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Pharmaceuticals and Medical Devices Agency

Electronic Data Submission and Utilization in Japan

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Outline

- Current situation of e-data submission
- Preparation for the end of the transitional period
- Utilization of accumulated data

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Accumulation and utilization of data

NDA submission

e-Submission of data

- Submission of electronic data from clinical and nonclinical studies

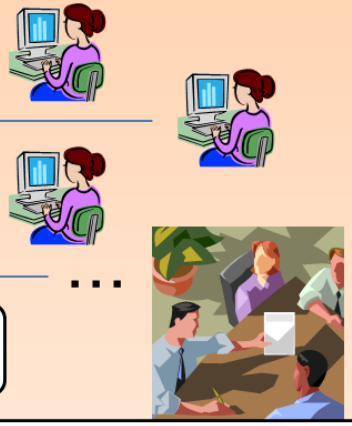
Storage of electronic data in the dedicated server and registration in the database

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

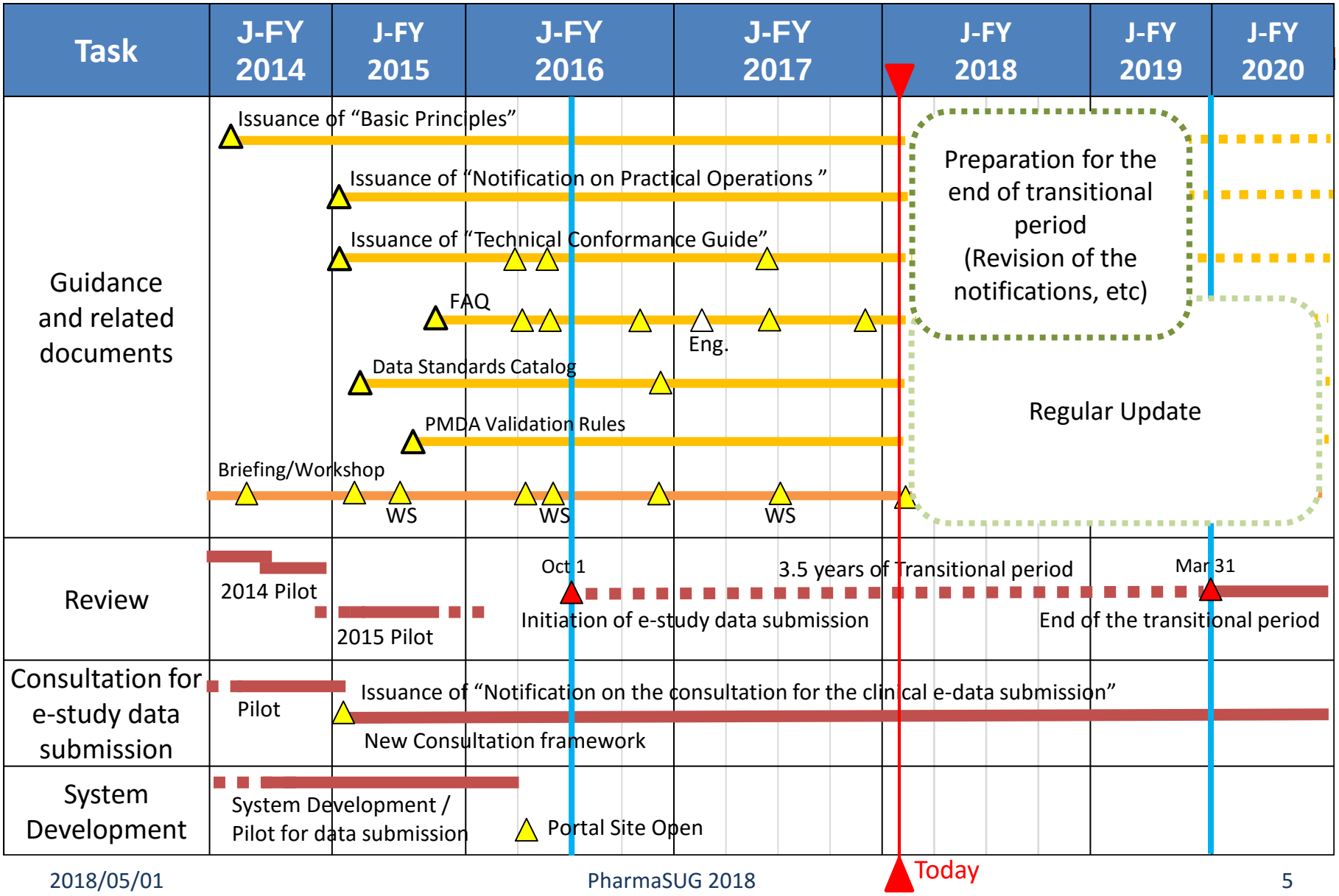
- Utilization of exhaustive information by therapeutic category for review/consultation
- Internal review on particular theme – e.g.) active utilization of M&S
  - Review on pediatric dosage
  - Preparation of disease model
  - Development of evaluation indicator
- Utilization in preparation of guideline

