Pharmaceuticals and Medical Devices Agency, Japan

Model informed drug development : Japanese regulatory perspectives

Naomi Nagai Ph.D.
Office of New Drug IV/Advanced Review with Electronic Data Promotion Group
Pharmaceuticals and Medical Devices Agency (PMDA)

Disclaimer

The views expressed in this presentation are those of the presenter and do not necessarily reflect the official views of Pharmaceuticals and Medical Devices Agency.

Outline

- Reviews and consultations in Japan
- Review experiences of clinical pharmacology (CP) data in global drug development
  - Guidance to promote global drug development
  - Recent trends of global clinical trials(GCTs) and CP data(PPK approach, PKPD/E-R): survey on approved NMEs in Japan
  - Recent review experiences of CP data in GCTs(Asian trials)
- Future perspectives
  - Advanced review with electronic data
- Summary

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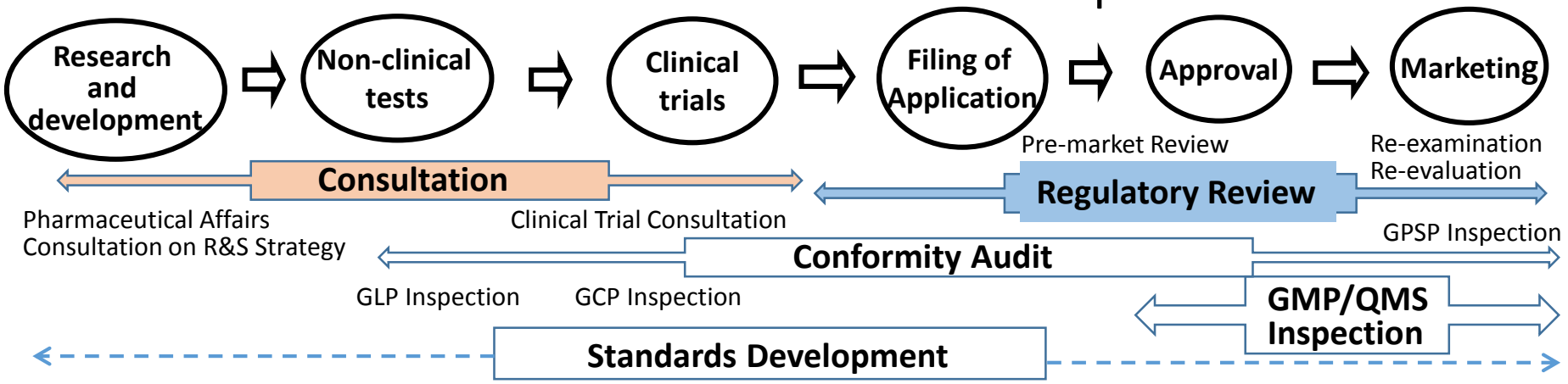
Reviews and consultations in Japan



PMDA

Scientific Review and Consultation/Safety/Relie

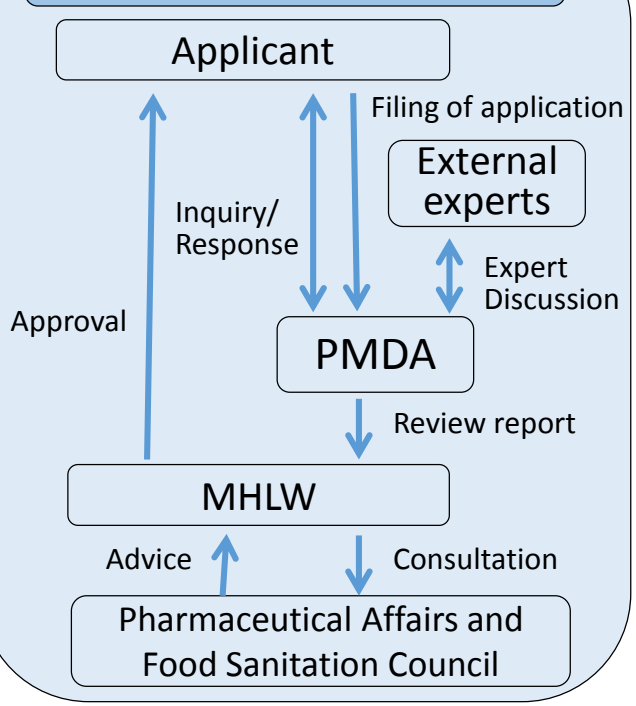
Post-marketing safety measures

Relief for adverse health effects

Consultation Meeting from Discovery to NDAs

- Non-clinical studies :animal test
- ⇩ Quality/Safety/Pre-Phase 1
- Phase I trials: healthy volunteers PK/Safety
- ⇩ Pre-Early Phase 2
- Early phase II trials: patients POC for efficacy
- ⇩ Pre-Late Phase 2
- Late phase II trials: patients Efficacy/Safety/Dose
- ⇩ End of Phase 2
- Phase III trials: patients Efficacy/Safety Confirmation
- ⇩ Pre NDA/Prior Assessment
- Filing of application

Review process for NDAs



as of April 1, 2015

Guidance to promote global drug development in Japan

ICH guideline

- E5:Ethnic Factors in the Acceptability of Foreign Clinical Data.

