Regulatory Evaluation and Perspectives on Dose-Exposure-Response Information in New Drug Applications

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Disclaimer

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

Outline

- Introduction:
  - Finding the dose for Japanese subjects
  - Guidance to promote efficient drug development
- Example and current status
  - NDA review: suvorexant
  - PK-PD(D-E-R) information in the NDAs
- Future perspectives:
  - About advanced review/consultation
  - Pilot projects for advanced review
  - Guideline development
- Summary

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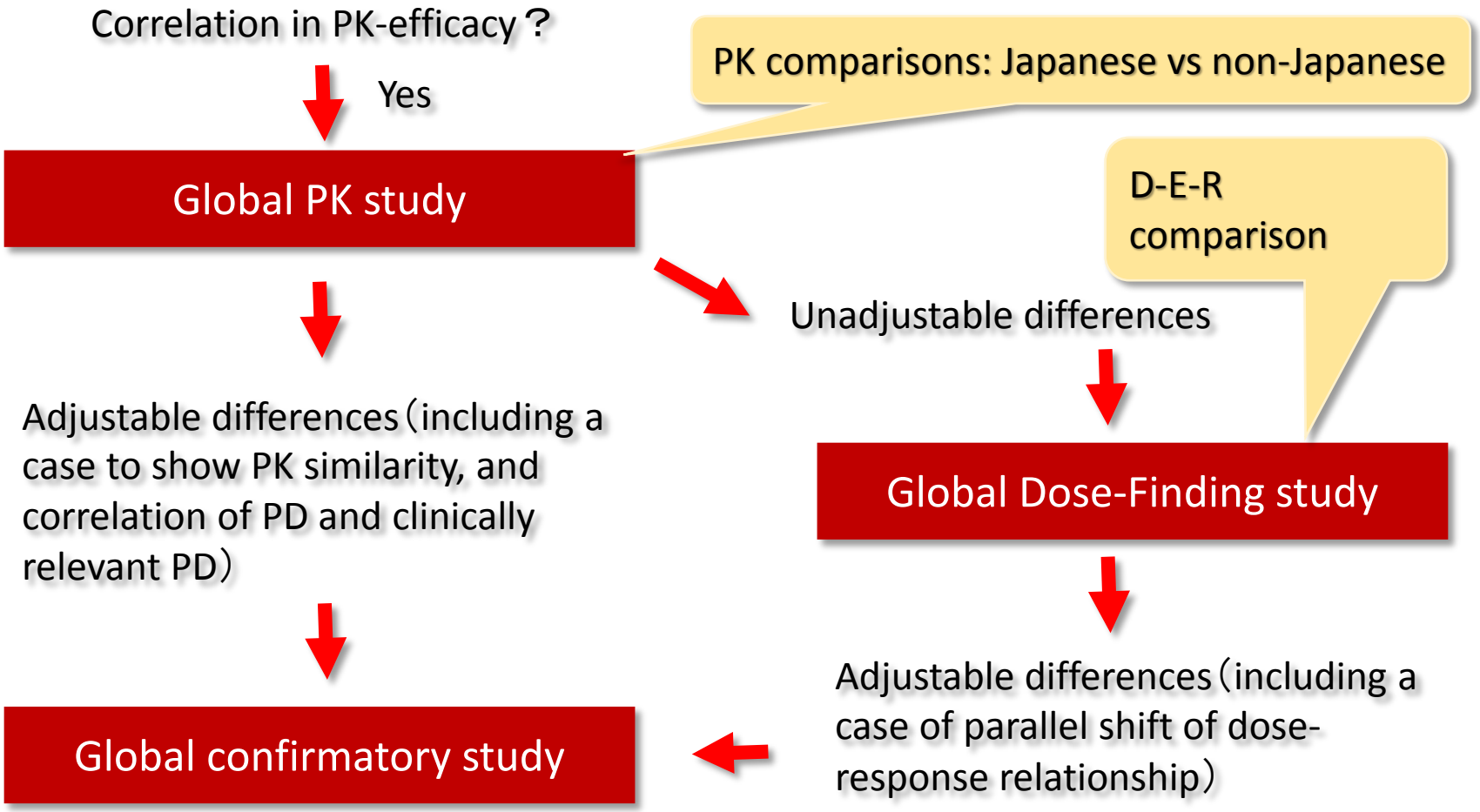
Finding the Appropriate Dose for Japanese Subjects

- Generally…
  - Definitive dose-response is not established in Ph2 studies
  - Sometimes the Ph2 endpoint differs from Ph3.
- In addition, to select a adequate dose range for licensing in Japan….
  - Understand the D-E-R data and ADME.
  - Consider the possibility that D-E-R or ADME may differ between Japanese and non-Japanese.

