

Role of Pharmacometrics in Drug Development and Regulatory Review: PMDA perspectives



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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

- Introduction
- Guidelines and review experiences
- Future perspectives
- Summary

Introduction

- Model informed approaches and global clinical trials are expected to improve drug development.
- Various approaches are utilized.
 - Multi-regional clinical trials/Asian clinical trials
 - Population analysis
 - Physiologically based pharmacokinetic model analysis
 - Modeling and simulation
 - Adaptive design etc.
- Global utilization/sharing of clinical data based on understanding of ethnic difference/similarity and appropriate applications of new methodology will contribute to more efficient drug development and more scientific regulatory decision-making.

Relevant guidelines and documents

MHLW (Ministry of Health, Labour and Welfare)

- Clinical PK studies of Pharmaceuticals (2001) and reference document including Pop PK (2003)
- Basic principles on Global Clinical Trials (2007, 2012, 2014)

ICH guidelines

- E4 (Dose – Response), E5 (Ethnic factors), E7 (Geriatrics), E11 (Pediatrics), M4 (CTD) E15 and 16 (Pharmacogenomics, Biomarkers)

Clinical Pharmacokinetic Studies of Pharmaceuticals

(1 June 2001)

6.2.2 Population Pharmacokinetic Approach

- This approach is considered suitable for special population such as the elderly and children.
- Representative values of pharmacokinetic parameters of population, factors that affect pharmacokinetics, the degree of the effects and inter- and intra-individual variability can be obtained from a population analysis that is appropriately planned and implemented.

Guideline on Population Pharmacokinetics and Pharmacodynamics (Draft)

Table of Contents

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- Data handling
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- Model qualifying

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- Clinical trial design

4. Reporting and providing information

- Population analysis reports
- CTDs
- Package inserts

5. Relevant guidelines and documents

6. Glossary

(draft for asking comments, Dec.2015)