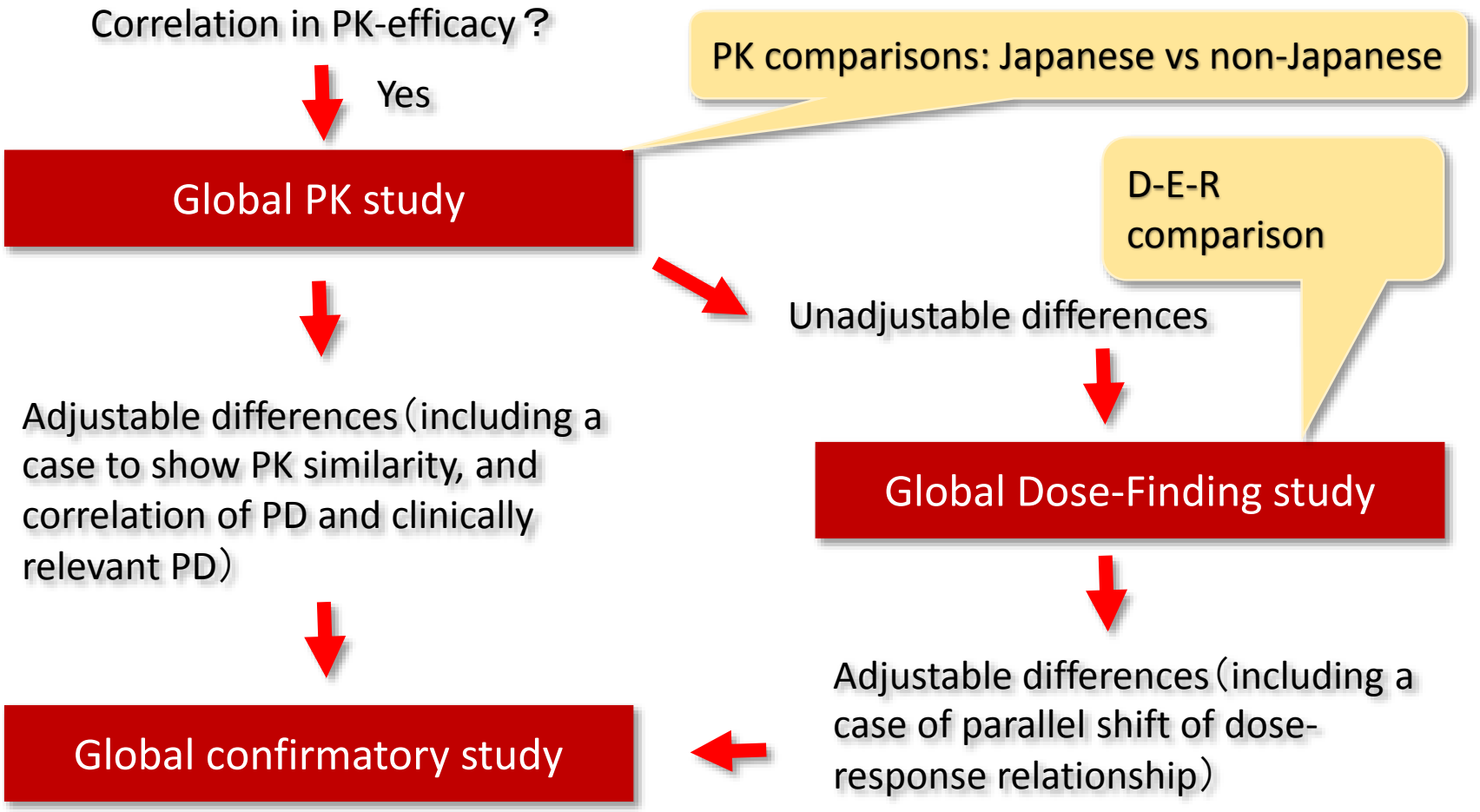
Japanese guidance document

- Basic principles on Global Clinical Trials (2007 Sept)
  - Basic requirements to conduct a Global Clinical Trial (GCT)
  - Importance of PK study prior to a GCT
  - Importance of global dose-finding study
  - Basic points to consider in designing a GCT
  - Sample size and proportion of Japanese subjects
- Basic principles on Global Clinical Trials – Reference Cases (2012)
- Basic Principles for Conducting Phase I Trials in the Japanese Population Prior to Global Clinical Trials (2014)

Impacts of global drug development on regulatory approval in Japan: literatures published by PMDA

- Successful bridging strategy based on ICH E5 guideline for drugs approved in Japan. Clin Pharmacol Ther 78,102-13(2005).
- Effective global drug development strategy for obtaining regulatory approval in Japan in the context of ethnicity-related drug response factors. Clin Pharmacol Ther 87,362-66(2010).
- Balancing societal needs and regulatory certainty : The case of peramivir in Japan. Clin Pharmacol Ther 93,342-44(2013).
- Regulatory challenges in the review of data from global clinical trials: thte PMDA perspective. Clin Pharmacol Ther 94,195-98(2013).
- How should ethnicity-related information be included on drug labels? Considerations based on comparison of multiregional clinical trial data on the label between Japan and the United States. Clin Pharmacol Ther (2015).

Basic scheme on global clinical trials including Japanese population



Dose finding/selection/adjustments Clinical pharmacology review points

- Study design for identifying the dose
  MRCTs/Asian regional clinical trials/Bridging strategy
- Specific Populations and medical practices in Japan
  Elderly population/Pediatric population/Asian population/Patients with impaired liver or renal function/Concomitant drugs etc.
- Dose-Exposure-Response (D-E-R) information
  utilization of D-E-R analysis and discussion on effectiveness and safety issues, labeling decisions, PMS and/or further development
- Utilization of analytical approaches and tools
  Population PK approach, PKPD/E-R analysis, PBPK analysis
  Modeling and Simulation

