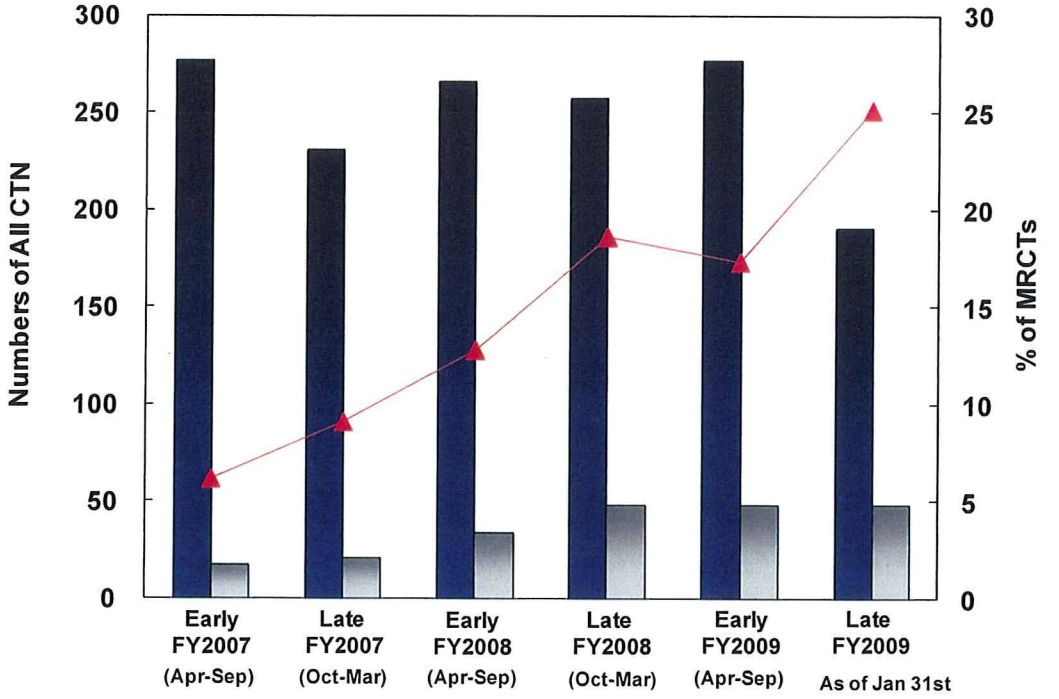
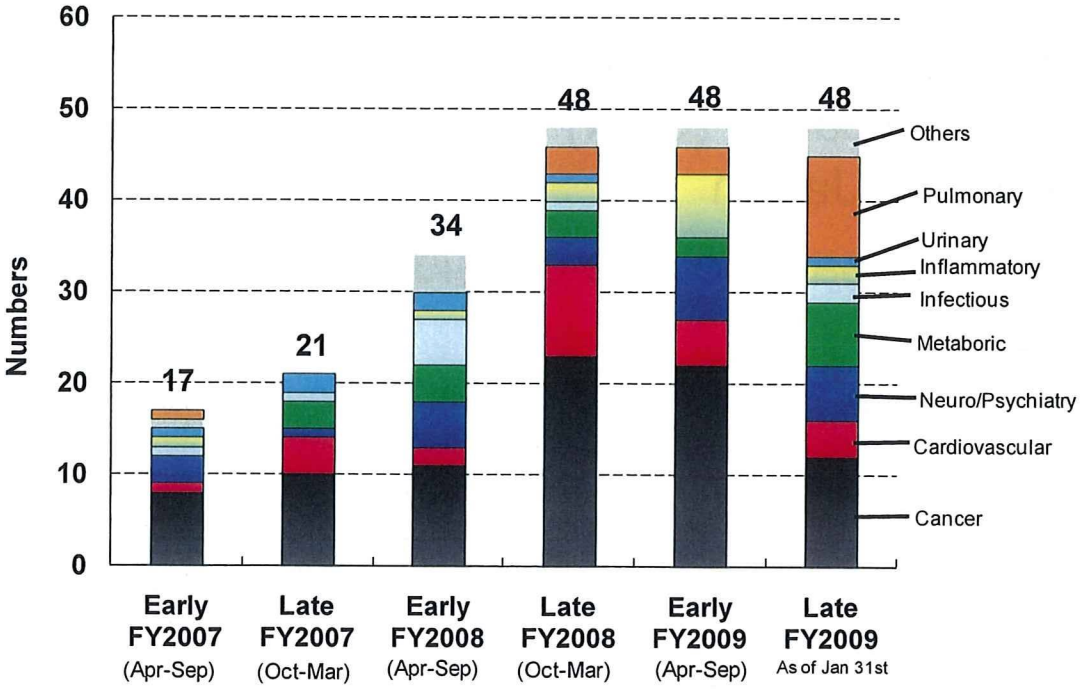
Trends of Global Clinical Trials including Japan -Percentage-

