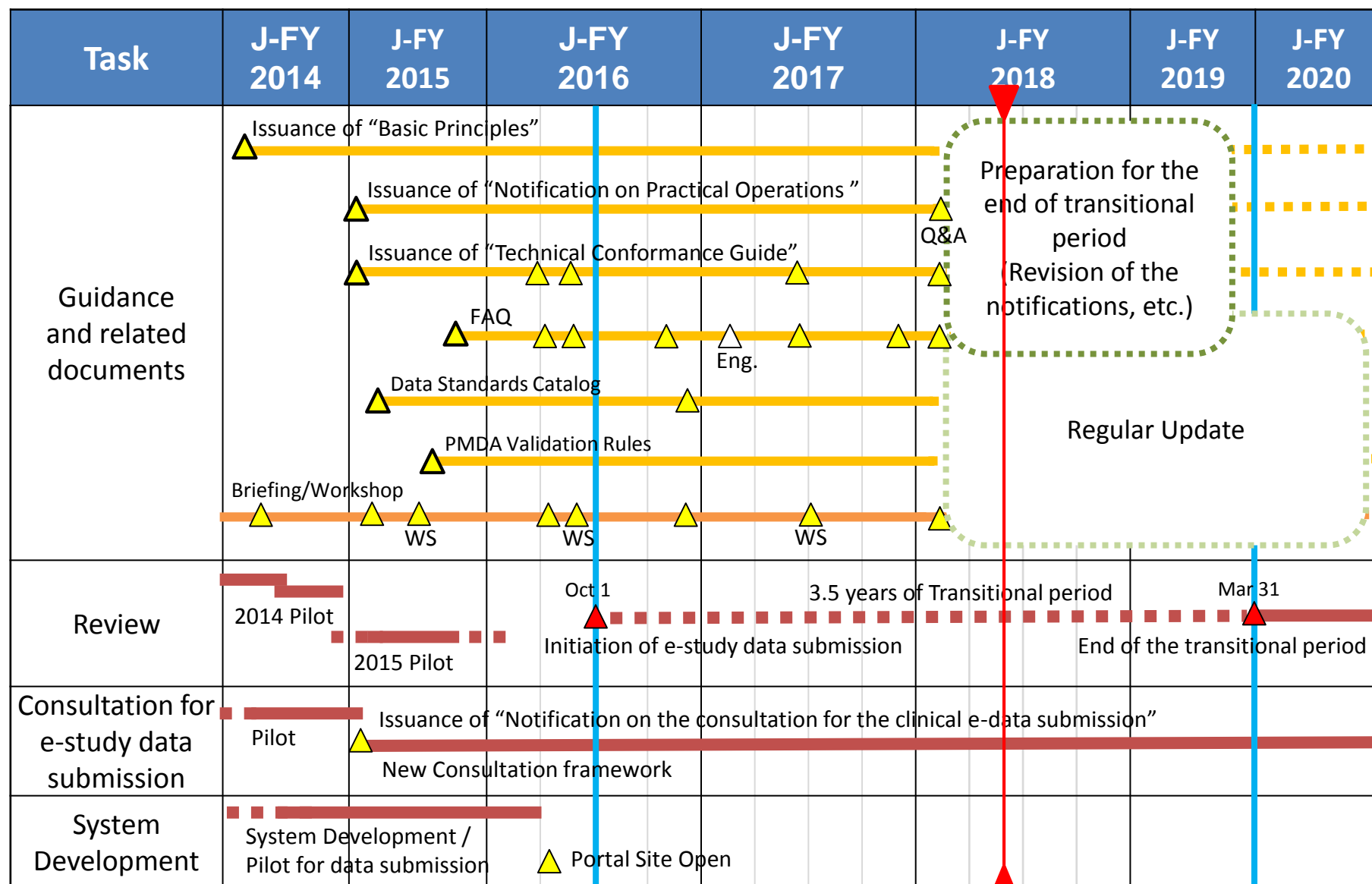


What the review authority can do with the information of all products.

Contribution to efficient development through review/consultation and GL publication based on further analyses by dry-lab

Submission of electronic clinical study data has started since Oct 1<sup>st</sup> 2016!

# Timeline for implementation of e-data submission



# Consultation for clinical e-data submission

- 169 consultation meetings have been requested by 49 companies as of July 31, 2018.