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 1st 2016!

Timeline for implementation of e-data submission



Notifications, Guide, FAQs, and Standards Catalog

- Basic Principles on Electronic Submission of Study Data for New Drug Applications (Jun 20, 2014) and Q&A
  - The first official announcement that MHLW/PMDA will require CDISC-standardized study data for NDA.
- Notification on Practical Operations of Electronic Study Data Submissions (Apr 27, 2015) and Q&A
  - Practical issues on e-Study data submission
- Technical Conformance Guide on Electronic Study Data Submissions (Latest update on Sep 11, 2017)
  - Technical details on e-Study data submission
- FAQ website (Latest update on Mar 7, 2018)
  - Supplemental explanations based on the frequently asked questions at the meeting with sponsors and the comments to the notifications and the guide
- PMDA Data Standards Catalog (Latest update on Mar 3, 2017)
  - List of acceptable versions of Data Exchange Standards and Terminology Standards

CDISC validation in PMDA

- PMDA validation rules were published on Nov 18, 2015
- We use Pinnacle 21 Enterprise for CDISC validation
  - Apply to SDTM, ADaM, CT, and Define-XML
  - PMDA validation rules are provided on the PMDA website for sponsor's use.
  - Sponsors should use the same validation rules and check the results in advance.
- Three levels of severity of the errors
  - Reject (a) Rules which, if violated, will cause the review to be suspended until corrections have been made
  - Error (b) Rules which, if violated without any prior explanation, will cause the review to be suspended until corrections have been made
  - Warning (c) Rules which, even when violated, will not necessarily require any explanation

Consultation for clinical e-data submission

- 140 consultation meetings have been requested by 44 companies as of March 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
Total	140

- Multiple meetings have been held for some products.
- Various characteristics
  - With/without official minutes
  - Japanese/foreign company
  - Oncology and other therapeutic areas
  - Time of consultation meeting during drug development

Frequently raised issues at consultation meetings

- Majority of issues is explanation of validation results at this point
  - Sponsor's validation results and reasons of "Error"
- Other issues
  - Product dependent issues such as use of SUPPQUAL, custom domains, and traceability
  - Information to be included in the Trial Design Model
  - Issues related to WHO DDs coding
  - SI units
  - How to submit study data for multiple time points
  - Use of particular variables such as USUBJID, RACE
  - Submission format for clinical pharmacology data
- Corrections of consultation materials
  - Ex. Application form, SDRG, ADRG…

Data submitted with new drug applications

- 41 NDAs were submitted with electronic study data by 26 companies as of Mar 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.

Other topics of e-data submission

- CDISC Validation in PMDA
  - We plan to update our CDISC validation software and PMDA validation rules in the near future.
  - We are considering smooth transition to the new version and the detailed information will be provided in advance.
- Use of non-clinical data (SEND)
  - We continue to discuss how we can efficiently use non-clinical study data in our review process.
  - Submission timing will be one of the topics in the discussion.
- Therapeutic Area Standards
  - We continue to work for incorporating medical practices in Japan to Therapeutic Area User Guides in collaboration with academic societies and industry, mainly in the Public Review period.
  - We basically accept that applicants implement the published TAUGs.