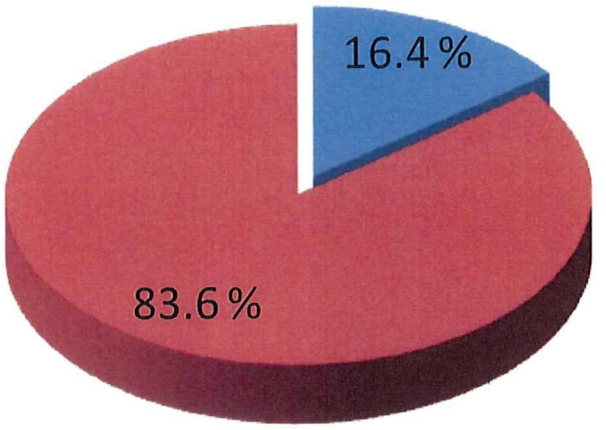


Trends of Global Clinical Trials including Japan -Target Therapeutic Area-



Trends of Global Clinical Trials including Japan -Sponsor-

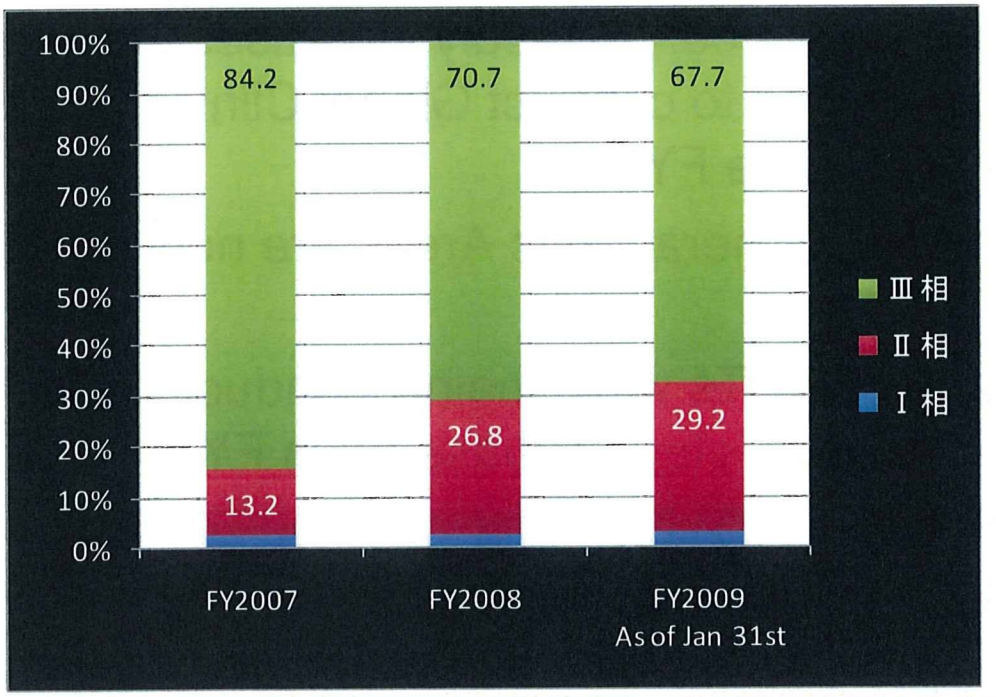
Japan based Company



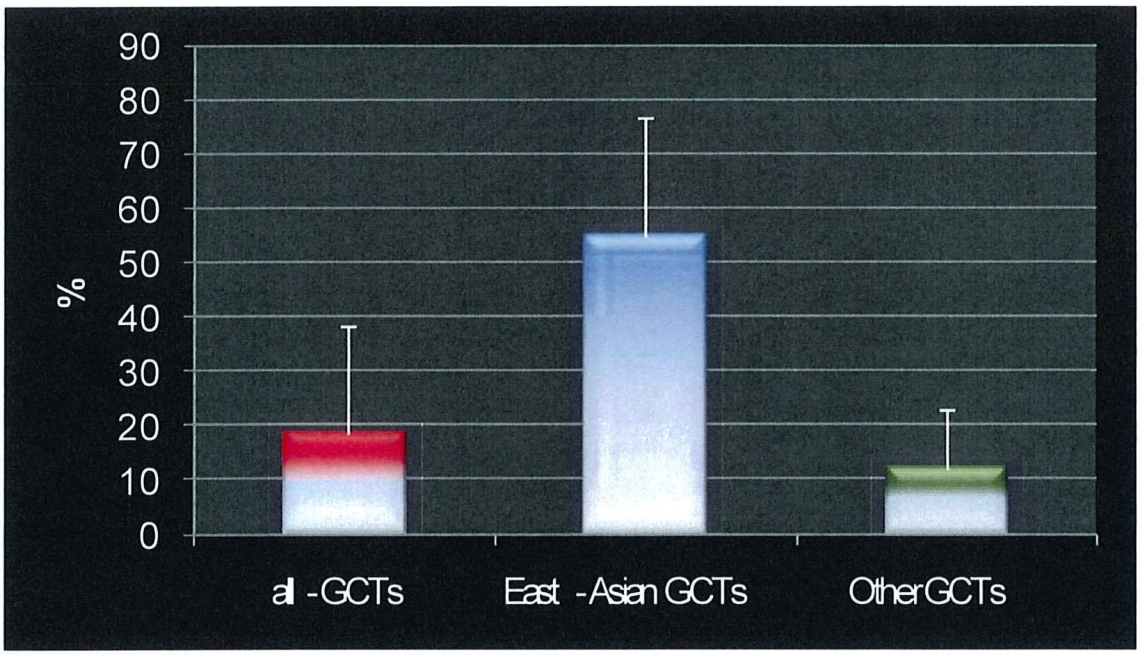
US/EU based Company

As of FY2009 Jan. 31st

Trends of Global Clinical Trials including Japan -Trial Stage-



Trends of Global Clinical Trials including Japan -Sample Size: Japanese Patient-



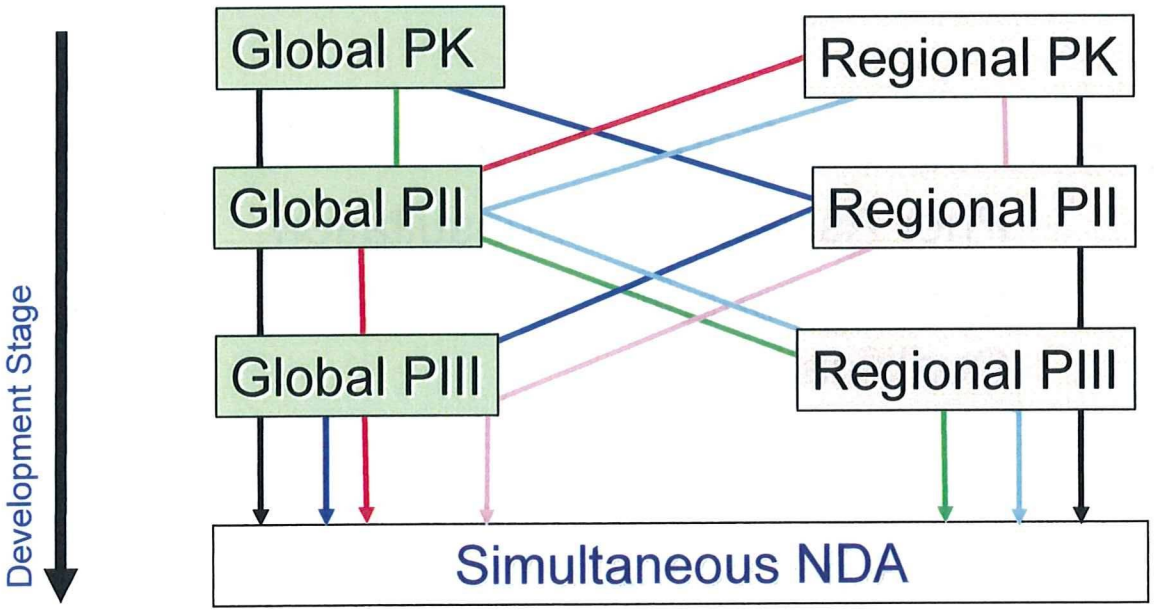
Summary of Current Situations of Global Clinical Trials in Japan