Guidance to promote efficient drug development in Japan

- Japanese guidance document “Basic principles on Global Clinical Trials” (2007 Sept)
  - Basic requirements to conduct a 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 GCT including Japan



Global dose finding study

- D-E-R may differ across differing populations and regions.
- Where differences in D-E-R are known and understood, doses may be adjusted by population and regions to provide equivalent dose in GCT.
- To understand the differences in D-E-R between Japanese and non-Japanese, global dose finding study is important.

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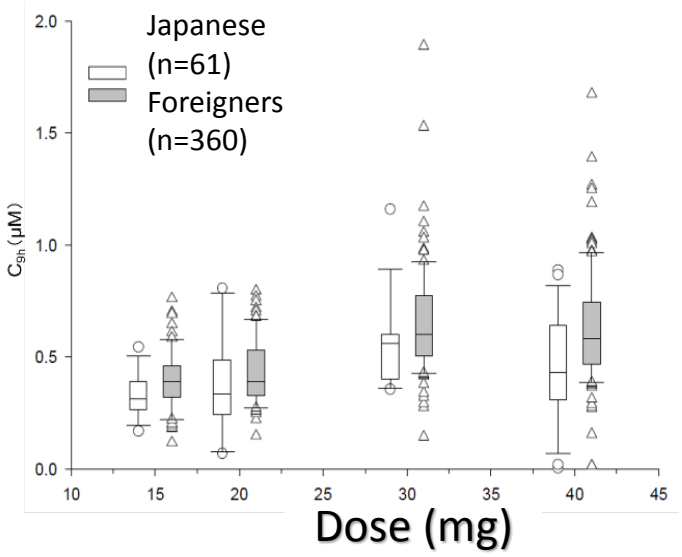
Example: Suvorexant (1)

- Sleep drug of new MOA (antagonist for orexin receptors)
- In Ph2 study (P006) the D-E-R of Suvorexant 10-80 mg was examined and 40 mg was considered to be appropriate for further evaluation in the subsequent Phase 3 trials.
- 30 mg and 15 mg doses in elderly subjects were considered to be equivalent to 40 mg and 20 mg in non-elderly subjects respectively.
- Ph3 studies (P028, P029) were designed to evaluate the efficacy of Suvorexant high dose (HD: 40 mg/30 mg) compared with placebo. Low dose (LD: 20 mg/15 mg) was also examined to evaluate for secondary objectives.
- 34 and 247 Japanese patients (approx. 13% and 24% of the total) were enrolled in P006 and P028 respectively.

Example: Suvorexant (2)

- Japanese exposure similar to western population in clinical trials.
- D-E-R differences were not found between Japanese and western population