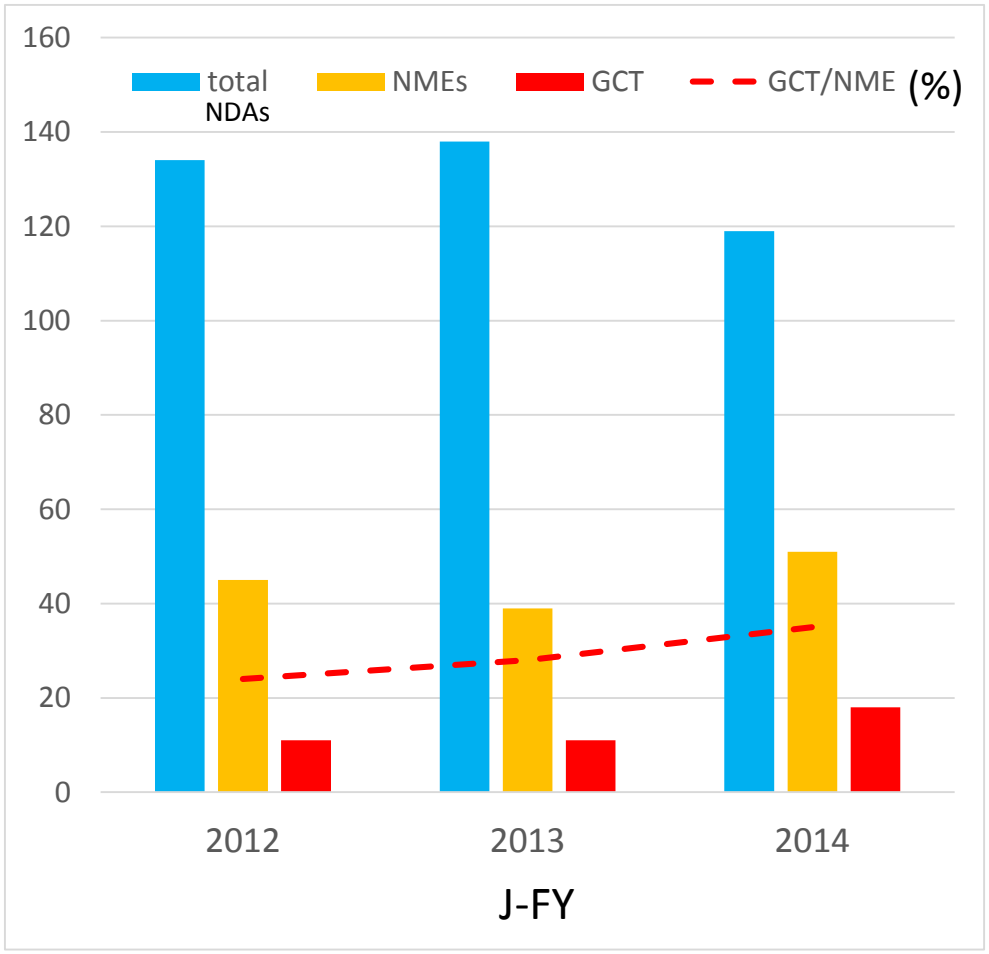
Recent trends of global clinical trials in Japan

J-FY	2008	2009	2010	2011	2012	2013	2014
Number of Notifications of GCTs	82	113	134	121	130 (556)	169 (601)	178 (601)
Number of consultations on GCTs for NMEs	51	56	66	73	64	59	67

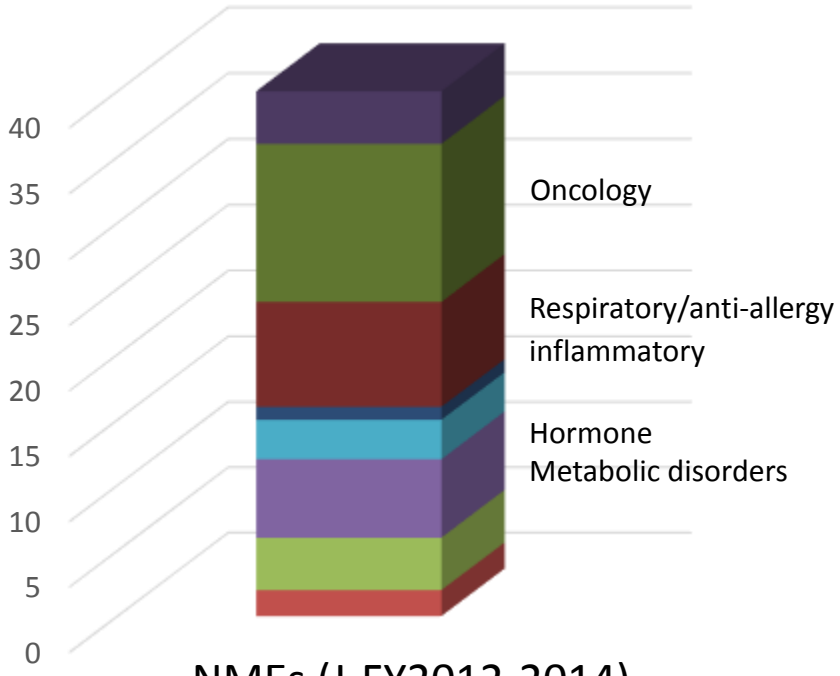
J-FY: the financial year in Japan, NMEs: new molecular entities
In J-FY 2014, of 601 clinical trial notifications submitted, 178 were for GCTs, and 67 consultations were GCTs for NMEs.
https://www.pmda.go.jp/english/about-pmda/annual-reports/0001.html

Trends of GCTs on approval reviews in Japan :
NMEs approved between 2012 and 2014

Number of approved drugs



Therapeutic Area (Category)