- Rapid advance: Markedly increases Japanese experiences to conduct Global Clinical Trials (GCTs) since FY2007
- Almost all Therapeutic Areas are now a target for GCTs
- Stage of GCTs were mainly conducted at confirmatory stage (Phase III) in FY2007 but have shifted to an earlier stage (Phase II)
- Sample Size of Japanese population was higher in East-Asian Global Clinical Trials

Future Drug Development Strategy in consideration of ethnic factors

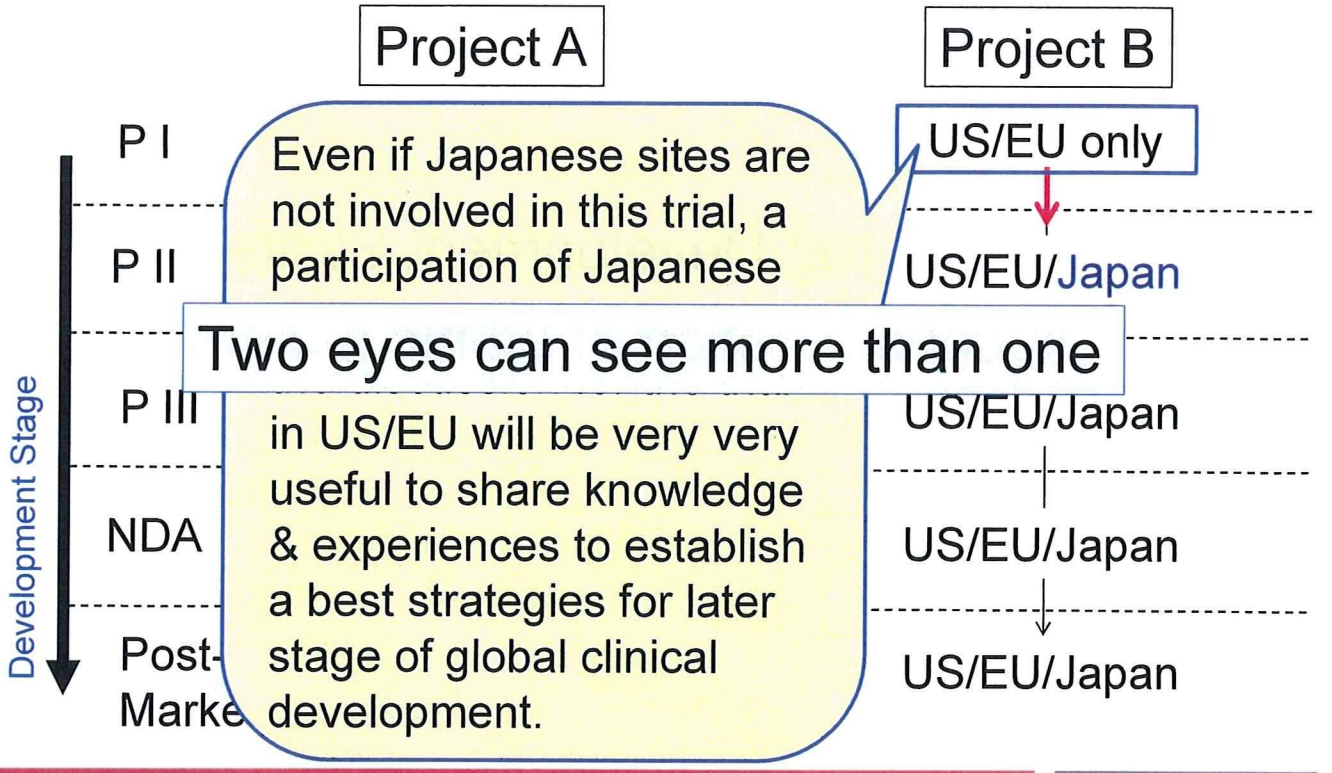
Flexible Global Drug Development Strategy