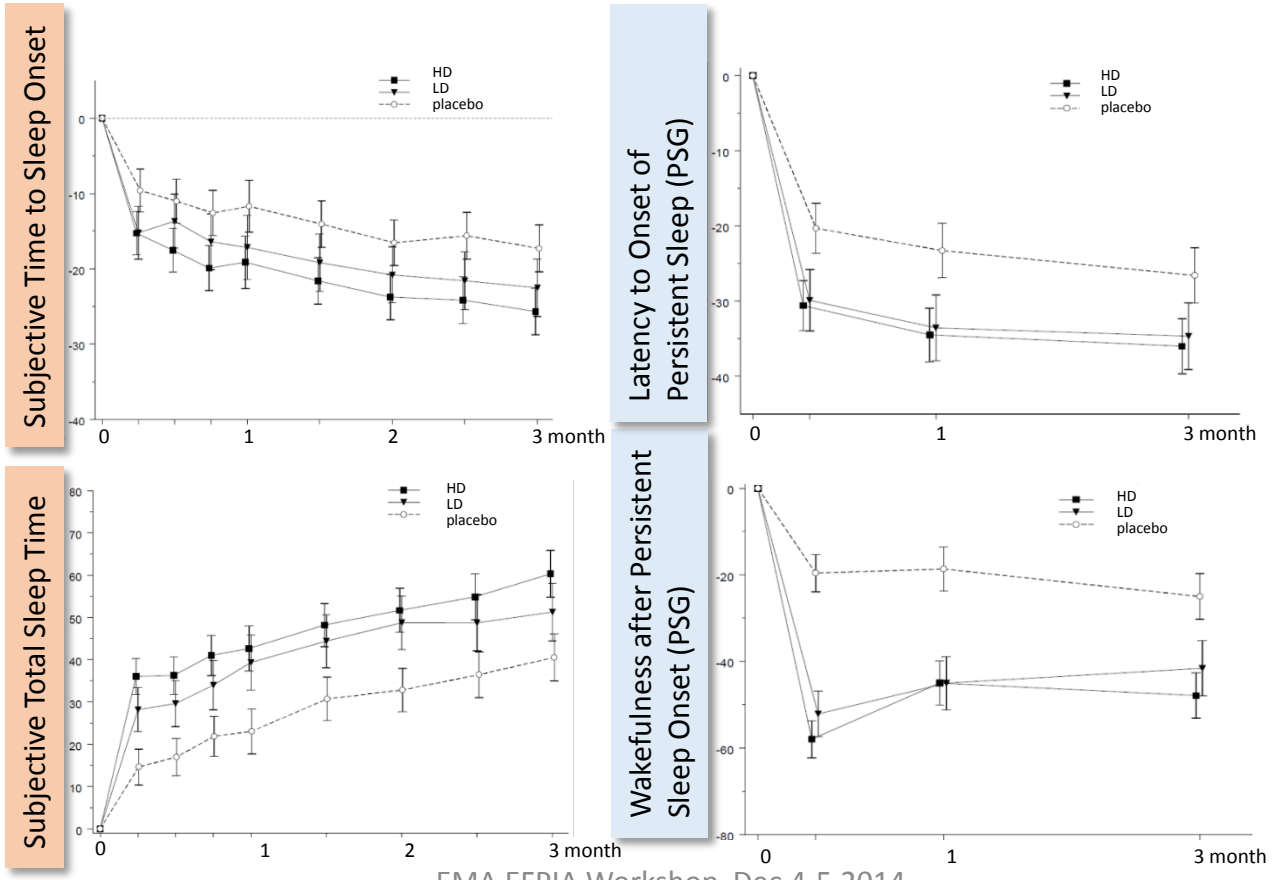


			LD	HD
sTSOm	1month	Japanese	-4.8[-17.2, 7.7]	-9.2[-20.3, 1.9]
		western	-6.3[-12.4, -0.3]	-7.9[-13.3, -2.5]
	3month	Japanese	-3.4[-12.9, 6.1]	-4.9[-13.4, 3.5]
		western	-6.5[-12.2, -0.8]	-10.3[-15.5, -5.2]
sTSOm	1month	Japanese	14.9[1.5, 28.3]	12.2[0.3, 24.2]
		western	17.2[6.9, 27.6]	22.6[13.3, 31.8]
	3month	Japanese	7.1[-7.4, 21.5]	11.7[-1.1, 24.5]
		western	12.5[1.9, 23.2]	23.1[13.6, 32.7]

LS Means versus placebo in minutes[95%CI]

Example: Suvorexant (3)

- D-E-R in Ph3 trials appears different between the subjective and the objective endpoints.



Example: Suvorexant (4)

- Suvorexant was approved in August 2014 in US and September 2014 in Japan.
- Approved recommended dosage in Japan is higher than in US.

Japan	US
Recommended dose is 20 mg once daily in non-elderly adults, 15 mg once daily in elderly adults.	Recommended dose is 10 mg once daily in non-elderly and elderly adults. If the 10 mg dose is well-tolerated but not effective, the dose can be increased, not to exceed 20 mg once daily

Example: Suvorexant (5)

- In US, the 10 mg dose was concluded as effective for many patients, though there were only limited number of subjects in P006 study.
- Since a study showed impairment of 20 mg Suvorexant in driving skills and there is overlap in exposure from 15 mg and 20 mg, 10 mg was judged as a starting and recommended dose.

- In Japan, PMDA concluded it is difficult to recommend the Suvorexant 10 mg, since there were only limited number of subjects of 10 mg dose in clinical trials and efficacy and safety were not fully evaluated.