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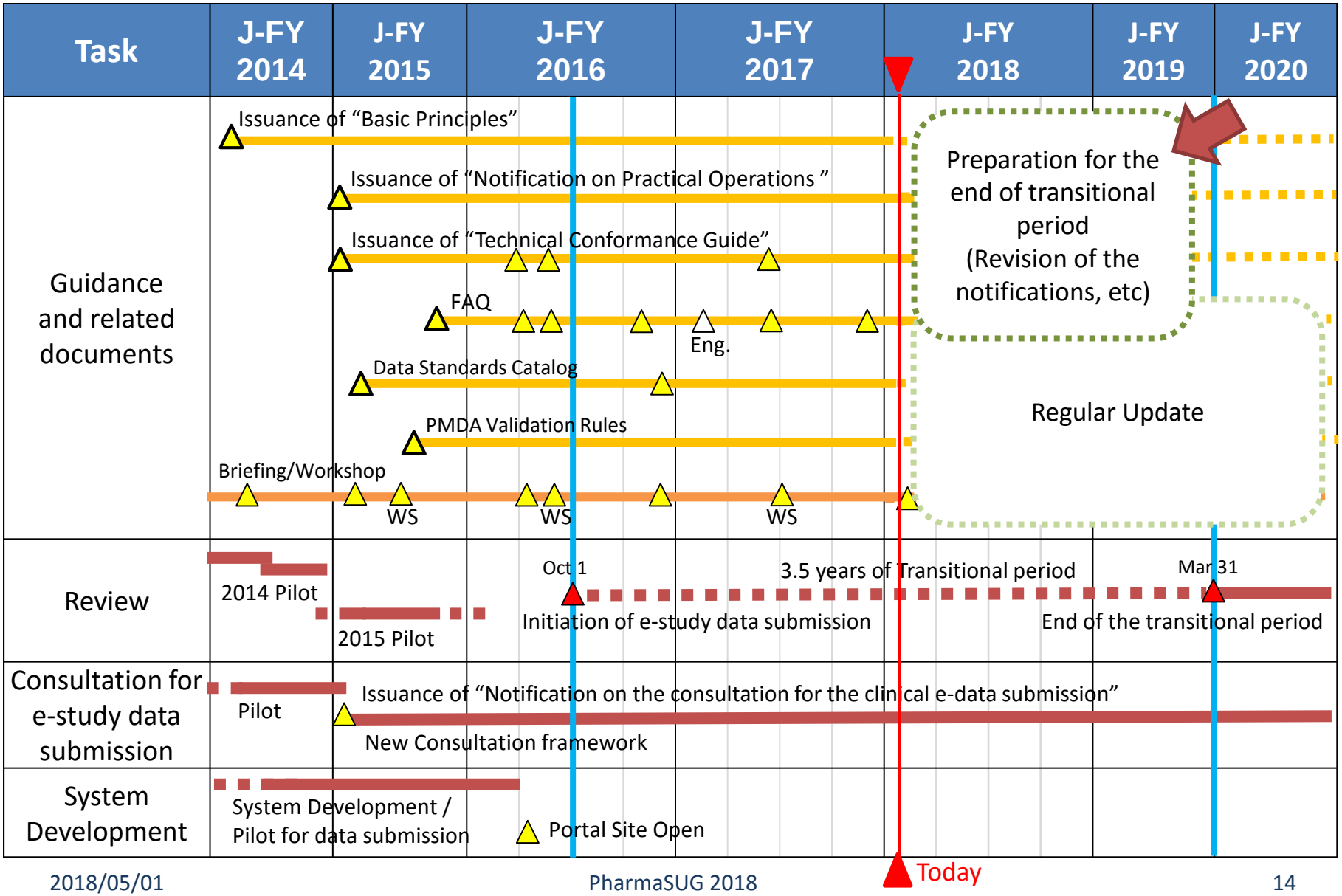