Global communications including communication with regulatory agency from an initial stage is the key to establish a best strategy



Ichimaru et al, *Clin Pharmacol Therapeut*, 87: 362-366, 2010

Importance of Global Network



Progress of New Consultation Process (Pilot)

- Prior Assessment Consultation
- Special Consultation on PGx/Biomarekr Qualification

Prior Assessment Consultation

What is "Prior Assessment Consultation"?

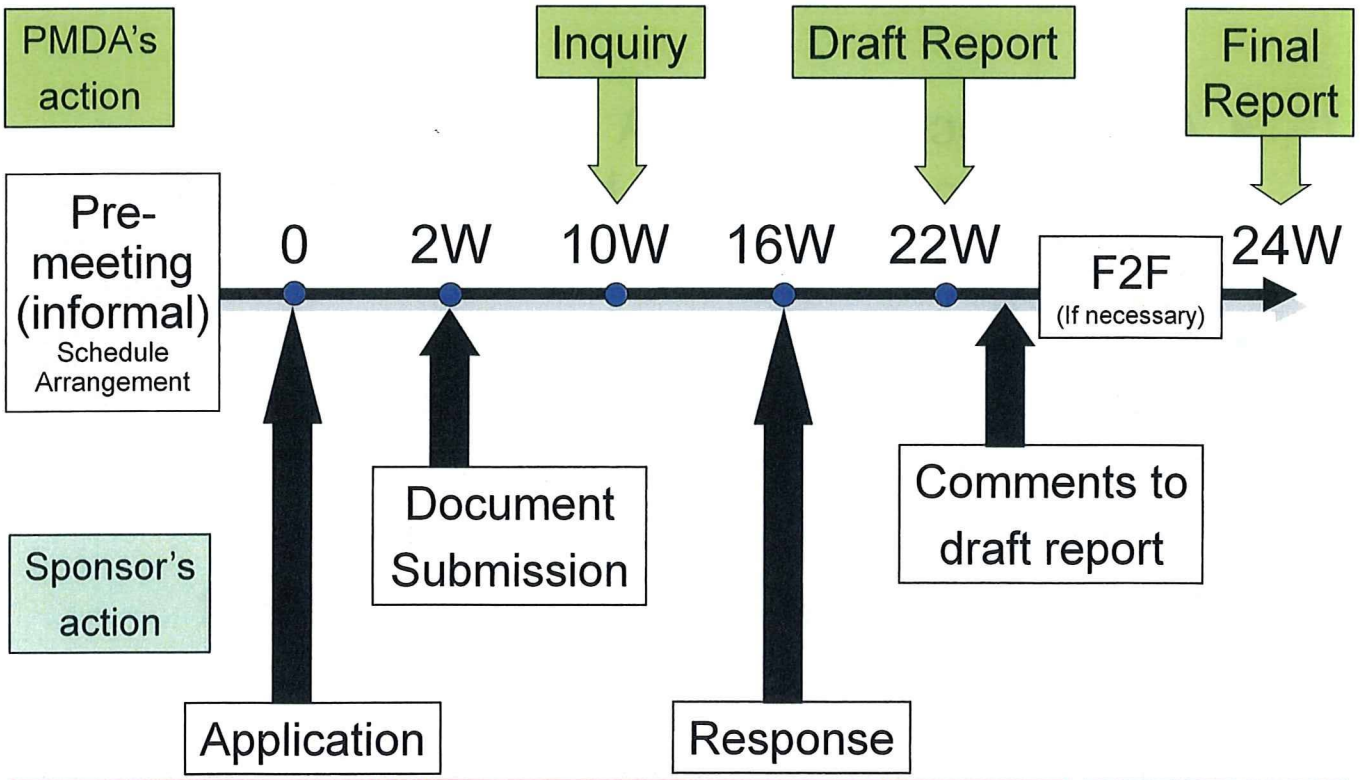
- A new process of PMDA Scientific Consultation at the time before formal NDA submission
- Focus on review of all available data from non-clinical and clinical studies (e.g. Quality, Non-clinical and early phase clinical data) at a time of consultation
- PMDA provides a prior-assessment report for the submitted data/study