Guidance to promote global drug development in Japan

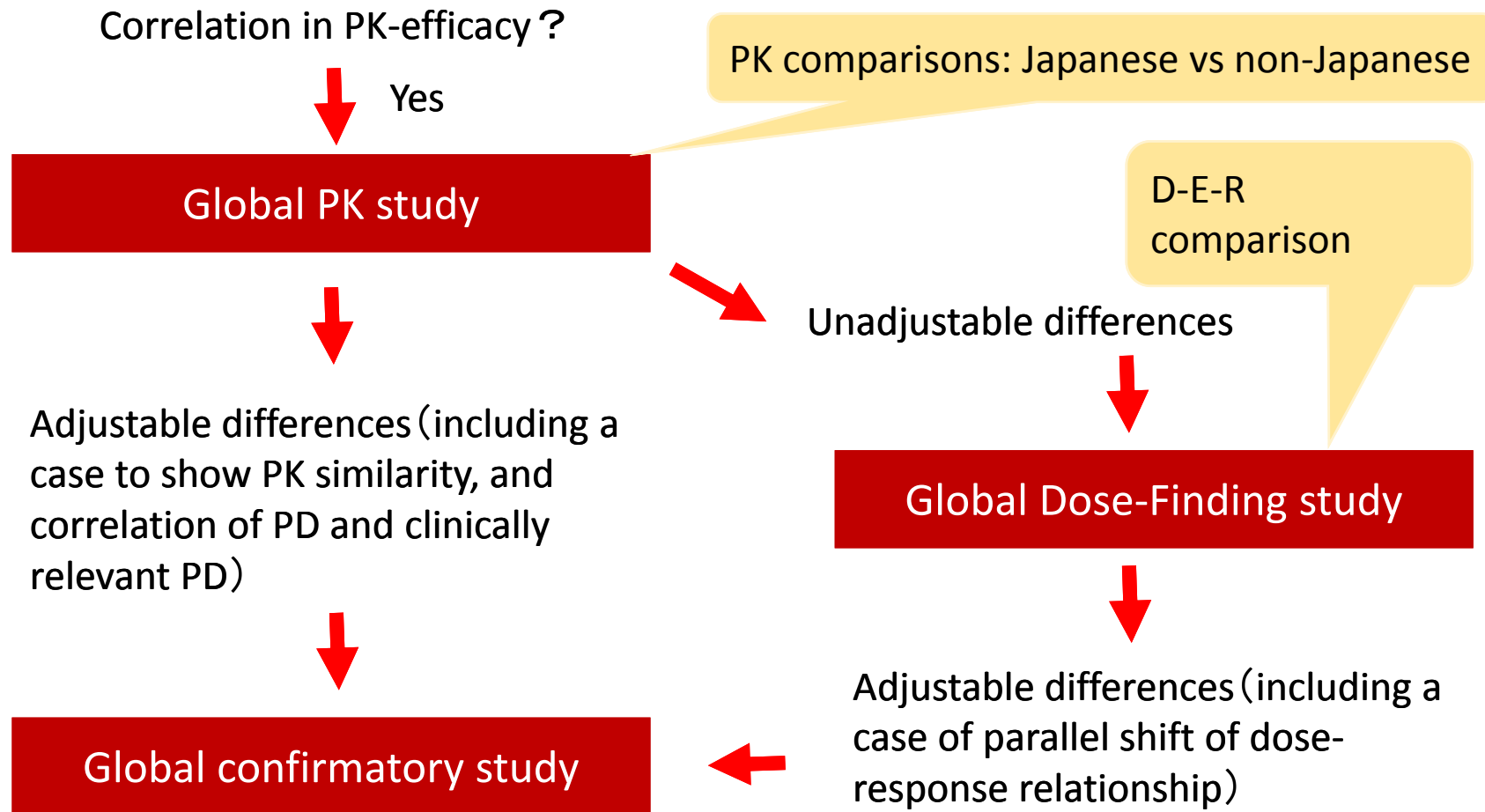
ICH guideline

- 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)