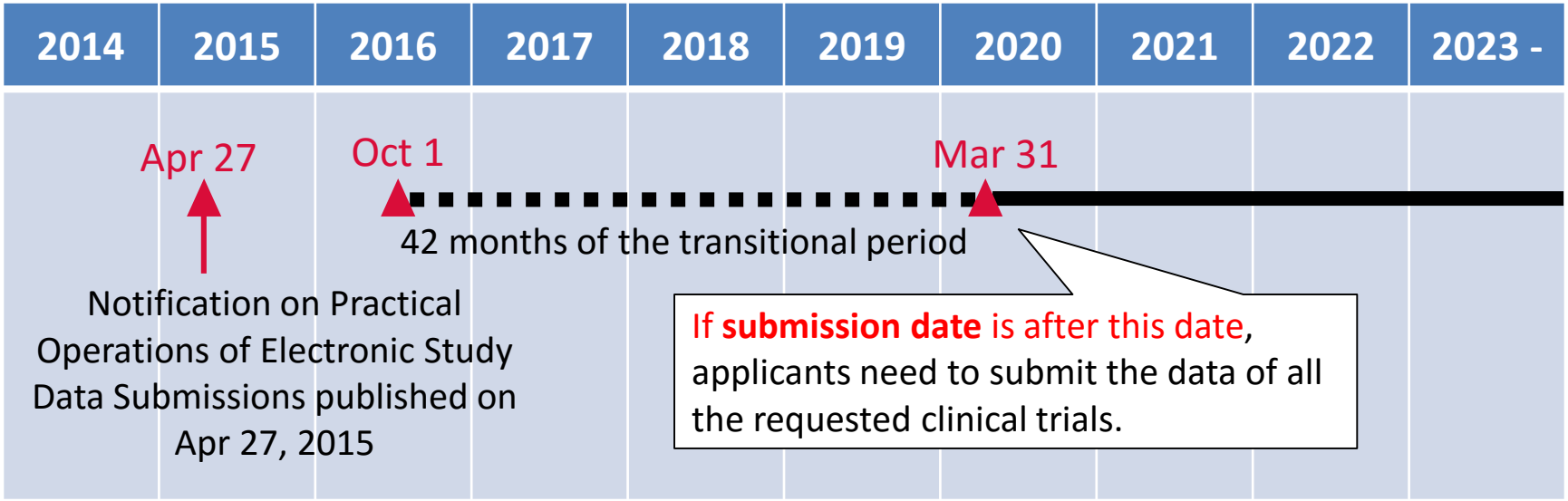
Timeline for implementation of e-data submission