Purpose

Data Evaluation by PMDA before a formal NDA submission can…

- Shorten NDA review time
- Maximize a efficiency of drug development
  - Identify major discussion points and tasks for the future NDA submission
  - Help sponsor to prepare a good CTD with inclusion of PMDA's interests
  - Avoid to find any critical issues for regulatory decision on NDA review

Timeline of Prior Assessment Consultation for *Pilot*



Progress (1)

- The Pilot was started in April 2009
- Initial expected applications were 3 products, but intentions for 9 products were received from 10 industries (incl. 1 collaborative development)
- Finally, 7 products were selected for the pilot
  - Criteria for the selection
    - At least, one product for each review team
    - New Molecular Entity
    - Data are available for many parts (Q, S, E)

Progress (2)
Therapeutic Area for the Selected Products

Team	Intention to submit	Selected for the Pilot
1 (Gastrointestinal Drugs etc.)	1	1
2 (Cardiovascular Drugs etc.)	1	1
3-1(Psychiatric & Neurological Drugs)	3	1
4 (Anti-bacterial & Anti-viral Drugs etc.)	3	3
Biologics (Vaccine etc.)	1	1

Progress (3)

- Currently(As of Feb 26th), the review for 5/7 products were completed in approximately 6M as scheduled.
- The review reports for the 5 products were already finalized and were sent to the applicants.
- Regarding the other 2 products remained, one is under the review, the other one is not started yet.

Next Steps

- A questionnaire will be circulated to both the applicant and the review team to examine a value of this pilot.

  e.g.
  - Did this pilot satisfy your expectation?
  - Were your concerns/issues clearly clarified for future NDA submission?
  - Did you see any points which should be improved ?
  - Will you use this pilot in the future?

- In FY2010, 2nd round of this pilot will be conducted
  - At least, 6 products will be selected.

Special Consultation on PGx/Biomarekr Qualification

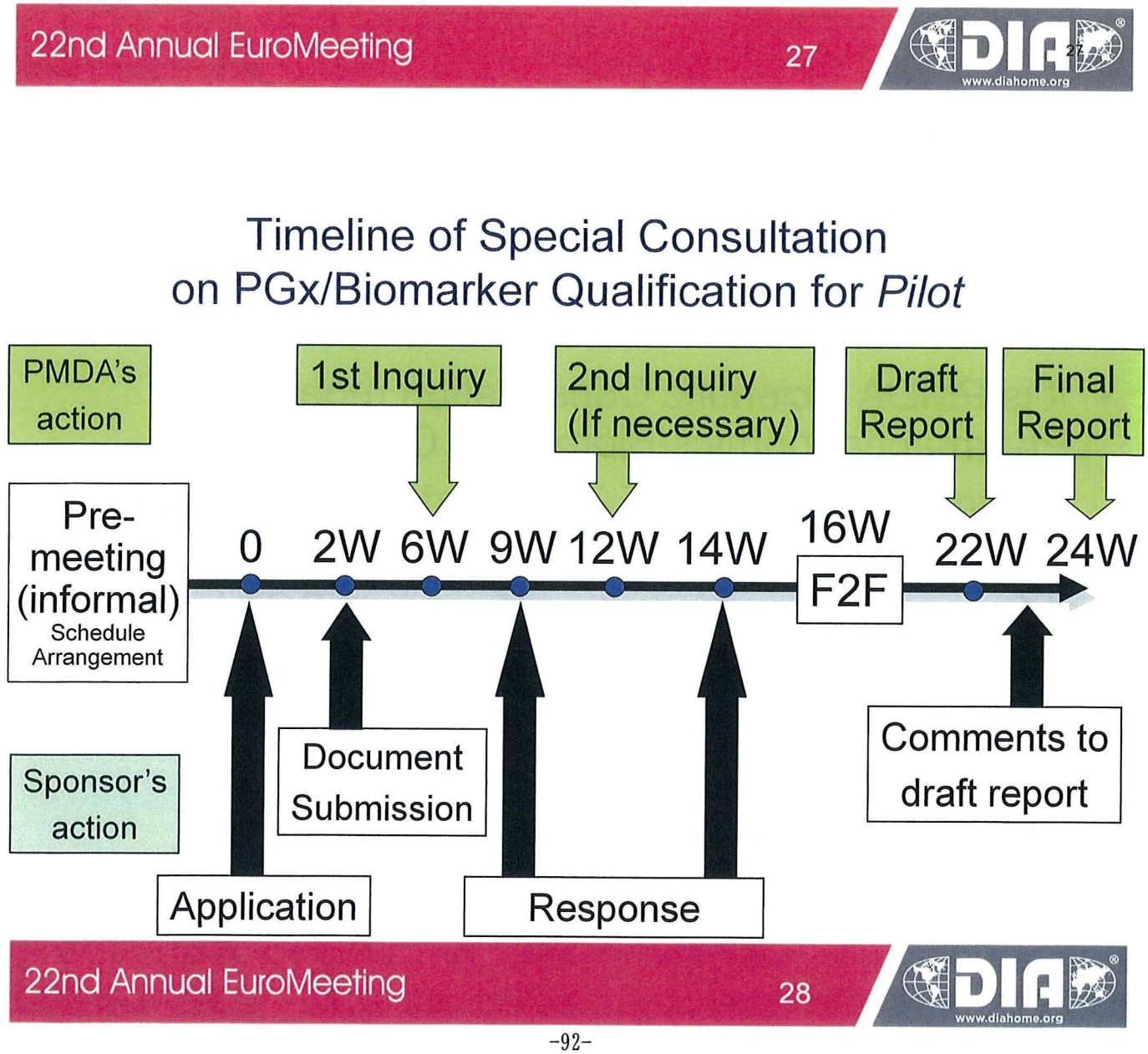
What is "Special Consultation on Pharmacogenomics/ Biomarker Qualification"?