Year	N of request
J-FY 2015 (May 15, 2015 – Mar 31, 2016)	13
J-FY 2016 (Apr 1, 2016 – Mar 31, 2017)	62
J-FY 2017 (Apr 1, 2017 – Mar 31, 2018)	65
J-FY 2018 (Apr 1, 2018 – Jun 30, 2018)	29
Total	169

- Multiple meetings have been held for the some products.
- The number of consultation for NDA after transitional period is increasing.
- Various characteristics
  - With/without official minutes
  - Japanese/foreign company
  - Oncology and other therapeutic areas

# Data submitted with new drug applications

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- 51 NDAs were submitted with electronic study data by 27 companies as of July 31, 2018.
  - Although several issues below have occurred during data transmission, all the submitted data are successfully received.
    - System issues
    - Validation failure because of violations categorized “Reject”.
    - Lack of explanations for “Error” issues.
  - Various characteristics on the NDAs
    - Domestic/global company
    - Oncology holds majority, but submissions in other areas are also increasing
    - Initial application / application for partial changes (supplemental application)
    - Clinical pharmacology study

# Explanation on electronic data for reviewers

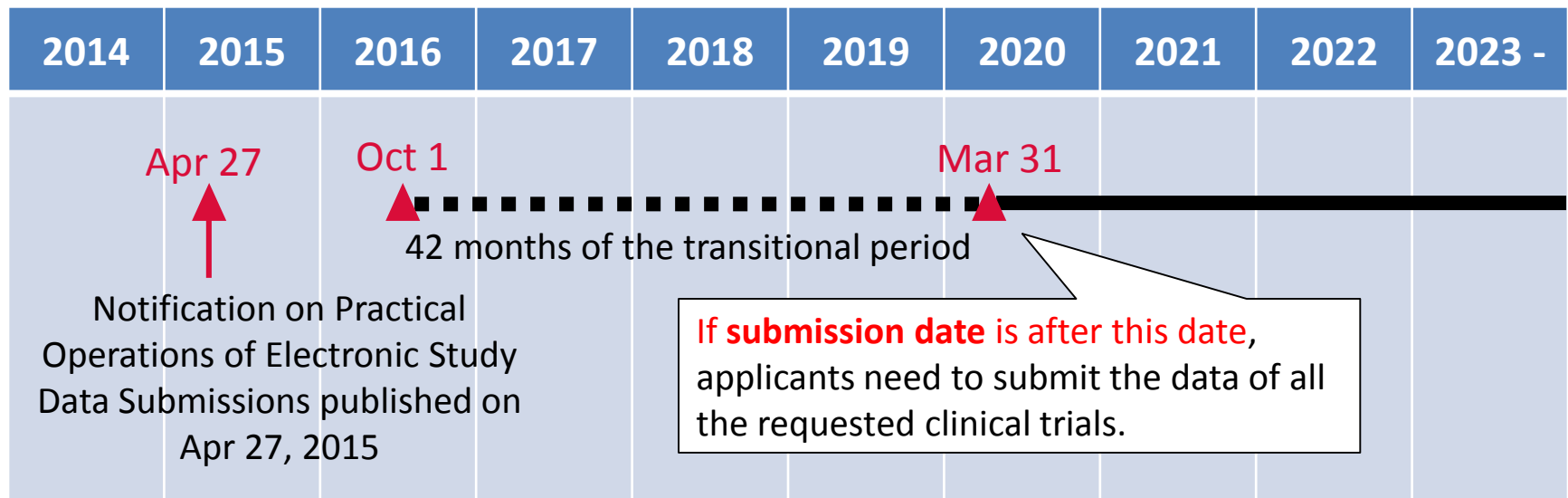
So far, we have not received major questions/concerns about the submitted data or data format during new drug review period.

- PMDA requests applicants to submit various information for explanation on study data, and they are very useful for reviewers.
  - Analysis Results Metadata
  - Reviewer's Guide (SDRG, ADRG)
  - Define.xml
  - Programs for creating ADaM datasets
- Analysis Results Metadata will be the key in their review with electronic data.
  - Most reviewers usually start with confirming the reproducibility of the primary results in CTDs, and Analysis Results Metadata is very useful for reviewers for their quick access to the analysis datasets used.

We strongly recommend that you include “Creating ARM” in your plan of organizing submission datasets.