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

We are considering revision of 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
- 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.

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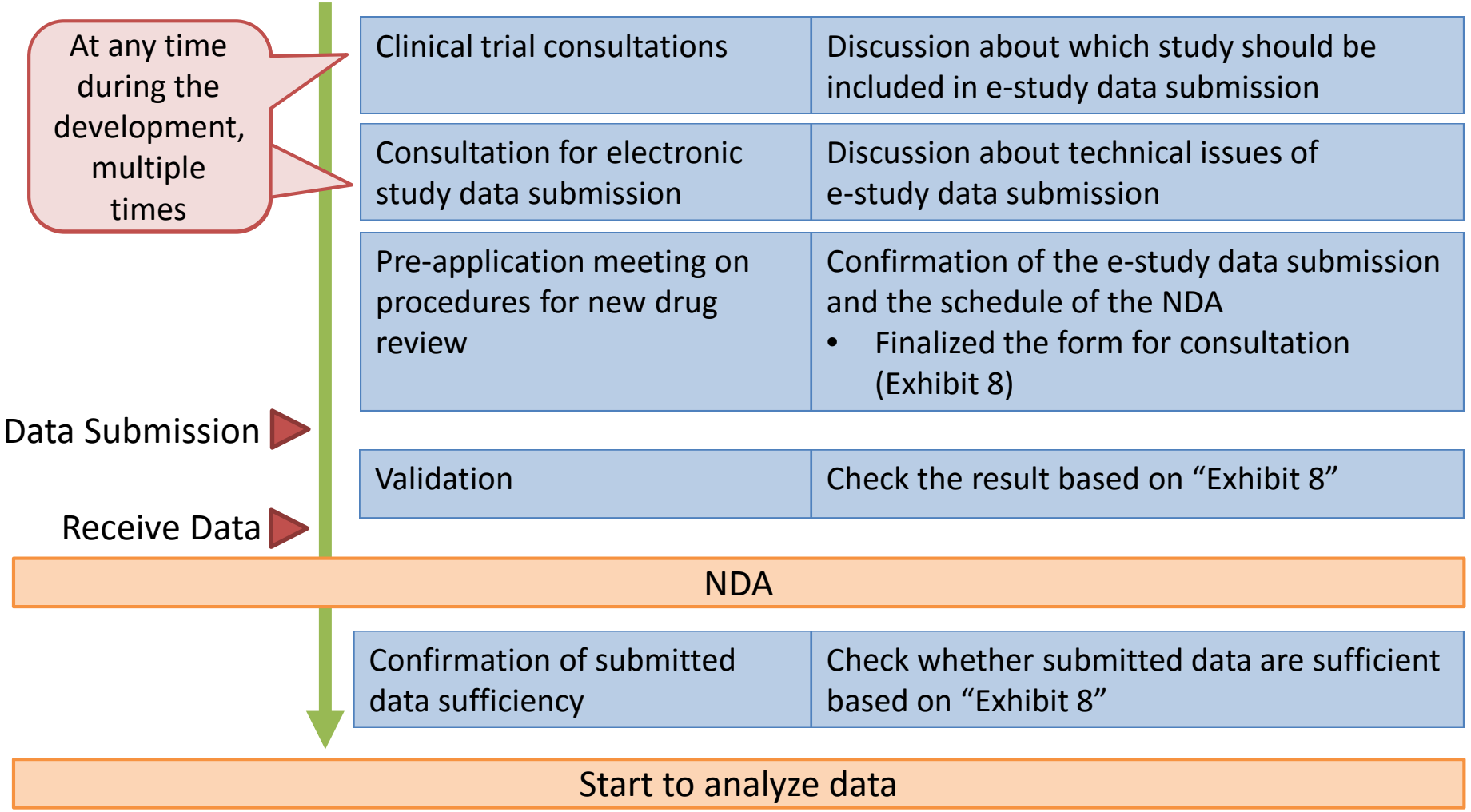
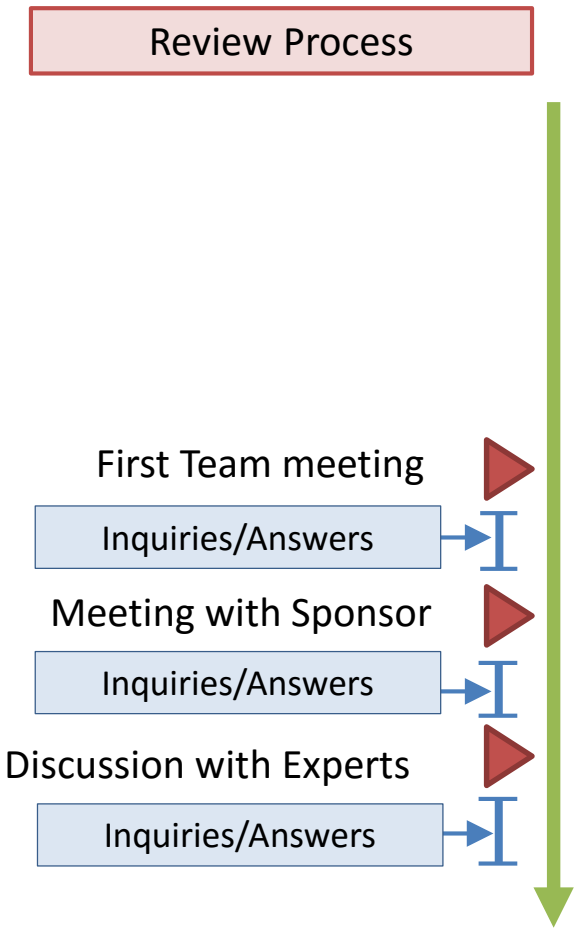
Process of starting to analyze data