Basic scheme on global clinical trials including Japanese population

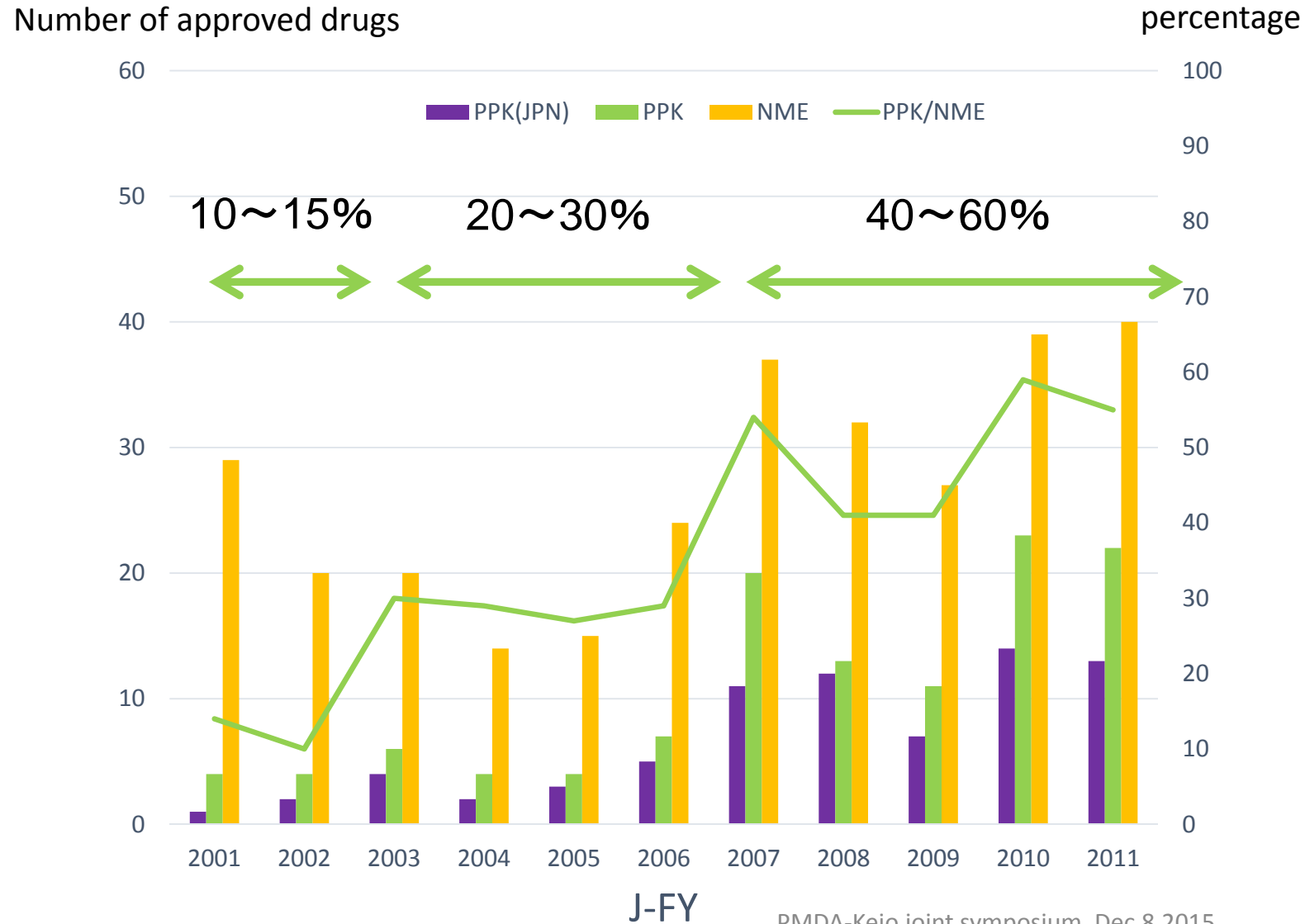


Dose finding/selection/adjustments