# Transitional period will be ended...

- The transitional period will be ended **on March 31, 2020**.
  - During the transitional period, applicants can submit the data of at least one clinical trial included in their clinical data packages.
  - **After the period, applicants need to submit the data of all the requested clinical trials.**





# Preparation for the end of transitional period

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We have already revised notifications and clarification, for example,

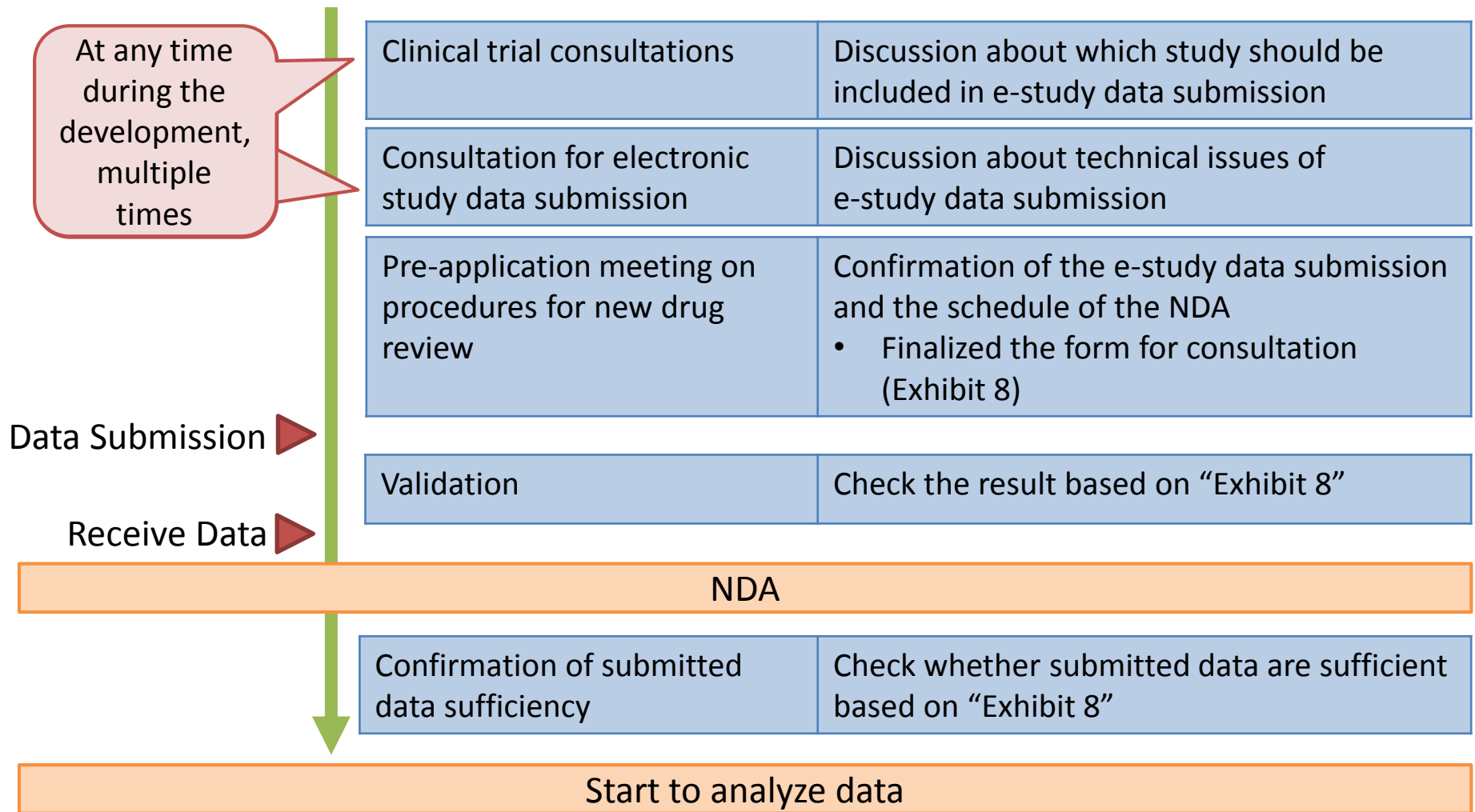
- Revision of notifications with considering situation when applicants can not use Electronic Submission Gateway
- Clarification of relationship between
  - Electronic study data submission
  - Submission of eCTD
  - Use of Electronic Submission Gateway