Review process and data analysis



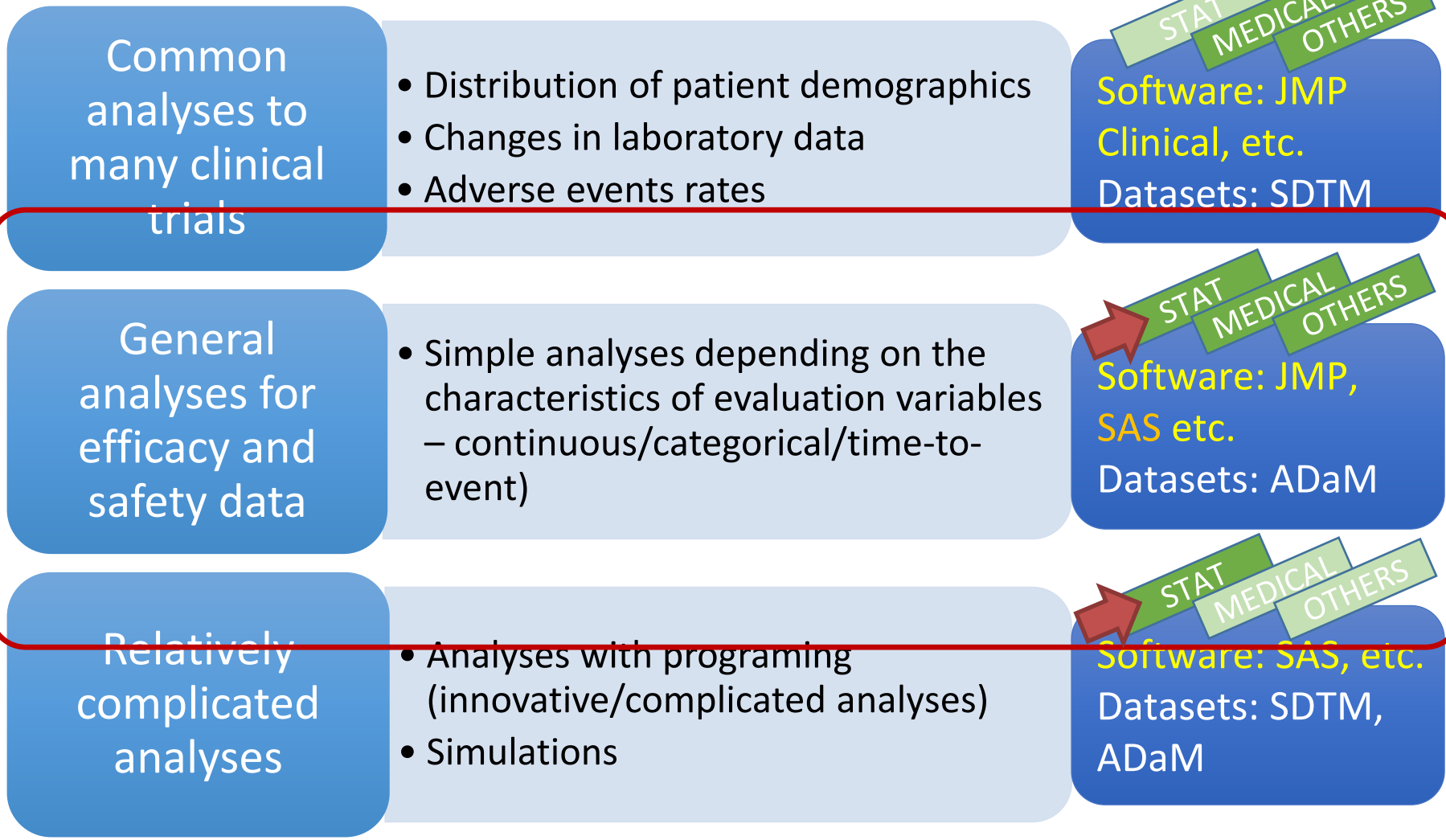
Review Process	Analysis Timing	Contents of Analyses

	Before the First Team Meeting	• Confirmation of reproducibility of the primary analysis
		• Analyses for review points
		  • Indication, dosage, etc
		  • Consistency, AE, individual patient profile, etc
		• Analysis for exploring review points
		  • Factors affecting efficacy and safety