- It is PMDA Scientific Consultation regarding Pharmacogenomics/Biomarker Qualification
  - Similar to FDA/EMEA Biomarker Qualification Meeting
- It focus on general strategy for using PGx in drug development or Biomarker Qualification
  - Individual issues related to a individual drug are covered by Existing Consultation
- PMDA provide an assessment report for this consultation

Purpose

This Consultation can

- Maximize a efficiency of drug development
- Realize a personalized medicine
- Promote international harmonization in PGx
  - Identify regulatory issues and tasks for using PGx/Biomarker in drug development
  - Help sponsor to make a study design using PGx/Biomarker with inclusion of PMDA's intersts
  - Promote regulatory collaboration on PGx/Biomarker Qualification



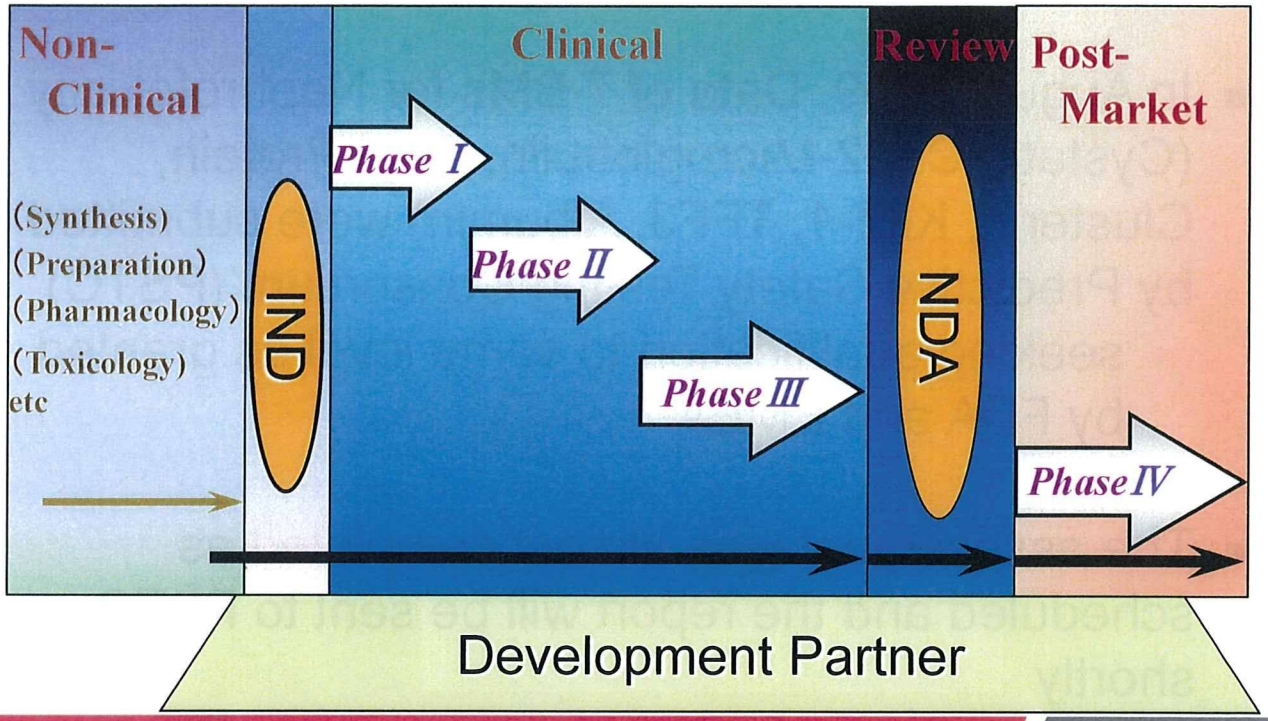
Progress

- The Pilot was started in April 2009
- In August 2009, Data of 7 BMs for Nephrotoxicity (Cystatin C, β2-Microglobulin, Total Protein, Clusterin, KIM-1, TFF3, Albumin) were submitted by Predictive Safety Testing Consortium (PSTC)
  - seeking qualification to same level as granted by FDA and EMEA
- The assessment was almost completed as scheduled and the report will be sent to PSTC shortly