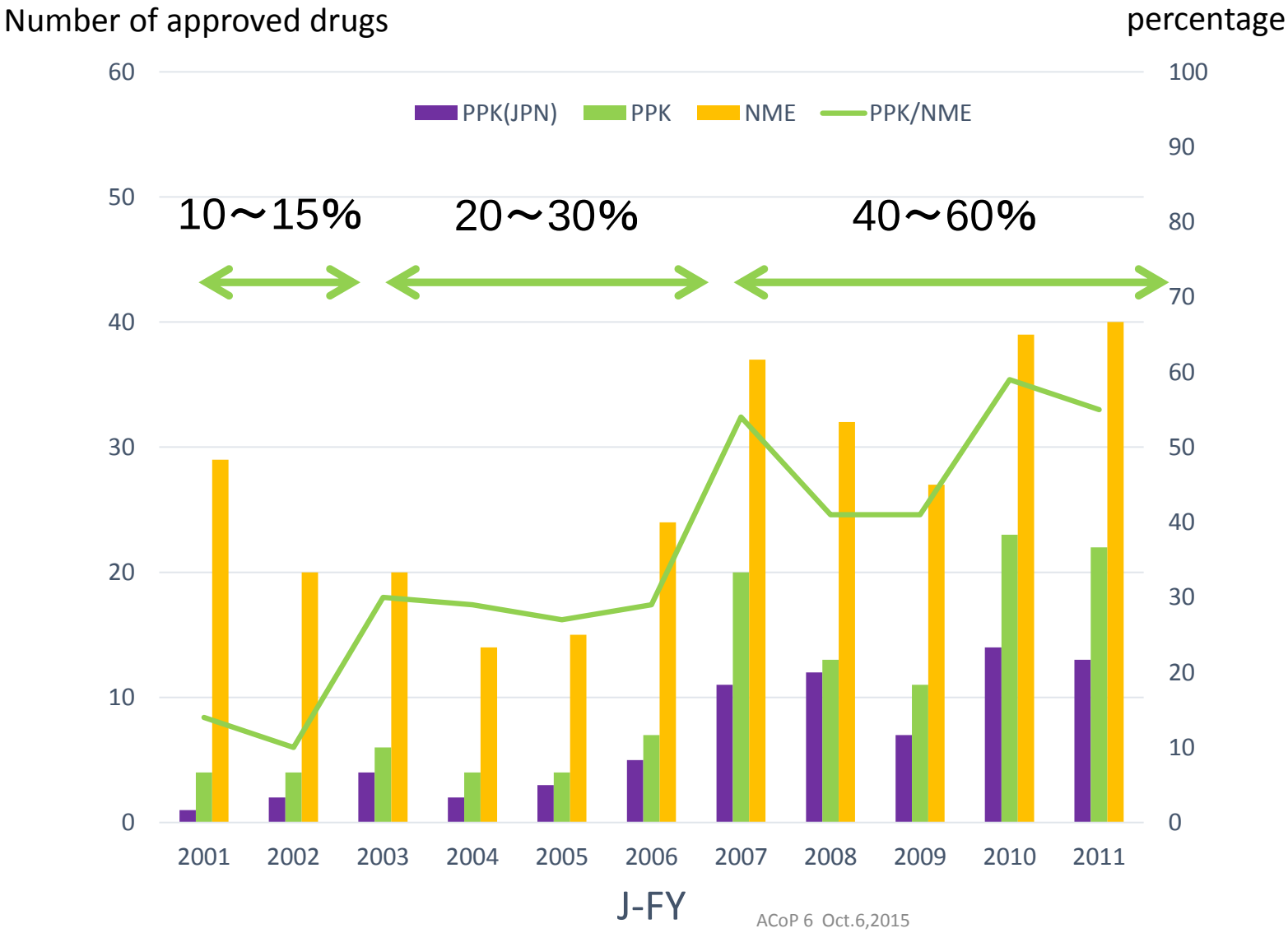


NMEs (J-FY2012-2014)

from top to bottom,
Others, Oncology, Respiratory/anti-allergy/ inflammatory, urogenital system, Anti-bacterial/viral/fungal, Hormone/ metabolic disorders, Central & peripheral nervous/anesthetic drugs, Cardio-renal,