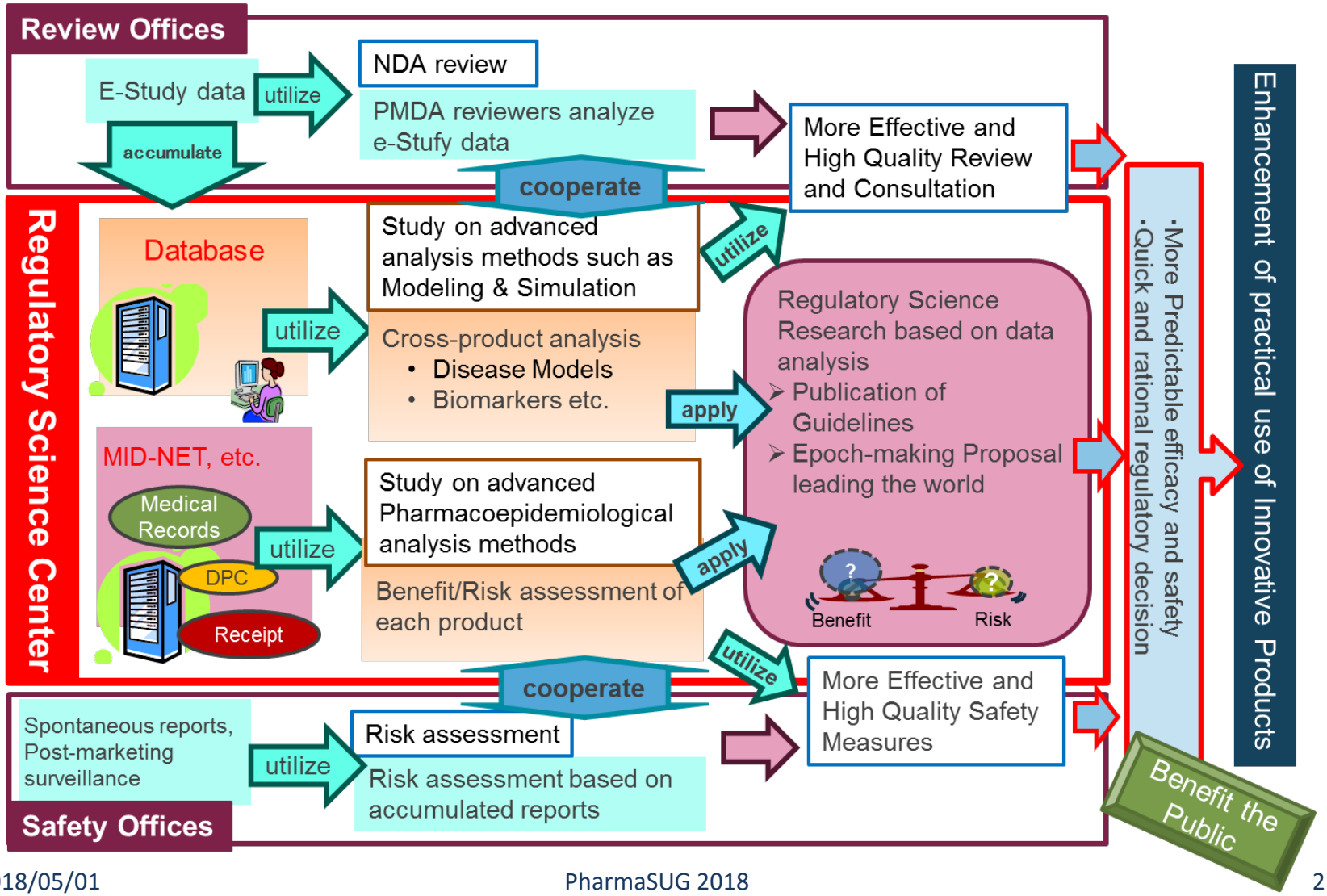
	After the First Team Meeting	• Analyses related to inquiries
		  • Consider contents of inquiries based on results of analyses
		  • Consider necessity for additional inquiries after receiving answers

	After Expert Discussion	• Additional analysis taking comments from external experts into account • Indication, dosage, special population
Completion of Review		