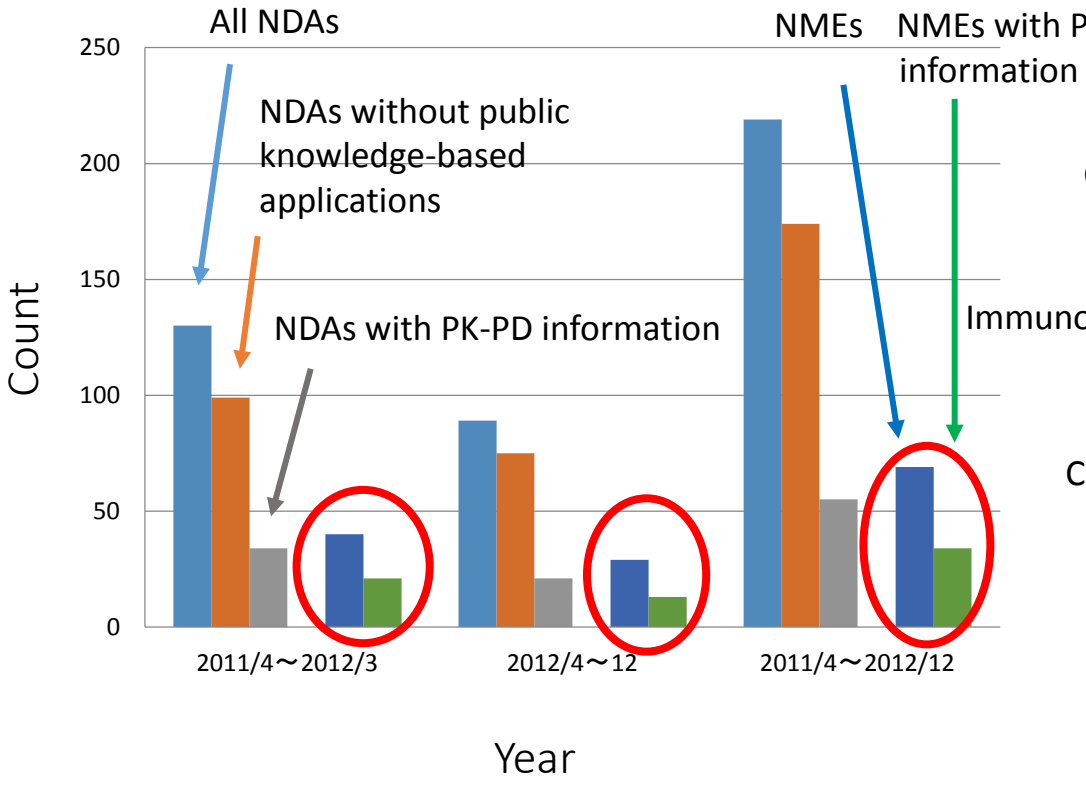
Finding the Appropriate Dose

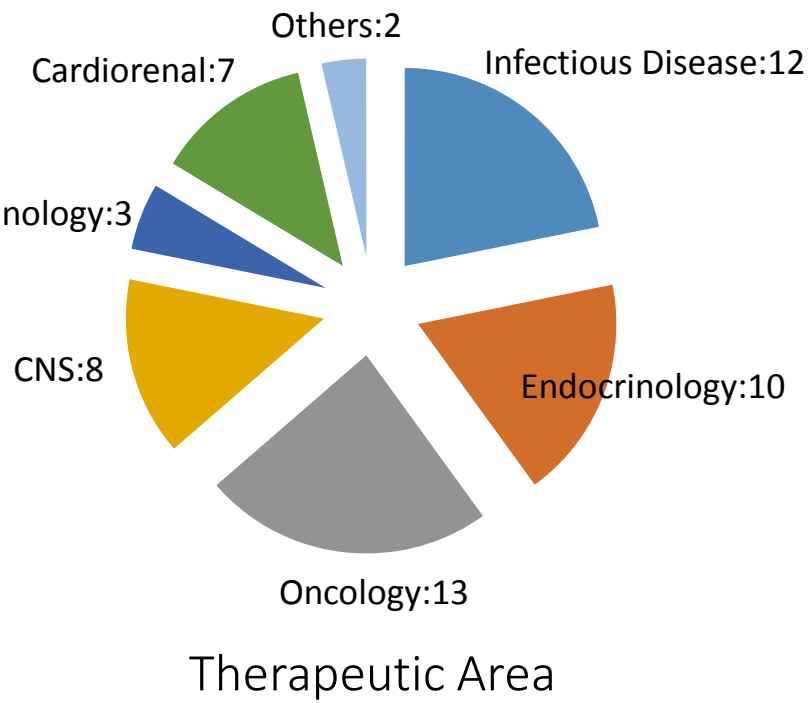
- ☑ Study design for identifying the dose
- ☑ Considerations for Specific Populations
  - ☑ Elderly subjects
  - ☑ Asian subjects
- □ Is the D-E-R information sufficient to judge the approved dose ?

…We are still in the regulatory situation of differing decisions on dosing from single global clinical trial package.

PK-PD（D-E-R) information in the NDAs in Japan (Apr.2011～Dec.2012)

About half of the recent NDAs for NMEs include D-E-R information.





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Advanced workflow of review/consultation

Analysis by PMDA

Giving additional scientific value to submitted data

Cooperation with Academia

Regulatory Science

More rational & effective evaluation process for regulatory decision

Practical use of Innovative Medical Products

NDA etc.

e-Submission of study data

Data Accumulation

Database

Sophisticated review

- Each reviewer utilizes innovative assessment techniques

Cross-Products Analysis

- Advanced evaluation methods
- Active utilization of Modeling & Simulation
  - ➢ Disease model
  - ➢ Objective B/R assessment
  - ➢ Identifying AE-related factors etc.