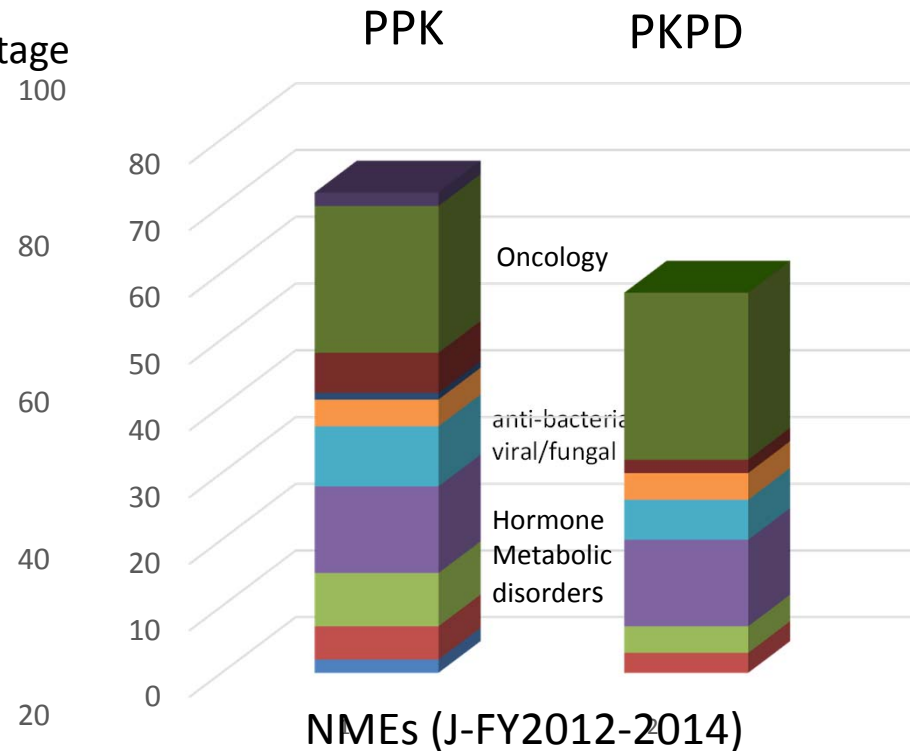
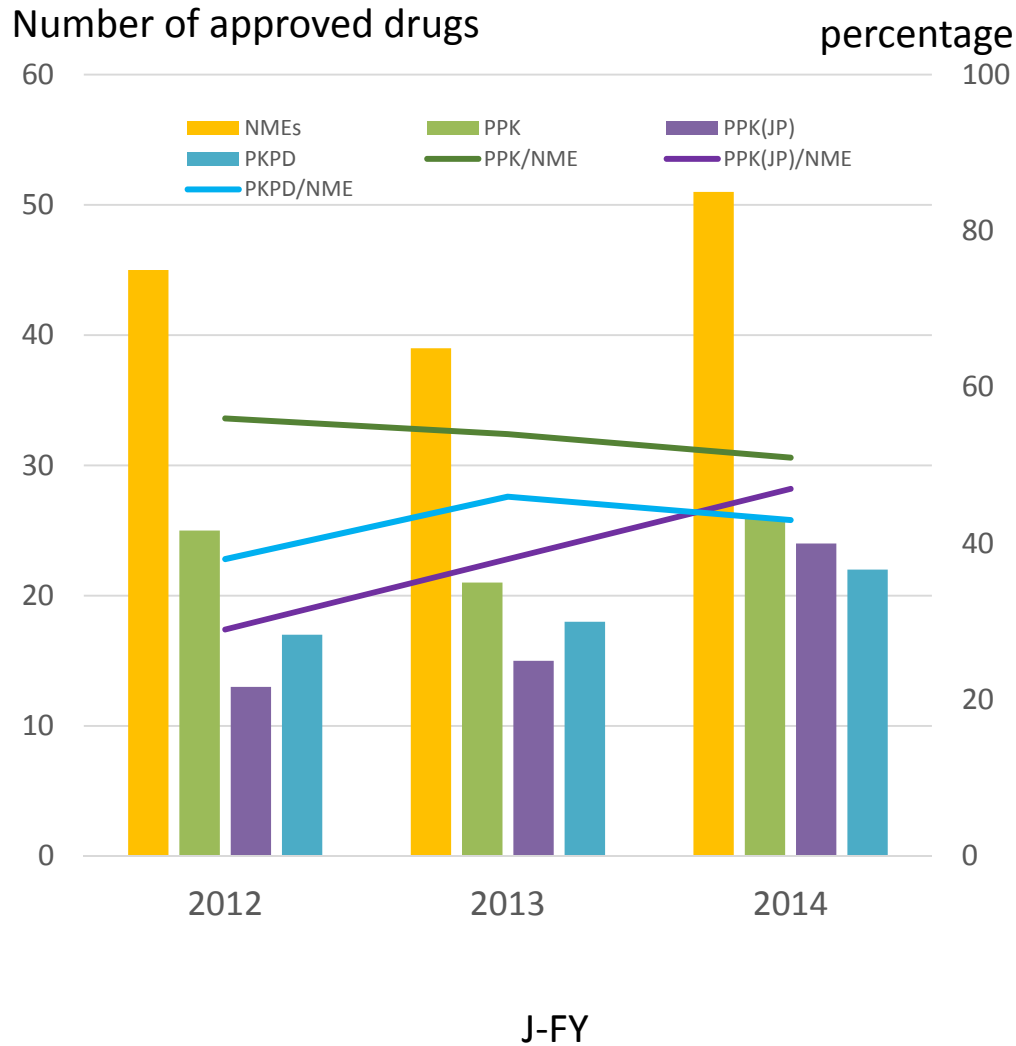
Clinical pharmacology review points