Next Steps

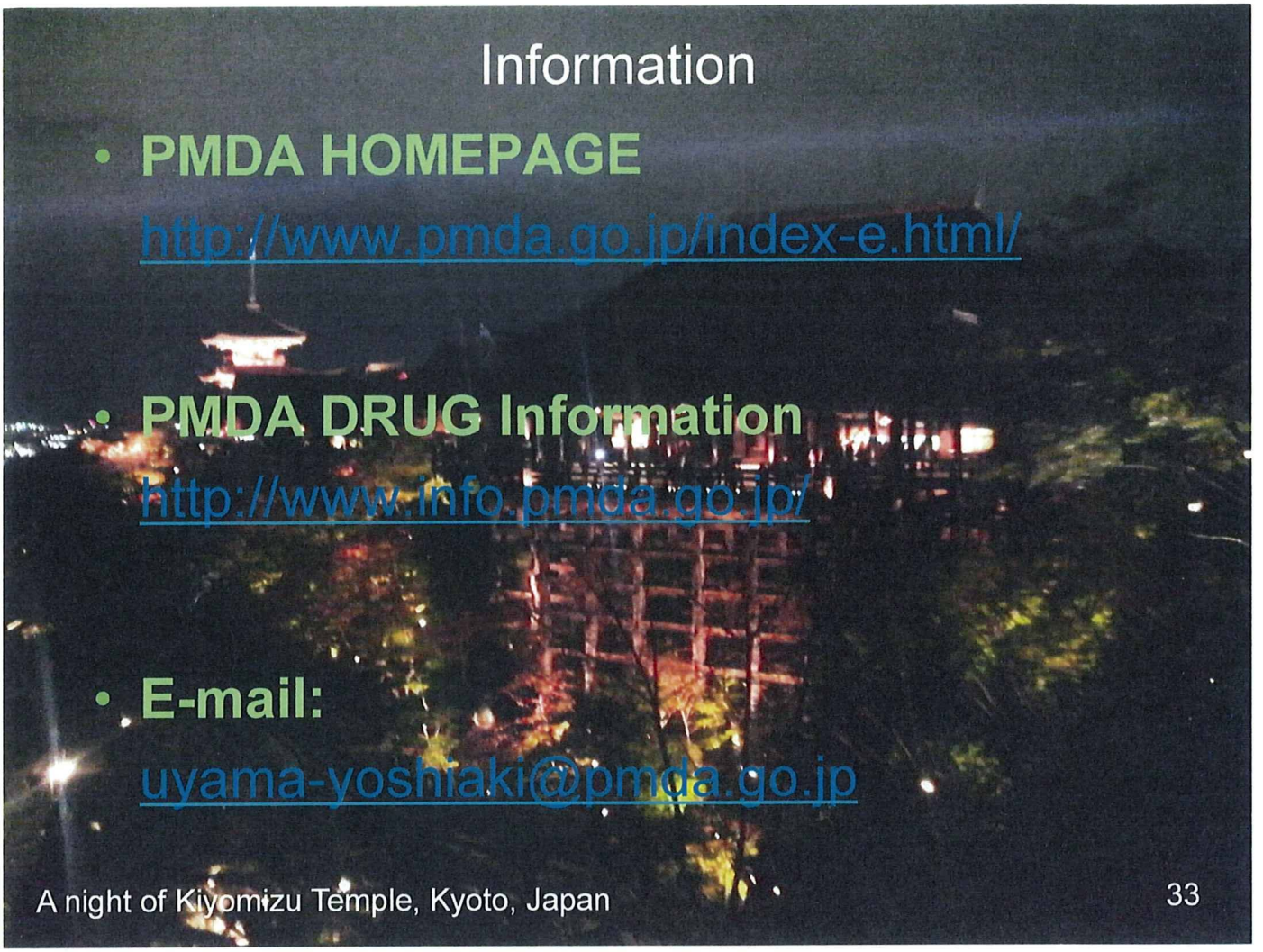
- lessons learned meeting with the applicant will be held at the time after completion of the pilot to examine a value of this pilot.
- In FY2010, 2nd round of this pilot will be conducted

More PMDA Contributions in drug development



PMDA challenges

- Many projects in PMDA support and encourage drug development for regulatory approval
- PMDA is happy to discuss about what is a most appropriate strategy/plan for your drug
- PMDA will continue our challenges to improve our processes and promote drug development for providing effective & safe drugs quickly to patients


Information
• PMDA HOMEPAGE
http://www.pmda.go.jp/index-e.html/
• PMDA DRUG Information
http://www.info.pmda.go.jp/
• E-mail:
uyama-yoshiaki@pmda.go.jp
A night of Kiyomizu Temple, Kyoto, Japan
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5th Workshop in a Series on Pharmacogenomics

Generating and Weighing Evidence in Drug Development and Regulatory Decision Making

February 2-4, 2010
Marriott Bethesda North Hotel and Conference Center
Bethesda, MD, USA

STEERING COMMITTEE CHAIRS

Issam Zineh, PharmD, MPH
Associate Director for Genomics, Office of Clinical Pharmacology
Center for Drug Evaluation and Research
U.S. Food and Drug Administration

Peter Shaw, PhD
Senior Director, Pharmacogenetics and Molecular Profiling
Merck & Co., Inc.