Sophisticated Consultation

- More evidence-based consultation

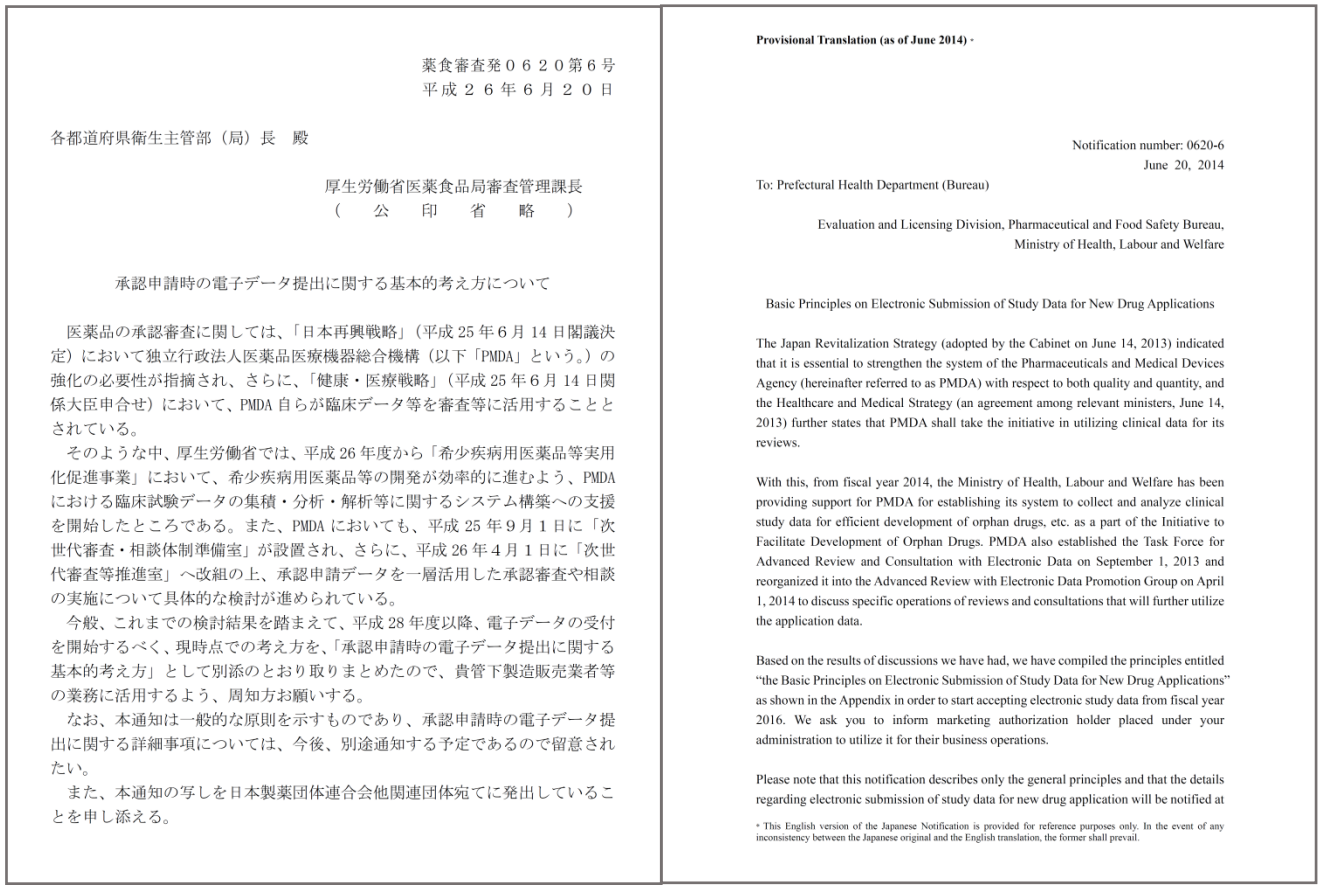
More effective and high quality Review

- More predictable efficacy/safety after approval
- Reduction of applicant's work load
- More scientific regulatory decision

More efficient and Successful Development

- Epoch-making proposal leading the world
- Proactive publication of guideline

The Basic Policy for electronic data submission



薬食審査発０６２０第６号
平成２６年６月２０日

各都道府県衛生主管部（局）長　殿

厚生労働省医薬食品局審査管理課長
（　公　印　省　略　）

承認申請時の電子データ提出に関する基本的考え方について

医薬品の承認審査に関しては、「日本再興戦略」（平成25年6月14日閣議決定）において独立行政法人医薬品医療機器総合機構（以下「PMDA」という。）の強化の必要性が指摘され、さらに、「健康・医療戦略」（平成25年6月14日関係大臣申合せ）において、PMDA自らが臨床データ等を審査等に活用することとされている。