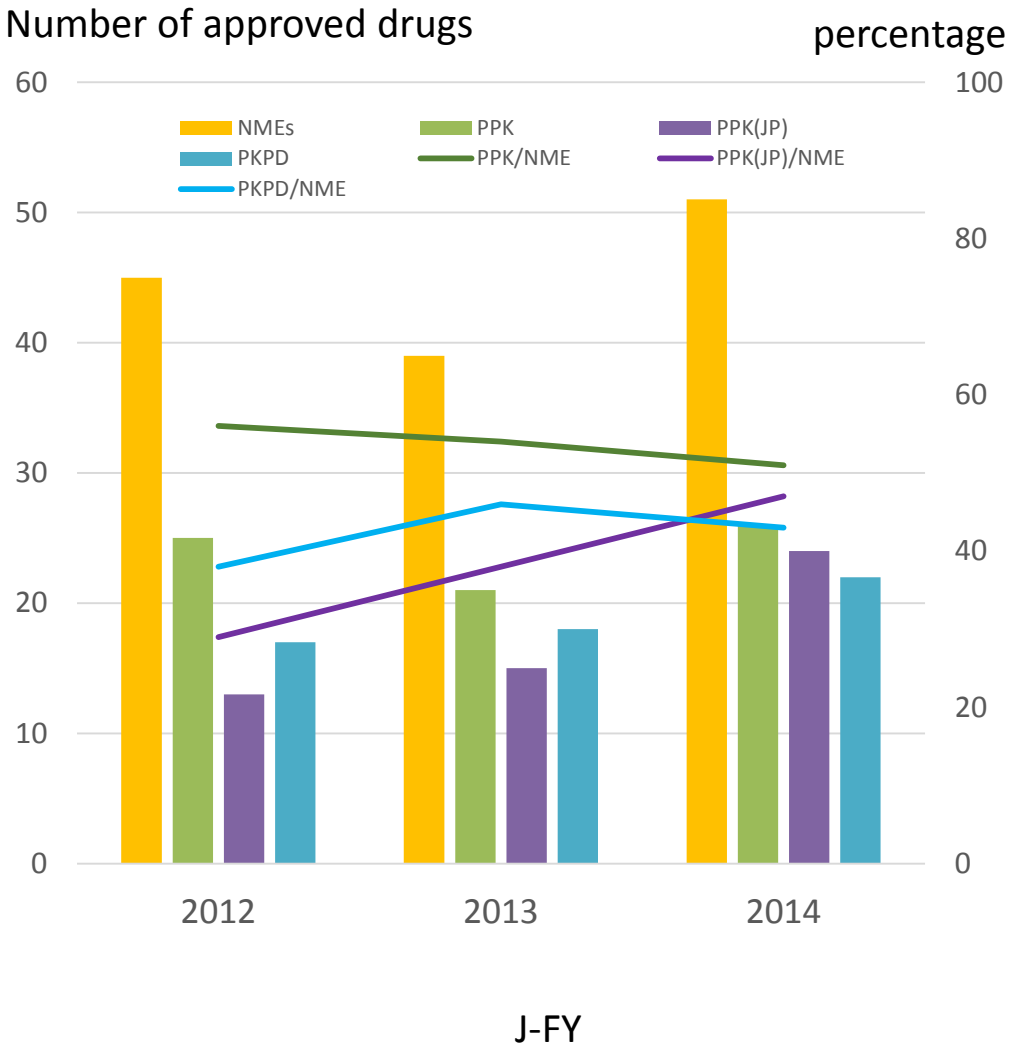
Trends of PPK approach

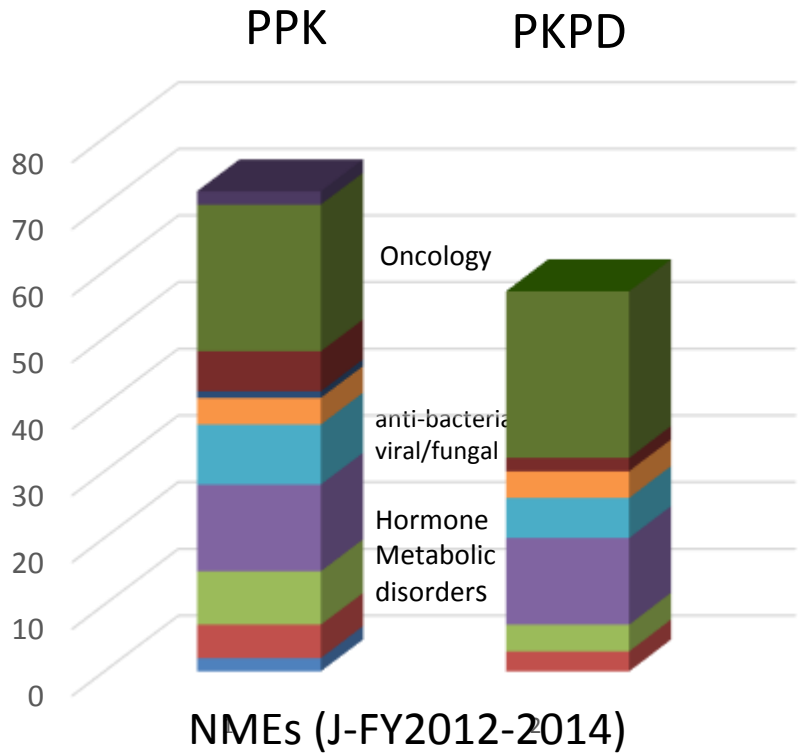
NMEs approved between 2001 and 2011



Trends of PPK approach and PKPD/E-R analysis

NMEs approved between 2012 and 2014





Therapeutic Area (category)

from top to bottom,
Others, Oncology, Respiratory/anti-allergy/ inflammatory, urogenital system, anti-HIV, Anti-bacterial/viral/fungal, Hormone/ metabolic disorders, Central & peripheral nervous/anesthetic drugs, Cardio-renal, Gastrointestinal

Summary: recent trends of GCTs and CP data in Japanese NDAs

- Number of notifications/consultations on GCTs including Japanese patients has been increasing.
- Number of NDAs(NMEs) with GCTs has been increasing
  - Of total NMEs: about 25% →30% →35%(from J-FY 2012 to 2014)
  - Development strategy: MRCTs/Asian regional trials/bridging studies
  - Development phase: not only phase 3 but also early clinical phase
  - Therapeutic Area: variety, top3 category (oncology >respiratory/allergy/inflammatory > hormone/metabolic disorders
- Number of NDAs(NMEs) with PPK approach, PKPD/E-R analysis and M&S has been increasing.
  - Of total NMEs: PPK approach, more than 50% (after J-FY 2010) PKPD/E-R analysis, about 40% (J-FY 2012-2014)
  - Therapeutic Area: variety, top3 category for both PPK and PKPD/E-R (oncology > hormone/metabolic disorders > antibacterial/antiviral/antifungal)
  - In J-FY2014, almost all NDAs for approved NMEs with PPK approach provided PPK information in Japanese population

Evaluation of Asian regional clinical trial/clinical pharmacology data in NMEs approval in Japan-1/3

NMEs (approval year)	Indication	Development strategy Asian regional clinical trial (phase)	CP data (PPK, PKPD/E-R , M&S) on approval review
Tolterodine tartrate (2006)	urinary urgency, urinary frequency and urge urinary incontinence associated with overactive bladder	Bridging Japan & Korea (III) Japan, Korea & US/EU(I)	1 and 3 (evaluated by STS approach)
Insulin glulisine * (2009)	diabetes mellitus where insulin therapy is indicated.	Type 1: Bridging Type 2: Global(Asian) Japan & Korea (III) Japan & Korea, Japan & US/EU(I)	1 and 3 (evaluated by STS approach)
Peramivir hydrate (2010)	Influenza A or B virus infections	Global(Asian) Japan, Korea & Taiwan (III)	1,2 (patients with renal impairment), 3 (within east Asia) and 4(PK Section)
Temsirolimus (2010)	unresectable or metastatic renal cell carcinoma.	Global(Asian) Japan, Korea & China (II)	1and 3 (within east Asia, US/EU vs non-US/EU)

* geneticalrecombination STS: standard two stage

http://www.pmda.go.jp/review-services/drug-reviews/review-information/p-drugs/0019.html

https://www.pmda.go.jp/english/search_index.html

1: Supporting dosing regimen for labeling, 2: Supporting dose adjustment for special population , 3: Consideration of PK and PD variabilities, including ethnic difference/similarity, 4:providing information in drug label

Evaluation of Asian regional clinical trial/clinical pharmacology data in NMEs approval in Japan-2/3

NMEs (approval year)	Indication	Development strategy Asian trial (phase)	CP data (PPK, PKPD/E-R , M&S) on approval review
Laninamivir octanoatehydrate (2010)	Influenza A or B virus infections	Global(Asian) Japan, Korea, Taiwan & Hong Kong (III)	1,2(patients with renal impairment, pediatrics) and 3 (within east Asia)
Edoxaban tosilate hydrate (2011)	prevention of venous thromboembolism in patients undergoing orthopedic surgery of lower limbsincluding total knee arthroplasty, total hiparthroplasty and hip fracture surgery.	Global(Asian) Japan & Taiwan (IIb) Japan & Taiwan (III)	1,2 (patients with renal impairment) and 3 (Japanese vs Chinese)
Indacaterol maleate (2011)	alleviation of various symptoms due to airway obstructive impairment in chronic obstructive pulmonary diseases (chronic bronchitis andemphysema).	Global(Asian) Japan, Korea, Taiwan, India, Hong Kong & Singapore (III)	1,2 (elderly patients) and 3 (US/EU vs Asia, Japanese vs non-Japanese)
Fesoterodine fumarate (2012)	urinary urgency, urinary frequency and urge urinary incontinence associated with overactive bladder	Bridging Japan, Korea, Taiwan & Hong Kong (II)	1,2 (patients with renal/liver impairment) and 3 (Japanese vs non-Japanese, within east Asia)

http://www.pmda.go.jp/review-services/drug-reviews/review-information/p-drugs/0019.html
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Evaluation of Asian regional clinical trial/clinical pharmacology data in NMEs approval in Japan-3/3