See page 2 and 3 for a complete list of Steering Committee and Scientific Advisory Group members.

Who Should Attend

- Physicians
- Legal community
- Statisticians
- Nurses
- Pharmacologists
- Clinicians
- Biologists
- Healthcare providers
- Molecular biologists
- Reimbursement specialists
- Clinical scientists
- Human geneticists
- Regulatory affairs professionals
- Academic researchers

The field of genetics and its applications continue to evolve rapidly with the publication of multiple genome-wide association studies, the availability of new DNA sequencing technologies, and examples of biomarkers that are being used to help define patient response in myriad diseases (eg, oncology, HIV, autoimmune, cardiovascular). In addition, the increased pressure to demonstrate value of medicines is refocusing efforts and attention on how to effectively and practically define patients who are grouped by biomarkers during and following clinical development.

Between 2002 and 2007 the FDA, in collaboration with industry, has co-sponsored four major workshops on pharmacogenetics and pharmacogenomics (PGx) that have facilitated understanding of issues that surround implementation of PGx studies during clinical development and led to the development and drafting of several documents pertaining to the use of PGx in clinical development.[1] This workshop will develop and advance approaches and ideas to improve the value of PGx and other biomarker studies during clinical development and for regulatory decision making and provide networking opportunities with colleagues from academia, regulatory authorities, industry, payors and providers who work on personalized medicines.

continued on page 2

In collaboration with

PhRMA

Bio BIOTECHNOLOGY INDUSTRY ORGANIZATION

INDUSTRY I-PWG PHARMACOGENOMICS WORKING GROUP

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Summary of Meeting

5th Workshop in a Series on Pharmacogenomics
Generating and Weighing Evidence in Drug Development and Regulatory Decision Making
February 2-4, 2010
Marriott Bethesda North Hotel and Conference Center
Bethesda, MD, USA

Peter M. Shaw, Ph. D.
Merck and Co.

Issam Zineh, PharmD, MPH
U.S. FDA

Disclaimer

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Conflict of Interest Disclosure
Peter Shaw, PhD

- Receipt of Intellectual Property Rights/Patent Holder: **Bristol-Myers Squibb**
- Ownership Interest (stocks, stock options or other ownership interest excluding diversified mutual funds): **Merck**

Conflict of Interest Disclosure
Issam Zineh, PharmD, MPH

Has no real or apparent conflicts of interest to report.

Many thanks to all those who helped!

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Jennifer L. Weisman, PhD

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Building on the Past

- Conversation further enriched driven by:
  - Less inhibition, more scientific focus on the issues
  - Recognition for need for flexibility and information exchange in changing field of drug/device development
  - Multiple actual examples, not theoretical anymore
  - Collective broader experience
  - Prior workshops
- Recognition that field is still developing and nascent
  - Not many examples of co-development
  - Efficacy vs. safety (different considerations for these categories)

6

Learning from Experience

- PGx application scenarios range:
  - Prognostic enrichment
  - Dose adjustment
  - Predictive
- Different evidentiary expectations in a safety/efficacy scenarios
- PK and PD data may be compelling for label changes
- Comprehensive review of labels→Heterogeneity in content, location, degree of "actionability"
- Central Theorem of Pgx in Drug Labels
- Started a dialogue on the role of the labels in providing information and was questioned as an appropriate vehicle for education

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RetroPro Past and Future

- Key features for successful use (Patterson): Prior data to generate a hypothesis, single marker, pre-specified SAP, sufficiently powered, independent testing, high sample acquisition
- Recapitulated by Dr. Flamion and independently replicated by Dr. Carl
- Difference in EU and US labels with respect to efficacy vs. safety
- Conundrum of pre-pivotal evidence generation
  - How to generate data to sufficiently "pull the trigger"
  - Alternative paradigms for evidence generation and hypothesis testing
- A widely available assay is required for translation

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The Front and Back Ends

- Significant challenges still remain for routine collection of specimens
- Backdrop of numerous legislation and heterogeneity in individual countries in terms of EC/IRB/Culture
- Focused initiatives can surmount these obstacles
- How to enable global adoption?

- IT going to change evidence generation and clinical practice (widespread data warehouses ~ 20 years)
- PGx is analogous to other innovations and prospective RCTs will be a requirement for broad adoption

9

Reasons to be Circumspect

- Hyperbole and technology booms followed by underwhelming application and translation (e.g., disease genetics)
  - Clear value in safety Pgx (most evolved)
  - Efficacy a big opportunity but nascent
- Pgx could have tremendous value for improving risk/benefit but uncertain whether it will translate to cost-effectiveness
  - New models for consultation to determine value/cost-effectiveness
- Prognostic factor imbalance and lack of randomization
- Determining whether bias has been introduced
- Distinguishing between prognostic and predictive performance
- Multiplicity
- Study designs exist to overcome limitations

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