そのような中、厚生労働省では、平成26年度から「希少疾病用医薬品等実用化促進事業」において、希少疾病用医薬品等の開発が効率的に進むよう、PMDAにおける臨床試験データの集積・分析・解析等に関するシステム構築への支援を開始したところである。また、PMDAにおいても、平成25年9月1日に「次世代審査・相談体制準備室」が設置され、さらに、平成26年4月1日に「次世代審査等推進室」へ改組の上、承認申請データを一層活用した承認審査や相談の実施について具体的な検討が進められている。

今般、これまでの検討結果を踏まえて、平成28年度以降、電子データの受付を開始するべく、現時点での考え方を、「承認申請時の電子データ提出に関する基本的考え方」として別添のとおり取りまとめたので、貴管下製造販売業者等の業務に活用するよう、周知方お願いする。

なお、本通知は一般的な原則を示すものであり、承認申請時の電子データ提出に関する詳細事項については、今後、別途通知する予定であるので留意されたい。

また、本通知の写しを日本製薬団体連合会他関連団体宛てに発出していることを申し添える。

Provisional Translation (as of June 2014) *

Notification number: 0620-6
June 20, 2014

To: Prefectural Health Department (Bureau)

Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau,
Ministry of Health, Labour and Welfare

Basic Principles on Electronic Submission of Study Data for New Drug Applications

The Japan Revitalization Strategy (adopted by the Cabinet on June 14, 2013) indicated that it is essential to strengthen the system of the Pharmaceuticals and Medical Devices Agency (hereinafter referred to as PMDA) with respect to both quality and quantity, and the Healthcare and Medical Strategy (an agreement among relevant ministers, June 14, 2013) further states that PMDA shall take the initiative in utilizing clinical data for its reviews.

With this, from fiscal year 2014, the Ministry of Health, Labour and Welfare has been providing support for PMDA for establishing its system to collect and analyze clinical study data for efficient development of orphan drugs, etc. as a part of the Initiative to Facilitate Development of Orphan Drugs. PMDA also established the Task Force for Advanced Review and Consultation with Electronic Data on September 1, 2013 and reorganized it into the Advanced Review with Electronic Data Promotion Group on April 1, 2014 to discuss specific operations of reviews and consultations that will further utilize the application data.

Based on the results of discussions we have had, we have compiled the principles entitled "the Basic Principles on Electronic Submission of Study Data for New Drug Applications" as shown in the Appendix in order to start accepting electronic study data from fiscal year 2016. We ask you to inform marketing authorization holder placed under your administration to utilize it for their business operations.

Please note that this notification describes only the general principles and that the details regarding electronic submission of study data for new drug application will be notified at

* This English version of the Japanese Notification is provided for reference purposes only. In the event of any inconsistency between the Japanese original and the English translation, the former shall prevail.