We are considering revision of notifications and clarification, for example,

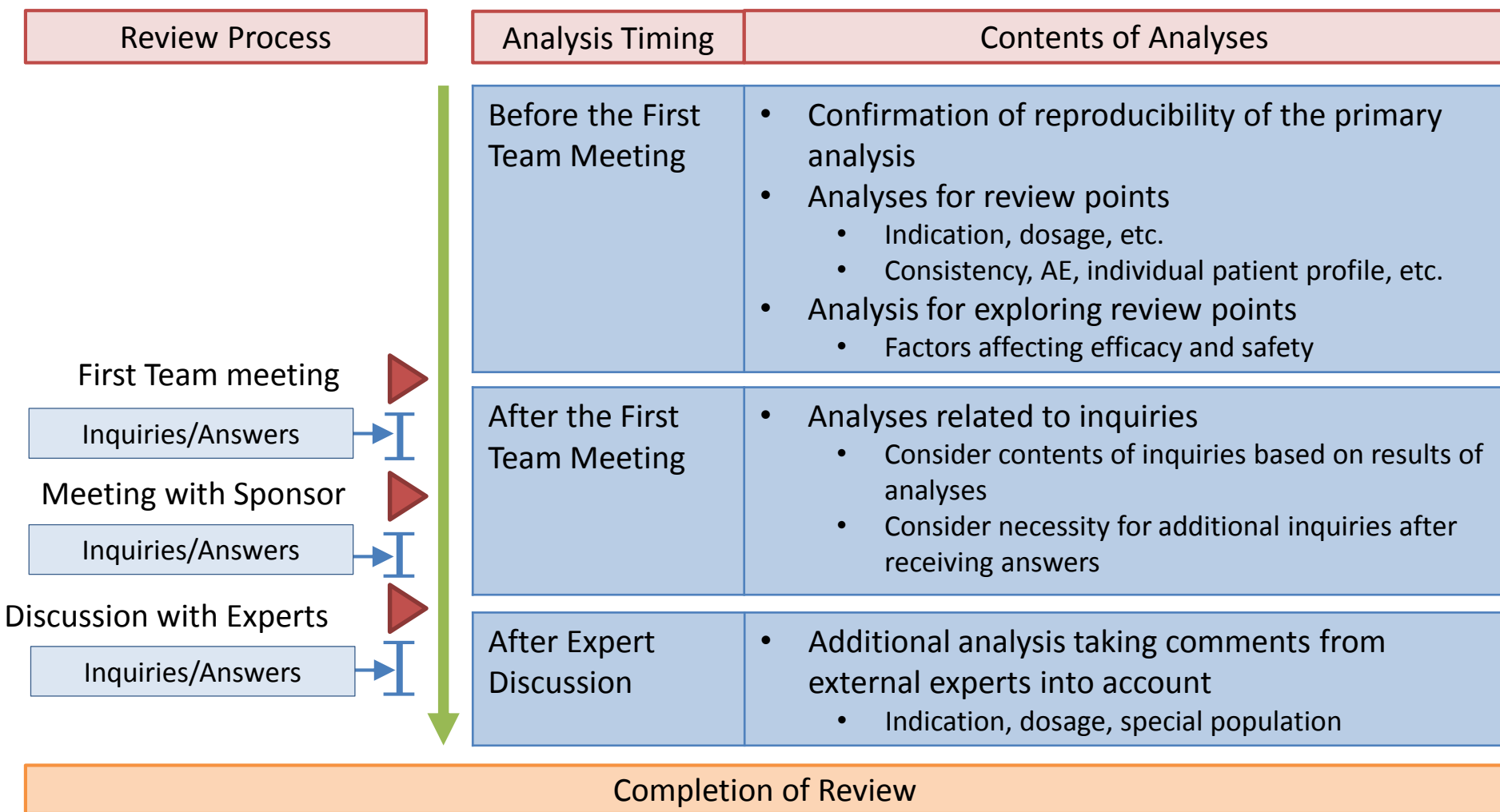
- Clarification of timing of data submission for special situation
  - Ex. New drug applications for anti-HIV drugs

We will proceed the project with continual discussion with industry for the smooth transition to the next phase.

# Process of starting to analyze data



# Review process and data analysis



# Analyses of CDISC data in review team

## Common analyses to many clinical trials

- Distribution of patient demographics
- Changes in laboratory data
- Adverse events rates

STAT MEDICAL OTHERS  
Software: JMP  
Clinical, etc.  
Datasets: SDTM

## General analyses for efficacy and safety data

- Simple analyses depending on the characteristics of evaluation variables – continuous/categorical/time-to-event)

STAT MEDICAL OTHERS  
Software: JMP, SAS etc.  
Datasets: ADaM

## Relatively complicated analyses

- Analyses with programming (innovative/complicated analyses)
- Simulations

STAT MEDICAL OTHERS  
Software: SAS, etc.  
Datasets: SDTM, ADaM

# Practical case for utilization of submitted data in review process(1)

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- To check the appropriateness of applicant's idea that dosage adjusted according to patient's weight, reviewer(stat) performed subgroup analysis and searched other factors which affect efficacy/safety of the product.