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

Trends of Population PK analysis NMEs approved between 2001 and 2011



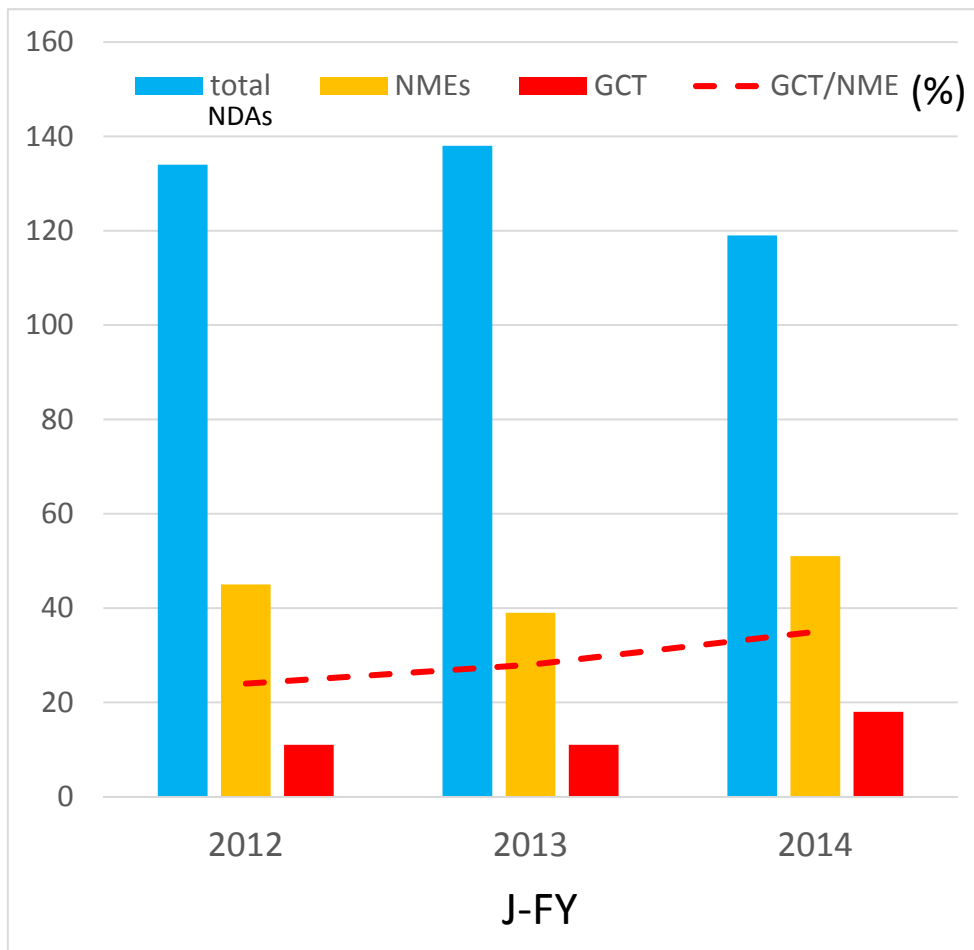
Trends of Population PK and PKPD/E-R analysis NMEs approved between 2012 and 2014



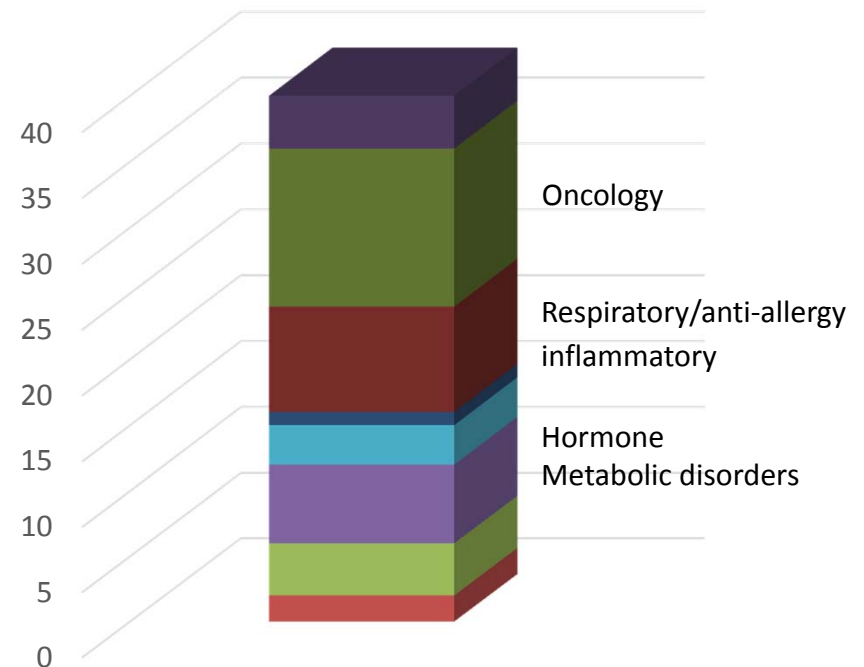
Therapeutic Area (category)
 from top to bottom,
 Others, Oncology, Respiratory/anti-allergy/
 inflammatory, urogenital system, anti-HIV,
 Anti-bacterial/viral/fungal, Hormone/
 metabolic disorders, Central & peripheral
 nervous/anesthetic drugs, Cardio-renal,
 Gastrointestinal