June 20, 2014

Notification Number0620-6

Notification of Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau,

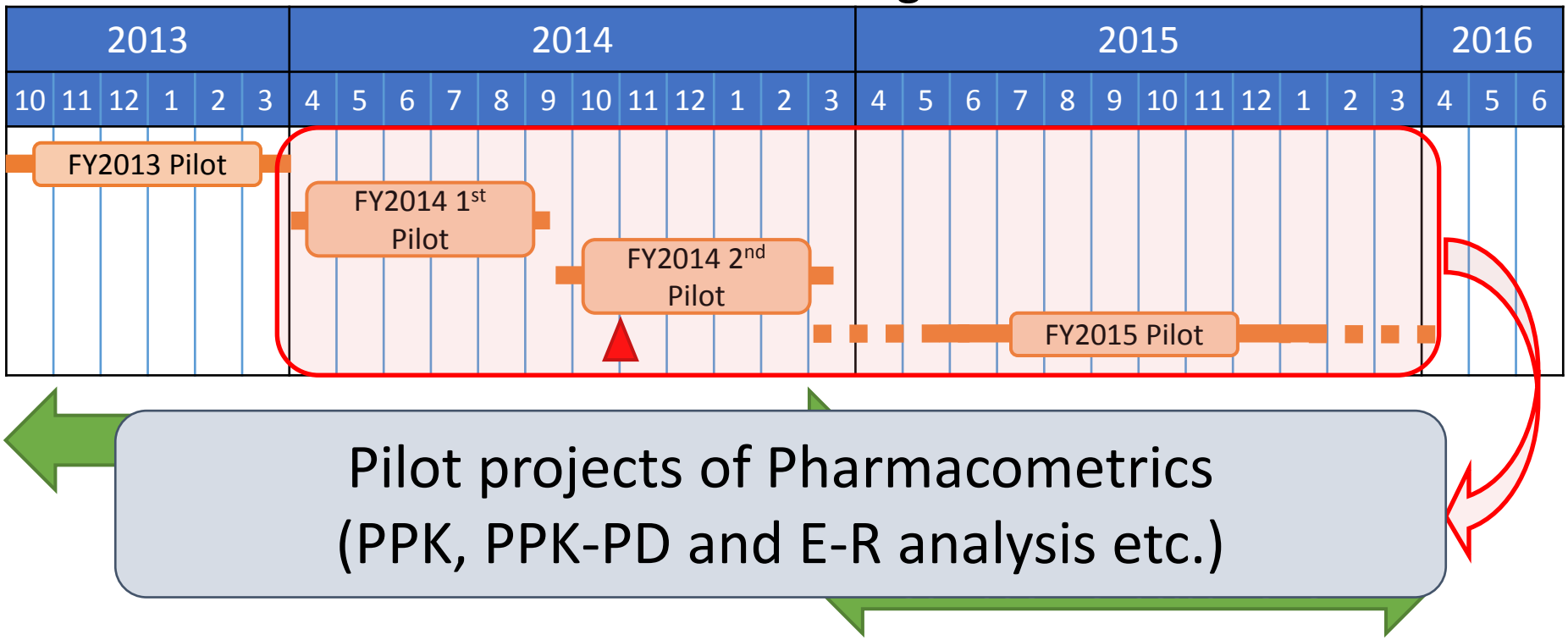
Ministry of Health, Labour and Welfare

Both Japanese and English versions are available at our webpage.

Japanese : http://www.pmda.go.jp/operations/shonin/info/iyaku/jisedai/file/140620-tsuchi.pdf
English : http://www.pmda.go.jp/operations/shonin/info/iyaku/jisedai/file/140620-tsuchi_e.pdf

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



FY2014 1st pilot project (outline)
(Apr. 2014 - Sep. 2014)

- Purpose
  - To confirm that the data for population pharmacokinetic (PPK) analysis can be stored and managed appropriately with in-house system, and that persons in charge* are able to analyze the stored data by utilizing introduced software.

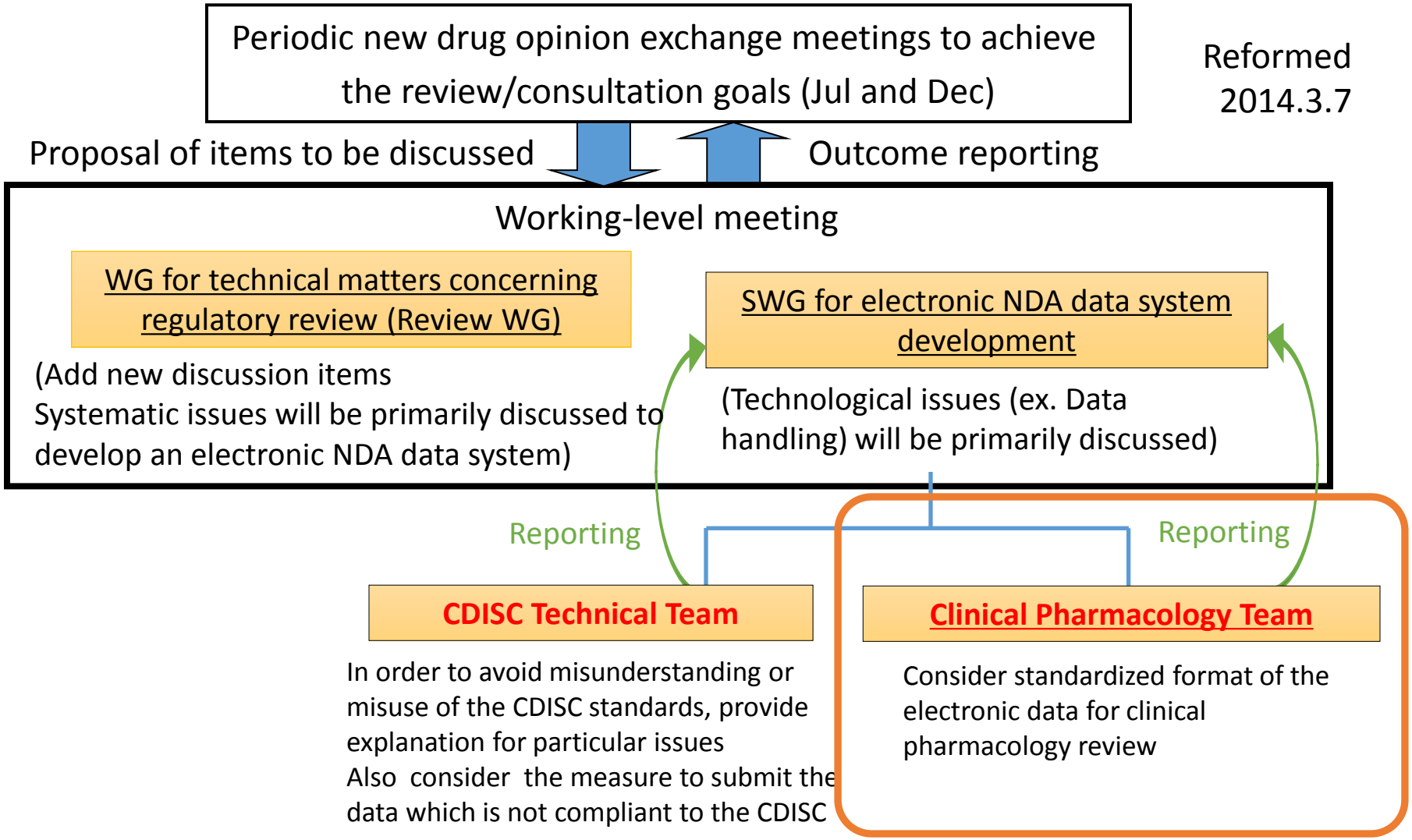
*more than 10 reviewers, in the areas of clinical pharmacology from each review office.