➤ Inquiries from PMDA can be more reasonable (reduced request for comprehensive analysis more than necessary)

## Practical case for utilization of submitted data in review process(2)

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- To check the consistency of efficacy among subjects in the trial, reviewer(stat) confirmed a relationship between inclusion/exclusion criteria and endpoint outcome(ex. subgroup analysis by baseline status).

➤ No need for inquiries from PMDA

## Practical case for utilization of submitted data in review process(3)

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- To check the robustness of the primary result which used value transformation, or assumption of distribution, or model for the primary analysis, reviewer(stat) performed supplementary analysis.

➤ Be able to quickly and efficiently cope with a point from the external expert, and prepared review report without delay

# Practical case for utilization of submitted data in review process(4)

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- To check whether PPK analysis result from multinational trial was valid for Japanese or not, reviewer(CP) checked goodness of fit and performed predictive check for Japanese.
- To check the impact of the result from *in vitro*, reviewer(CP) checked other scenarios by clinical trial simulation using PBPK model. (ex. worst case scenario prediction).

- Inquiries from PMDA can be more reasonable (reduced request for comprehensive analysis more than necessary), or no need for inquiries from PMDA
- Sometimes outlier is specified



# Practical case for utilization of submitted data in review process(5)

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- It often becomes an issue that how is the relationship between dose and efficacy/safety outcome in the optional titration(ex. based on response) design trial.

➤ It is favorable that some variable about dose change (ex. when and how much) is prepared in ADaM dataset for the supplementary analysis

# Summary of e-data review so far(1)

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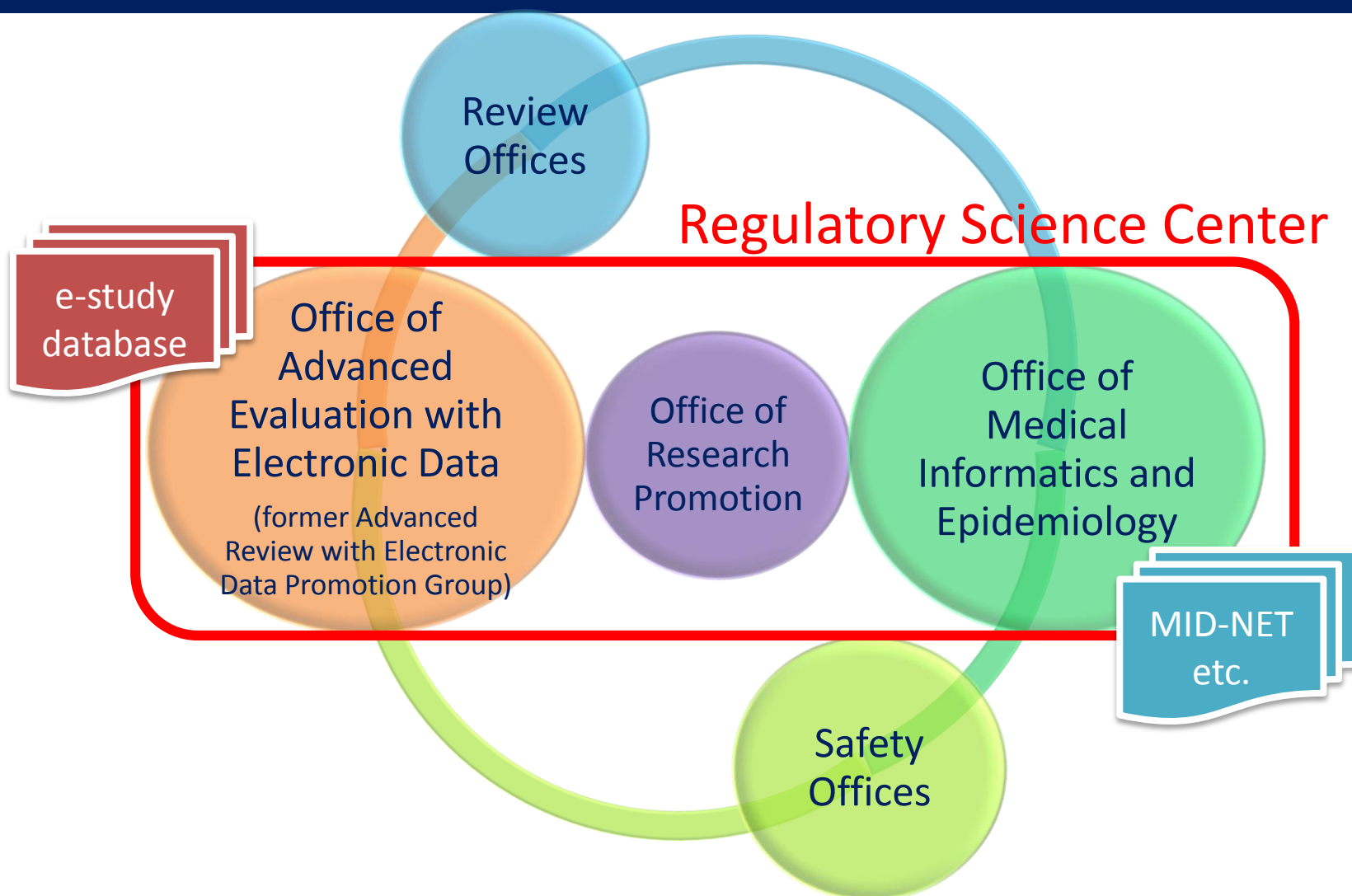
- Reviewers can develop an understanding about the e-data, trial design, and the product than ever.
- The timeline of review process isn't change.
- Sometimes inquiries from PMDA can be more reasonable (reduced request for comprehensive analysis more than necessary) or no need for inquiry.
- It becomes possible to quickly and efficiently cope with a point from the external expert.