Analyses of CDISC data in review team

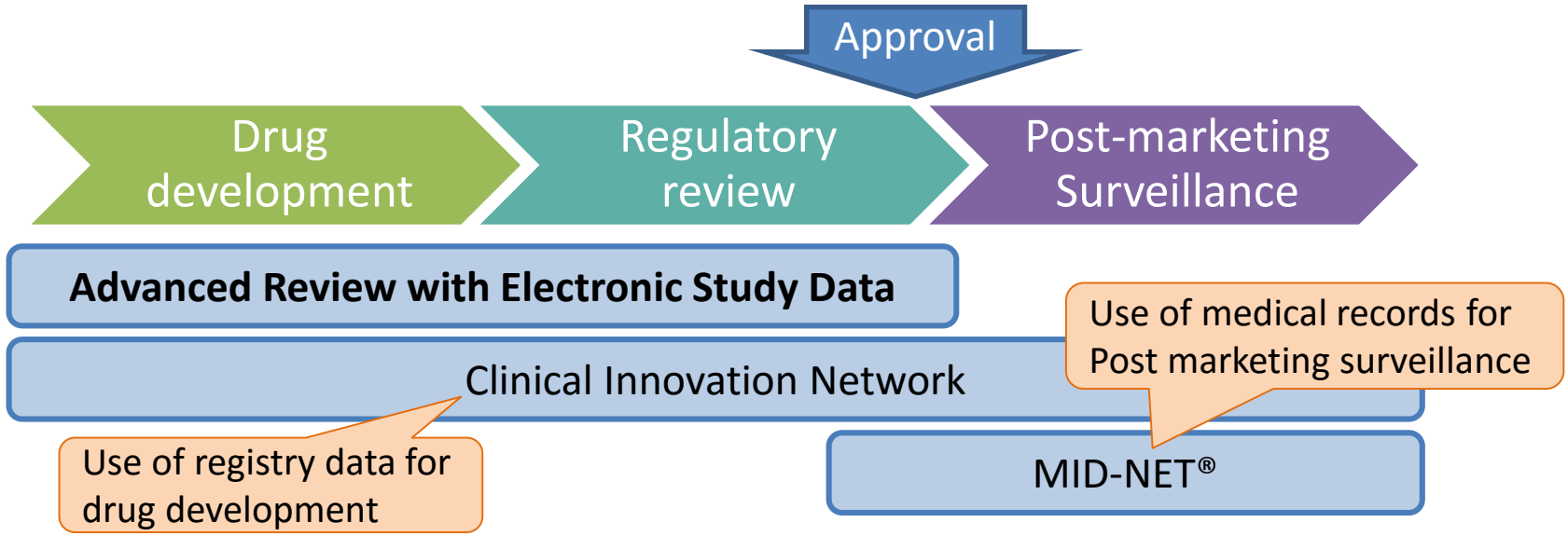


Regulatory Science Center established on Apr 1



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.



Use of data standards is the key for all the initiatives

International discussion about data sources

www.ich.org/products/gcp-renovation.html

Utilization of study data in the future

Utilization of study data for new drug review

- Improvement of predictability of efficacy and safety
- Reviewing M&S results
- Reviewing novel evaluation methods
- Swift and effective decision-making

- Data accumulation
- Experiences of data evaluation

Utilization of accumulated study data

- Information from cross-product analysis
- Active use of M&S
- Evaluation of innovative analysis methods based on the accumulated data
- Experiences of meta-analytic approach

Submission of standardized study data

- Consultation based on the cross-product information
- Guidance for therapeutic areas
- Issuance of points to considers for methodology

- Consultation/guidance about innovative analysis methods
- Contribution to data standardization

Efficient new drug development

- Use of consultation meeting based on the cross-product information by PMDA
- Active use of M&S
- Use of innovative and appropriate methods for the purpose

Use of various data sources in the future

- Importance of study quality, data quality, and data standardization
- Innovative methods for analyzing data from various data sources

Summary

- Advanced Review with Electronic Data Project is being executed successfully so far.
  - All data has been successfully received since Oct 1, 2016.
- 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.
- Utilization of various data sources will be on the table of international discussion. Data standards will be the key for the activities and further cooperation with industry, CDISC, and other regulatory agencies will be more important.
- We appreciate continual collaboration for the efficient drug development and predictability of the safety and the efficacy of the drug.