- Target studies
  - Datasets for PPK analysis of blood concentration data that include those of Japanese subjects obtained from one or more clinical studies on new drugs.
  - PPK datasets for three drug products, one from each of three companies, were provided.
- Implementation details
  - Confirm that the provided clinical study data can be stored and managed appropriately with in-house system, and analyzed by utilizing introduced software （NONMEM, R, Xpose, PDx-POP）.

FY2014 2nd pilot and future projects (outline)

- Period
  - Data collection: September – October 2014
  - Analysis: November 2014 – January 2015
- Purpose
  - To confirm that the data for PPK-PD analysis and exposure-response (E-R)analysis can be stored and managed appropriately with in-house system, and that persons in charge are able to analyze the stored data by utilizing introduced softwares.
  - To consider the utilization of the analysis results in the new drug review process.
- Target studies
  - Datasets for analysis of blood concentration, clinical endpoints and AE data that include those of Japanese subjects obtained from one or more clinical studies on new drugs (3 NMEs, from three companies).
- We already announced the pilot project in FY2015.
  - The pilot will be conducted under the actual situation of regulatory review using the electronic study data of new drug application submitted during the data receiving period (from Jan 1 to Sep 30, 2015).

Discussion with the industry



Guideline development

The new MHLW Working Group started discussion on D-E-R Relationships related issues in October, 2014

- Population Pharmacokinetics:
  - Updating existing document and establishing best practices/guidance in population analysis
  - Guidance publication in 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

Medium- and long-term prospect

Tentative assumption and expectation

FY2014*: April 2014 – March 2015

Present
FY2014*

- e-data can be received and managed appropriately
- e-data can be utilized in the review
- without extension of review period, industries' workload would decrease gradually

FY2016

Set up e-data management and utilization

FY2018

Ordinary utilization of e-data in the product review

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

Promotion of paperless

FY2019 - 2021

Starting earnest cross-product analysis

- Develop guidance and related documents
- Earnest cross-product analysis, development of disease models

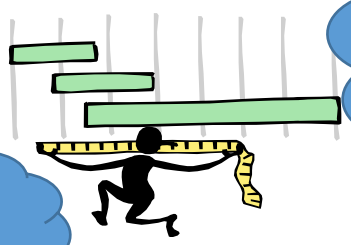
FY2022 - 2023

Publication of guidance to contribute to drug development

- Establishment of disease model
- Publication of disease-specific guidance

First-class review authority

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



Summary

- Regulatory experiences and current status on D-E-R information in the new drug review are presented.
- PMDA/MHLW have continuously been updating regulatory guideline, “Basic principles on Global Clinical Trials” to promote efficient drug development in Japan.
- New review/consultation process with submitted electronic data will be thoroughly considered based on the experiences of the pilot projects and active discussion with industry and academia.
- Effective utilization of submitted electronic data lead to efficient drug development and more predictable efficacy/safety evaluation, and finally benefit the public.
- We will proceed our project and guidance development to promptly reach future goal, such as the implementation of cross product analysis and high quality review.
- We appreciate your understanding and cooperation.

Thank you for your attention!

- PMDA Homepage
  - http://www.pmda.go.jp/english/index.html
- “Task force for advanced review and consultation with electronic data” Homepage
  - http://www.pmda.go.jp/english/service/taskforce.html