# Summary of e-data review so far(2)

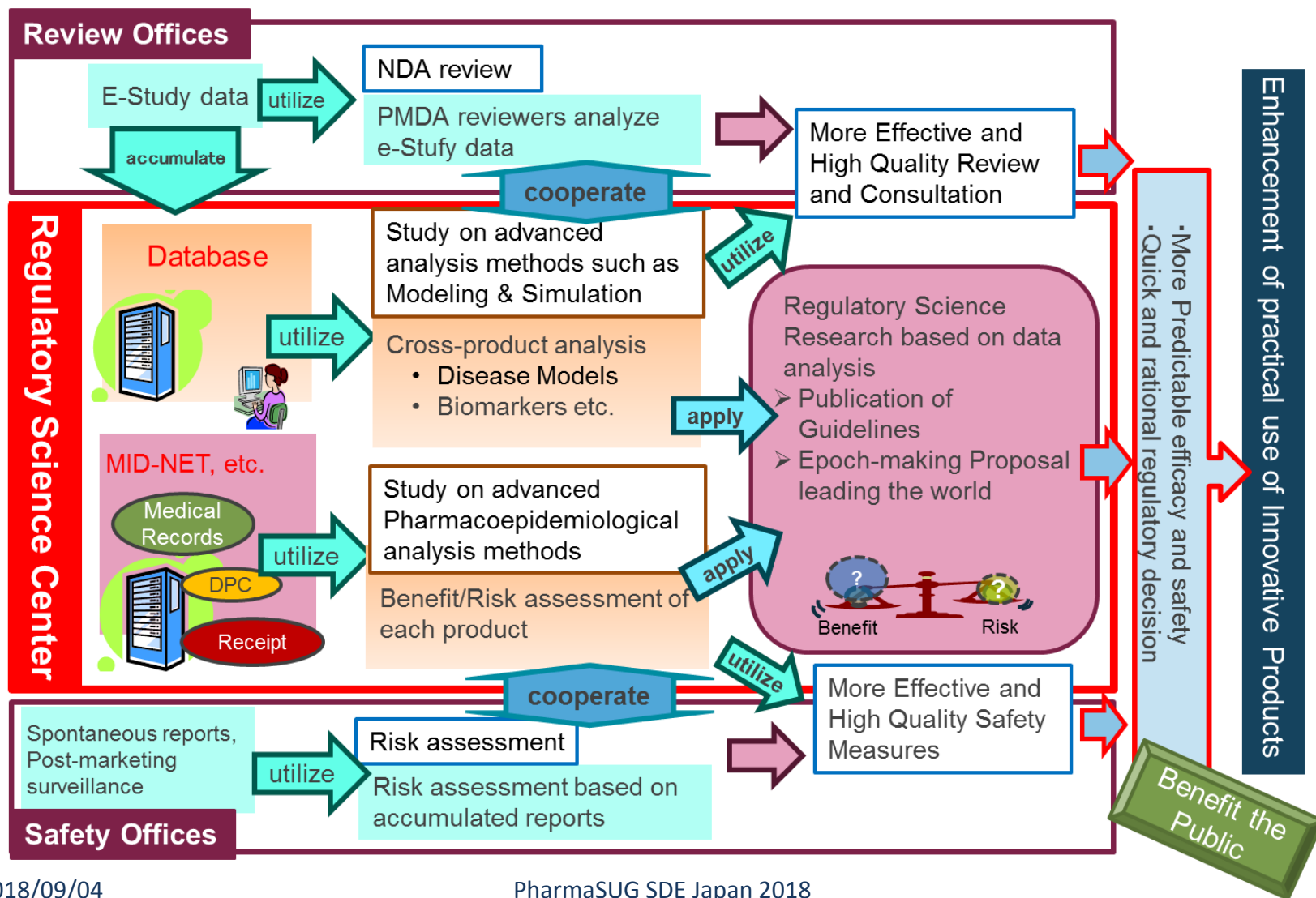
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- It often needs e-data analysis plan meeting before first team meeting, and even after that, needs to take time to analyze timely, so schedule management and business efficiency improvement are important than ever.
- It is necessary for reviewers to cooperate among their specialties(ex. stat and clinical) more than ever from an early stage.