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,

Review experiences in PMDA

NDA (approval year)	Indication	Development program (phase, region)	Pop PK, PKPD/E-R , PBPK and M&S evaluation on approval reviews
Peramivir hydrate (2010)	Influenza A or B virus infections	MRCTs (phase 3:Japan, Korea and Taiwan) Pediatrics	1,2(patients with renal impairment, pediatrics) 3 (within east Asia) and 4 (Precaution, PK Section)
Voriconazole (2014)	Fungal infections (serious,intolerant or refractory)	Local (phase 2: Japan) pediatrics, additional dosage form (oral suspension)	1,2 (pediatrics, patients with renal impairment) 3 (CYP2D6 phenotype, non-linear PK) and 4(PK Section)
Paliperidone palmitate (2013)	Schizophrenia	MRCTs (phase 3, MD-PK study: Japan, Korea and Taiwan)	1(dosing regimen), 2(patients with renal impairment) , 3(within east Asia) and 4(PK Section)
Panobinostat Lactate (2015)	Multiple myeloma	MRCTs (phase 3: 34 countries/regions including Japan)	1,2 (drug interactions) , 3 and 4(PK Section)

<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 dose and administration in approval labels, 2: Supporting dose adjustment for special population, 3: Consideration of PK or PD variability, including ethnic difference/similarity, 4:providing information in drug labels

Role of Regulatory Science

Importance of providing various tools (MRCTs, M&S etc)

Balancing Societal Needs and Regulatory Certainty: The Case Study of Peramivir in Japan

T Tominaga¹, Y Ando¹, N Nagai², J Sato¹ and T Kondo³

Regulators must balance societal and medical requirements against the need for certainty about benefit and risk for new medicines. This is described in a case study of the expedited review and approval of peramivir, a novel neuraminidase inhibitor, in Japan in the context of the emergence of new strain of influenza in 2009. The case illustrates the importance of regulatory science and transparency in supporting such decision making.

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Role of regulatory science

Regulatory science provides various tools used for development, review, and postmarketing assessment of drugs as stressed in the US Food and Drug Administration's Critical Path Initiatives.⁶ The development and review of peramivir were informed by regulatory science in several ways.

Conclusion

Drug regulators are often faced with a challenge of balancing the public's need for access to new medicines with the need for certainty. This can result in situations in which a previously uncharacterized adverse event can significantly change the benefit:risk profile of an approved medicine. Consideration of societal and medical needs, regulatory science, and transparency in regulatory decision making are crucial for building a regulatory framework that encourages innovation, enables balanced decisions, and maintains public confidence.

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



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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

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
<u>Basic Principles</u> on Electronic Submission of Study Data for New Drug Applications (“Basic Principles”)	June 20, 2014	Ministry of Health, Labour and Welfare	<ul style="list-style-type: none"> • 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
<u>Technical Notification</u> on the e-data submission (“Technical Notification”)	April 27, 2015	Ministry of Health, Labour and Welfare	<ul style="list-style-type: none"> • 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
<u>Technical Conformance Guide</u> (“Technical Guide”)	April 27, 2015	PMDA	<ul style="list-style-type: none"> • Explains technical details regarding e-study data submission • Subject to updates based on the accumulated experience and/or the revisions of the data standards

“Technical Notification”: handling of clinical study data subject to e-study data submission -1/2

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 -2/2

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	<ul style="list-style-type: none">• 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)	<ul style="list-style-type: none">• 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)	<ul style="list-style-type: none">• 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

M&S in regulatory decision making

Framework for M&S evaluation will be established in J-FY2016.

Objectives

- Scientific discussion on M&S issues
 - Clinical trial consultation
 - NDA review
- Sharing of knowledge and experiences across multi-offices/professionals
- International regulatory collaboration on M&S issues