NMEs (approval year)	Indication	Development strategy Asian trial (phase)	CP data (PPK, PKPD/E-R , M&S) on approval review
Insulin degludec * (2012)	diabetes mellitus in cases where insulin therapy is indicated	Type 1: Global (MRCT) Type 2: Global(Asian) Japan, Korea, Taiwan, Thailand, Hong Kong & Malaysia (III)	1 and 3 (Japanese vs non-Japanese, within east Asia)
Ofatumumab* (2012)	relapsed or refractory CD20-positivechronic lymphocytic leukemia.[Orphan drug]	Global Japan & Korea (I/II)	1 and 3 (Japanese vs non-Japanese)
Tapentadol hydrochloride (2013)	moderate to severe pain in varioustypes of cancer	Global (Asian) Japan & Korea (I and III)	3 (mainly evaluated by STS approach)
Paliperidone palmitate (2013)	schizophrenia	Global (Asian) Japan, Korea & Taiwan (MD-PK study and III)	1(dosing regimen), 2(patients with renal impairment) , 3(within east Asia) and 4(PK Section)

* geneticalrecombination
http://www.pmda.go.jp/review-services/drug-reviews/review-information/p-drugs/0019.html
https://www.pmda.go.jp/english/search_index.html
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Summary: recent review experiences
Asian regional clinical trials/Clinical Pharmacology Data

- Review experiences of GCTs including Asian regional clinical trials have rapidly been increasing since 2009.
- Oncology is the therapeutic area where GCTs is most actively conducted for new drug development.
- Asian regional clinical trials tended to be planned and conducted in the specific therapeutic areas/indications,
  - Influenza A or B virus infections
  - Diabetes mellitus (Type 2)
  - Some anti-neoplastic drugs, nervous system drugs
- CP data obtained in Asian regional clinical trials, especially PPK, PKPD/E-R and M&S has also been increasing and actively discussed in recent approval reviews in Japan.

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Health and Medical Care Strategy

(Agreement of Chief Cabinet Secretary, Minister of Health, Labour and Welfare and other concerned Ministers; June 14, 2013)

Three Basic Principles

- Achievement of a healthy, long-lived society
- Contribution to economic growth
- Global contribution

Specific strategy

Enhancing the PMDA

- Enhancement of the Pharmaceutical Affairs Consultation on R&D Strategy
- Organizing and enhancing the consultation service in close coordination with the Drug Discovery Support Network
- **PMDA-initiated promotion of research and analysis based on clinical study data**
- Increase of the quantity and quality of the large-scale medical information database for early achievement of the 10-million data set
- Identification of an appropriate financial base for the PMDA's tasks and necessary measures

* Including more proactive proposals than those made for the Japan Reconstruction Strategy and matters not discussed therein.

Accumulation and utilization of data

NDA submission

e-Submission of data

- Submission of electronic data from clinical and nonclinical studies

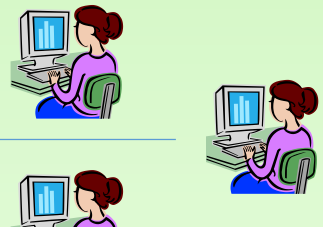
Storage of electronic data in the dedicated server and registration in the database

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

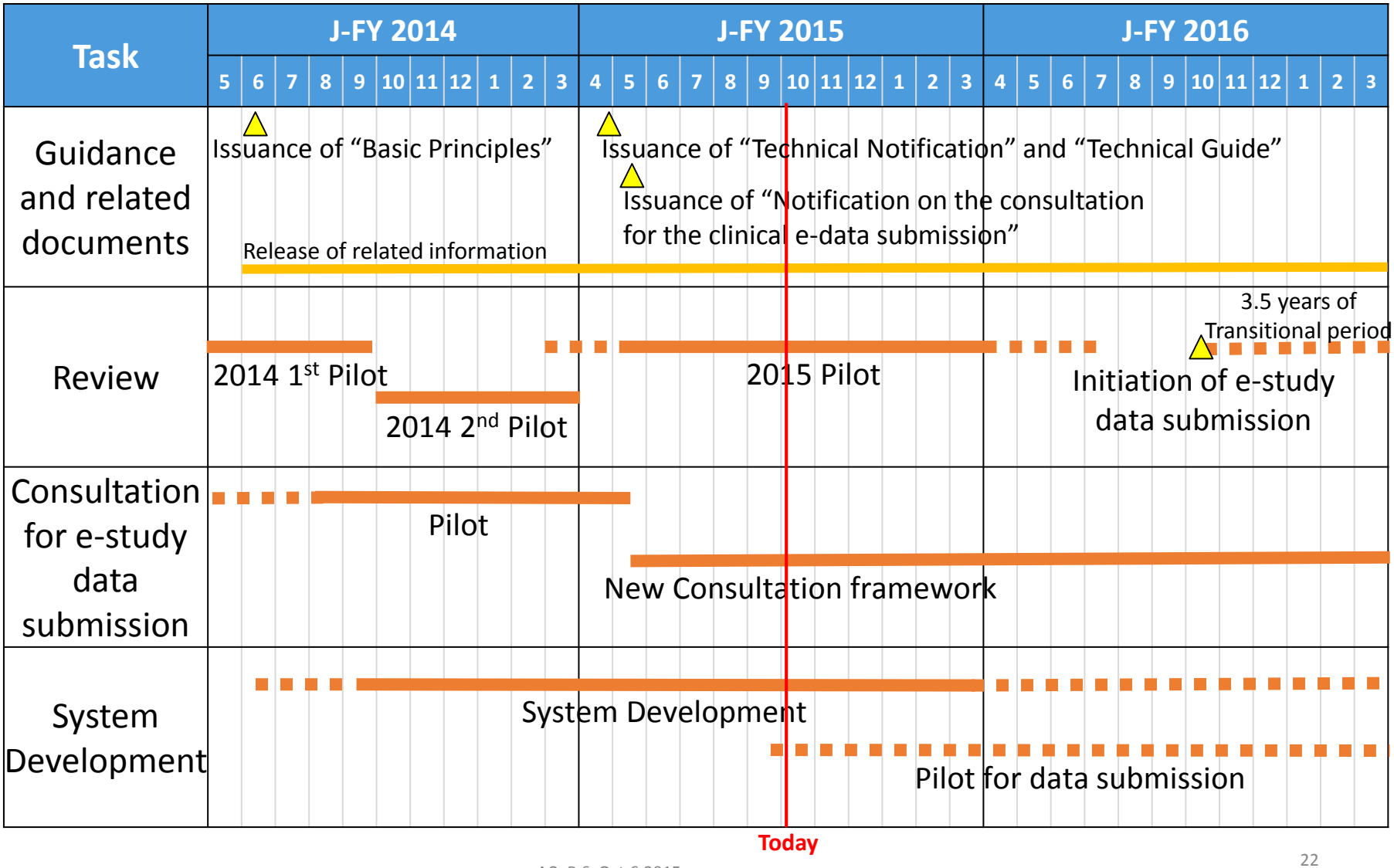
Integration of cross-products information