# Regulatory Science Center established on Apr 1

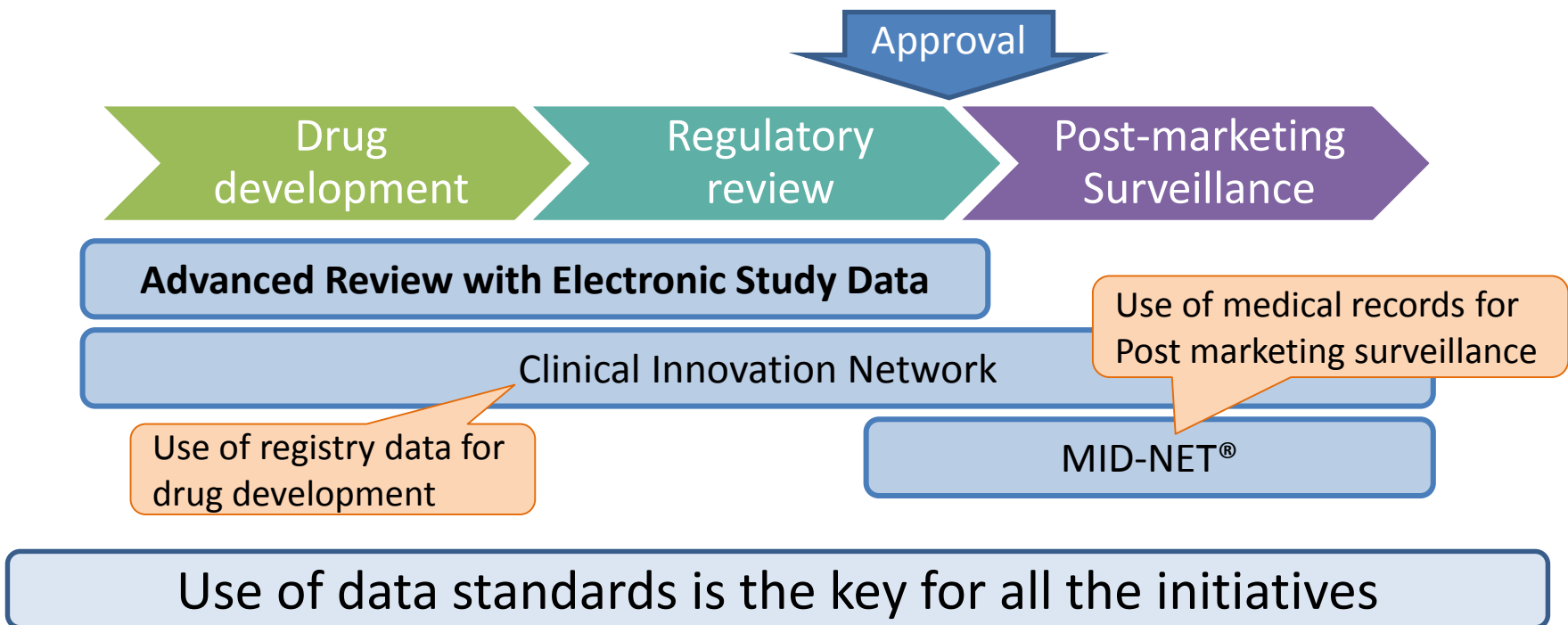


# Regulatory Science Center established on Apr 1

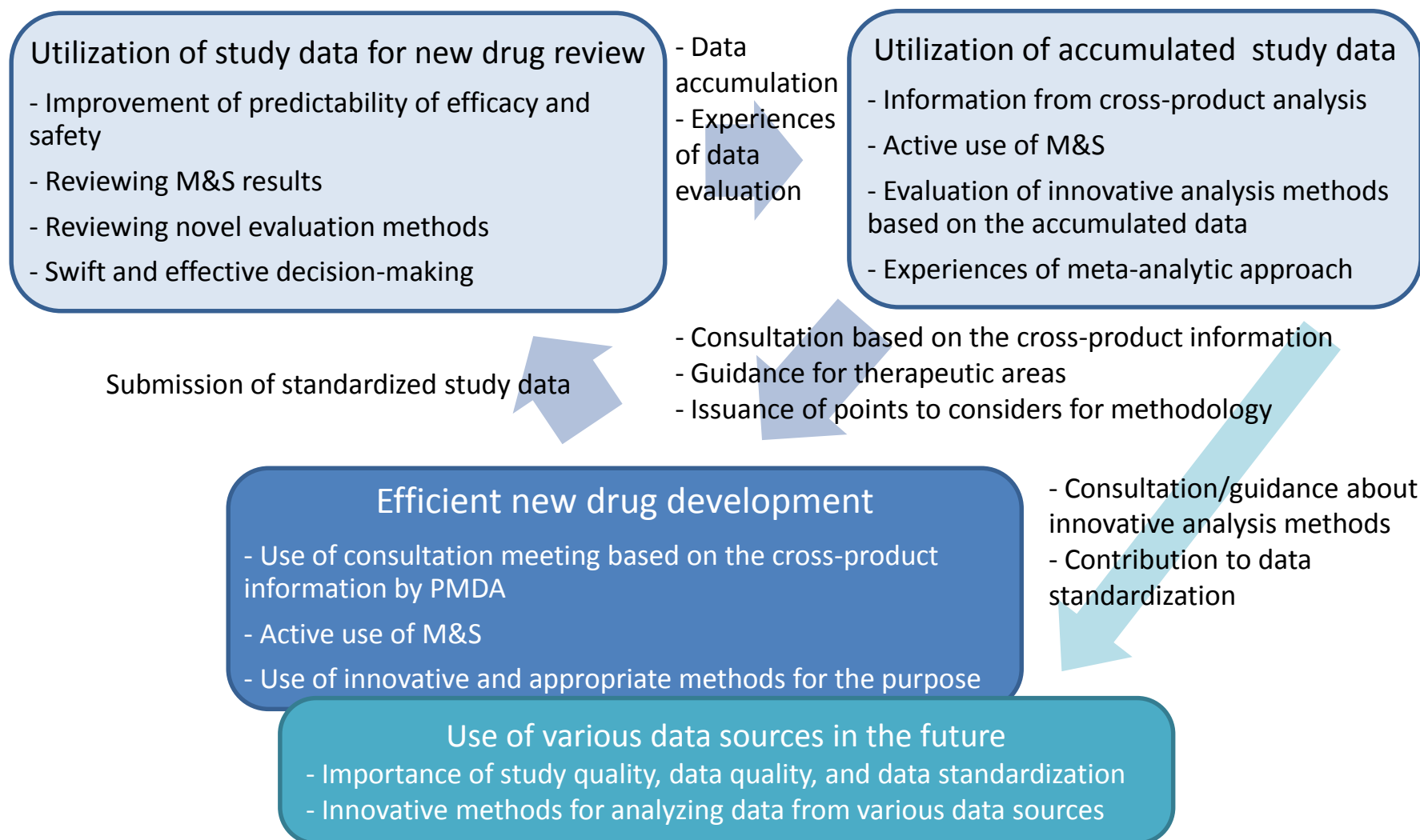


# PMDA initiatives for quantitative science

- Several initiatives/activities for quantitative science are established and are in execution for new drug/device development and review in Japan.
- We are considering how we can efficiently use those data that we will obtain in each stage of clinical development.



# Utilization of study data in the future



# Summary

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- Advanced Review with Electronic Data Project is being achieved successfully so far.
- PMDA will continue to provide information on the e-data submission for industries with considering the end of transitional period.
  - The transitional period will be ended on Mar 31, 2020.
- We appreciate continual collaboration for the efficient drug development and predictability of the safety and the efficacy of the drug.