Experts

- Clinical Pharmacology
- Biostatistics
- Clinical
- Others

Co-operation with other projects in PMDA

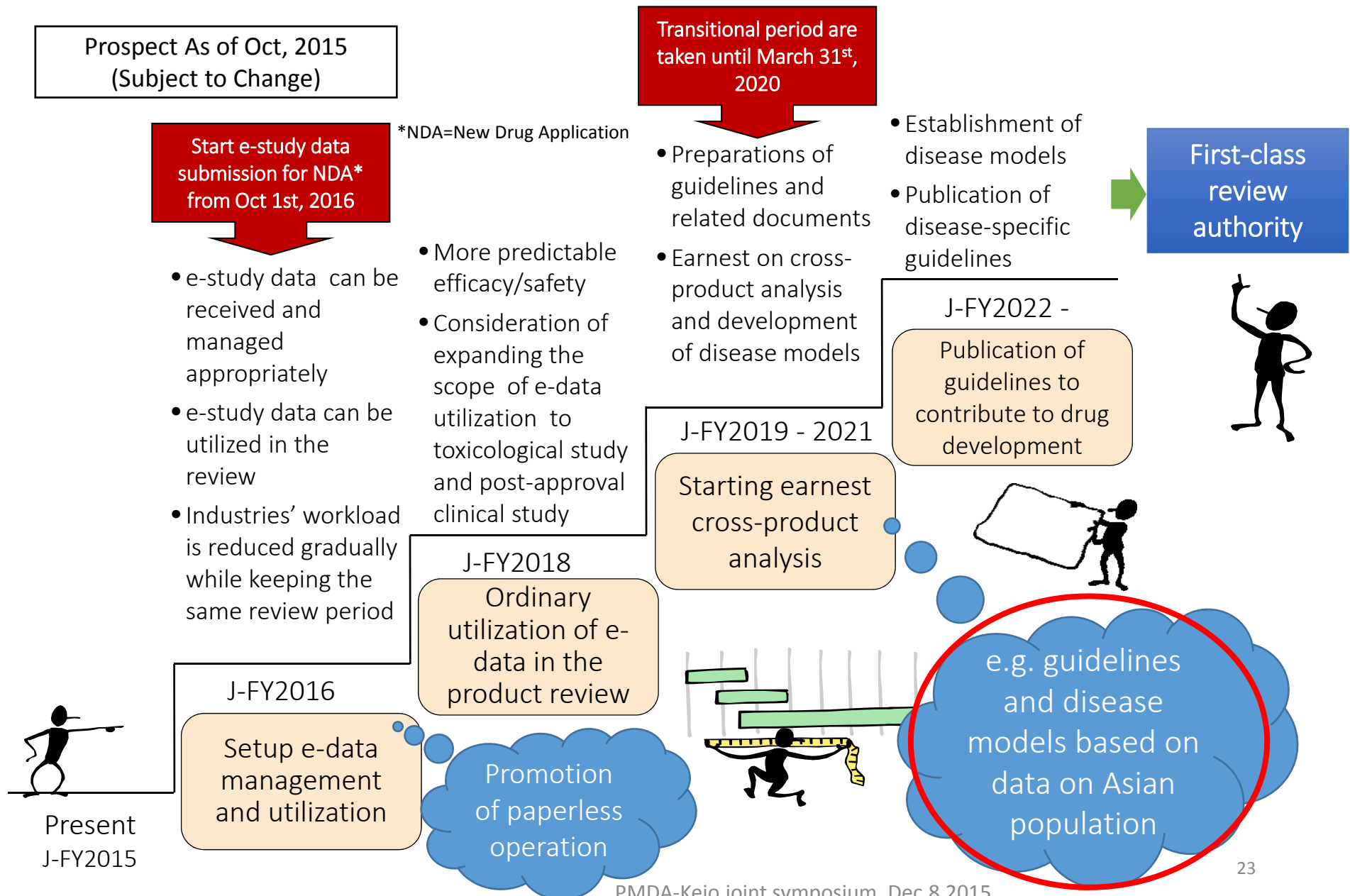
- Advanced review with Electronic Data Promotion Group
- Pediatric WG
- Orphan WG

Guideline development

PMDA-Keio joint symposium Dec.8,2015

- Population Pharmacokinetics:
 - Updating existing document and establishing best practices/guidance in population analysis
 - Guidance publication in FY2016 (tentative schedule)
- D-E-R Relationships and Modeling:
 - New guidance development
 - Drug development strategy and clinical study plan for rare disease and pediatric patients
- Cross-Product Analysis:
 - Discussion on the therapeutic areas
 - General considerations

Prospect of e-study data utilization in Japan



Summary

- Regulatory experiences and current status on pharmacometric review in Japan are presented.
- Advanced Review/consultation with Electronic Data Project is being executed successfully so far.
 - Publication of regulatory documents
 - Experiences of the step by step pilot projects
 - Active discussion with industry
- PMDA will proceed e-study data utilization to reach future goal, such as high quality reviews/consultations and implementation of cross product analysis to develop disease models/new guidelines.
- PMDA believe effective utilizations of submitted electronic data and PMx approach lead to more 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

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