- 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

Timeline for implementation of electronic study data submission



Notifications and guide released for industry

- **The most recent notification and guide provide practical procedures and technical information** regarding submissions of e-study data for new drug applications.

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, Labour and Welfare	• The first official announcement that MHLW/PMDA will require electronic study data in NDA. • Both of Japanese and English versions are available on PMDA website
Technical Notification on the e-data submission* ("Technical Notification")	April 27, 2015	Ministry of Health, Labour 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

* An English version is under preparation.

“Technical Notification”: major contents

“Technical Notification on the e-study data submission” mainly covers the following contents;

1. Handling of clinical study data subject to e-study data submission
2. Format and method of e-study data submission
3. Electronic datasets to be submitted
4. Process of consultations concerning e-study data
5. Initiation timing of submissions of e-study data and transitional period

“Technical Notification”: handling of clinical study data subject to e-study data submission -1/3

The scope of documents subject to e-study data submission:

- Evaluation data that **provide the major basis for the efficacy, safety, dose and administration** (i.e. results of phase II and III studies in most cases, including long-term studies)
- The following studies in phase I studies and clinical pharmacology studies
  - Phase I studies of oncology drugs
  - Phase I studies that have been conducted on both Japanese and non-Japanese subjects
  - QT/QTc studies based on ICH E14 guideline

“Technical Notification”: handling of clinical study data subject to e-study data submission -2/3

Documents from the following studies or analyses are **also subject to e-study data submission if PMDA deems necessary**.

Study or Analysis	Example
Standard two stage analysis	• Phase I and phase II studies of antibacterial drugs, where the results of pharmacokinetics or pharmacokinetics/pharmacodynamics provide a major evidence for the dosage and administration • Clinical pharmacology studies that provide a major evidence for dosage and administration or dose adjustment in pediatric, elderly, and hepatic/renal disorder patients
Population analysis (including simulations)	• Population analysis that investigated the similarity in pharmacokinetics or pharmacokinetics/pharmacodynamics between Japanese and non-Japanese subjects in a development using global and bridging studies • Population analysis that provides a major evidence for dosage and administration
Physiologically-based pharmacokinetic model analysis (including simulations)	• Physiologically-based pharmacokinetic model analysis that provides a major evidence for dose adjustment because of drug interaction and basis for dosage and administration or dose adjustment in pediatric, elderly, and hepatic/renal disorder patients

“Technical Notification”: handling of clinical study data subject to e-study data submission -3/3

Types and Submission Formats of Documents Subject to Electronic Submission

Section in notification of the Basic Principles	Content		Individual clinical study data	Analysis dataset	
				Concerning efficacy and safety analysis	Concerning PK or PK/PD analysis
2. (2) a	Data on results from all phase II and phase III studies (including long-term studies) that are generally regarded to be the major evidence for evaluation of efficacy, safety, and dosage and administration		SDTM	ADaM	ADaM
2. (2) b Note	For study results from phase I studies and clinical pharmacology studies, results from studies listed right are required to be electronically submitted.	Phase I studies of oncology drugs	SDTM	ADaM	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	ADaM	In principle, ADaM, but other formats may be acceptable in certain cases
		QT/QTc studies based on ICH E14 guideline	SDTM	ADaM	ADaM
2. (2) Note	Phase I and clinical pharmacology studies other than a and b, which were deemed necessary by PMDA	Clinical studies where standard pharmacokinetic analysis was performed	SDTM	ADaM	ADaM is preferable, but other formats are acceptable
		Population analysis	May be submitted in formats other than CDISC standard		
		Physiologically-based pharmacokinetic model analysis			
2. (2)	References other than a and b, which were deemed necessary by PMDA		SDTM	ADaM	ADaM
			*If necessary, consult beforehand）		
2. (2)	Integrated summary of safety and efficacy (ISS/ISE)		SDTM	ADaM	ADaM
			**In principle, submission of the analysis dataset by ADaM is required, but if the SDTM dataset had been used for analysis, submission of SDTM study data is acceptable		

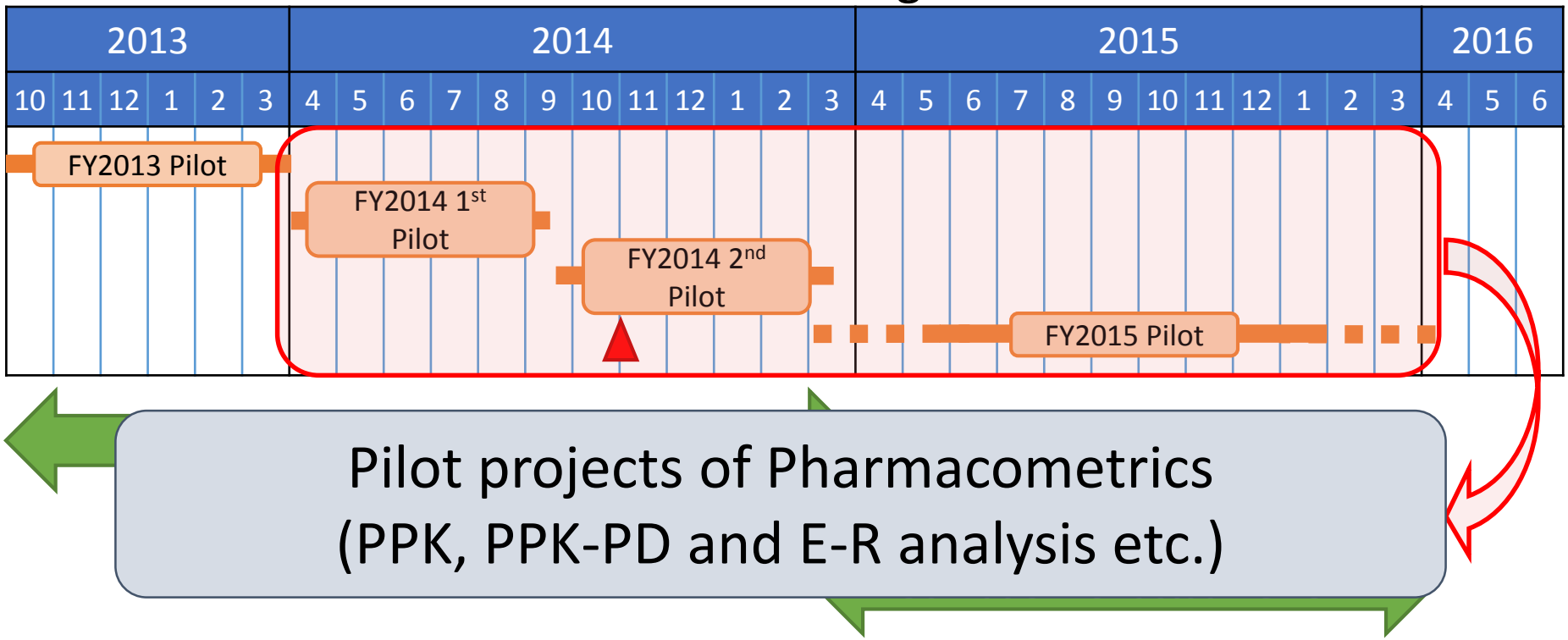
Development of related guidelines in Japan

The Working Group has been discussing on M&S related issues since October, 2014

- Population Pharmacokinetics
  - Updating existing document and establishing best practices/guidance in population analysis
  - Guidance publication in J-FY2015 (tentative schedule)
- D-E-R Relationships and Modeling
  - New guidance development
  - Drug development strategy and clinical study plan for pediatric patients
- Cross-Product Analysis
  - Discussion on the therapeutic areas
  - General considerations

Pilot projects for utilization of electronic data

- Step-by-step implementation of pilot projects
  - Confirmation of feasibility
  - Consideration of data utilization in the review process
  - Pilot intended for actual new drug review



Overview of the pilot projects

Now in Progress

	J-FY2013	J-FY2014-1	J-FY2014-2	J-FY2015
Purpose	Feasibility	Feasibility & utilization of study data in review process	Utilization of study data in review process	Utilization of study data for actual review
Target studies	5 drugs	CDISC: 4 drugs CP: 3 PPK datasets	CDISC: 3 drugs CP: 3 PPK/PD datasets	CDISC: 13drugs CP: Standard Two-Stage Approach: 4 datasets Population Approach : 7 datasets (As of May 29,2015)
Persons in charge	Around 80 reviewers + 20 from promotion group	Around 180 reviewers + 20 from promotion group	Around 190 reviewers + 20 from promotion group	Around 190 reviewers + 20 from promotion group (tentative)
Details	- All the reviewers try to reproduce the several analysis results in CTD	- All the reviewers try to replicate the main analysis results in CTD - Team meetings for the discussion on the review process with data analysis	- Some reviewers including biostatisticians in each review team are assigned mainly handle the data analysis - Team meetings for the discussion on the necessary analyses for the review and the review process with data analysis	- Pilot project which is almost parallel with actual new drug review - The pilot project will NOT affect the actual regulatory review of the drug

Prospect of e-study data utilization in Japan

Prospect As of Oct, 2015
(Subject to Change)

Present
J-FY2015

J-FY2016

Setup e-data management and utilization

Start e-study data submission for NDA* from Oct 1st, 2016

*NDA=New Drug Application

- e-study data can be received and managed appropriately
- e-study data can be utilized in the review
- Industries' workload is reduced gradually while keeping the same review period

Promotion of paperless operation

J-FY2018

Ordinary utilization of e-data in the product review

- More predictable efficacy/safety
- Consideration of expanding the scope of e-data utilization to toxicological study and post-approval clinical study

J-FY2019 - 2021

Starting earnest cross-product analysis

Transitional period are taken until March 31st, 2020

- Preparations of guidelines and related documents
- Earnest on cross-product analysis and development of disease models

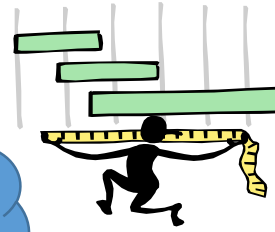
J-FY2022 -

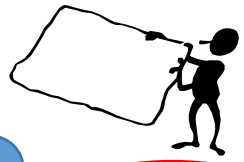
Publication of guidelines to contribute to drug development

- Establishment of disease models
- Publication of disease-specific guidelines

First-class review authority

e.g. guidelines and disease models based on data on Asian population





Summary

- Regulatory experiences and current status on GCTs including Asian trials and CP data(PPK, PKPD/E-R) are presented.
- PMDA/MHLW have continuously been updating regulatory guideline, “Basic principles on Global Clinical Trials” to promote efficient drug development in Japan.
- Advanced Review/consultation with Electronic Data Project is being executed successfully so far.
  - Publication of the Basic Principles, Technical Notification, and Technical Guide
  - Experiences of the step by step pilot projects
  - Active discussion with industry and academia
- We will proceed our project to promptly reach future goal, such as high quality reviews/consultations as well as implementation of cross product analysis to develop disease models/new guidelines based on data on Asian population.
- We believe effective utilizations of submitted electronic data and PMx approach lead to efficient drug development and more predictable efficacy/safety evaluation, and finally benefit the public.

Thank you for your attention!

PMDA Homepage

http://www.pmda.go.jp/english/index.html

PMDA Advanced Review with Electronic Data Promotion Group

E-mail: jisedaiPT@pmda.go.jp

http://www.pmda.go.jp/english/review-services/reviews/advanced-efforts/0002.html