PMDA Considerations for Outcome Assessments

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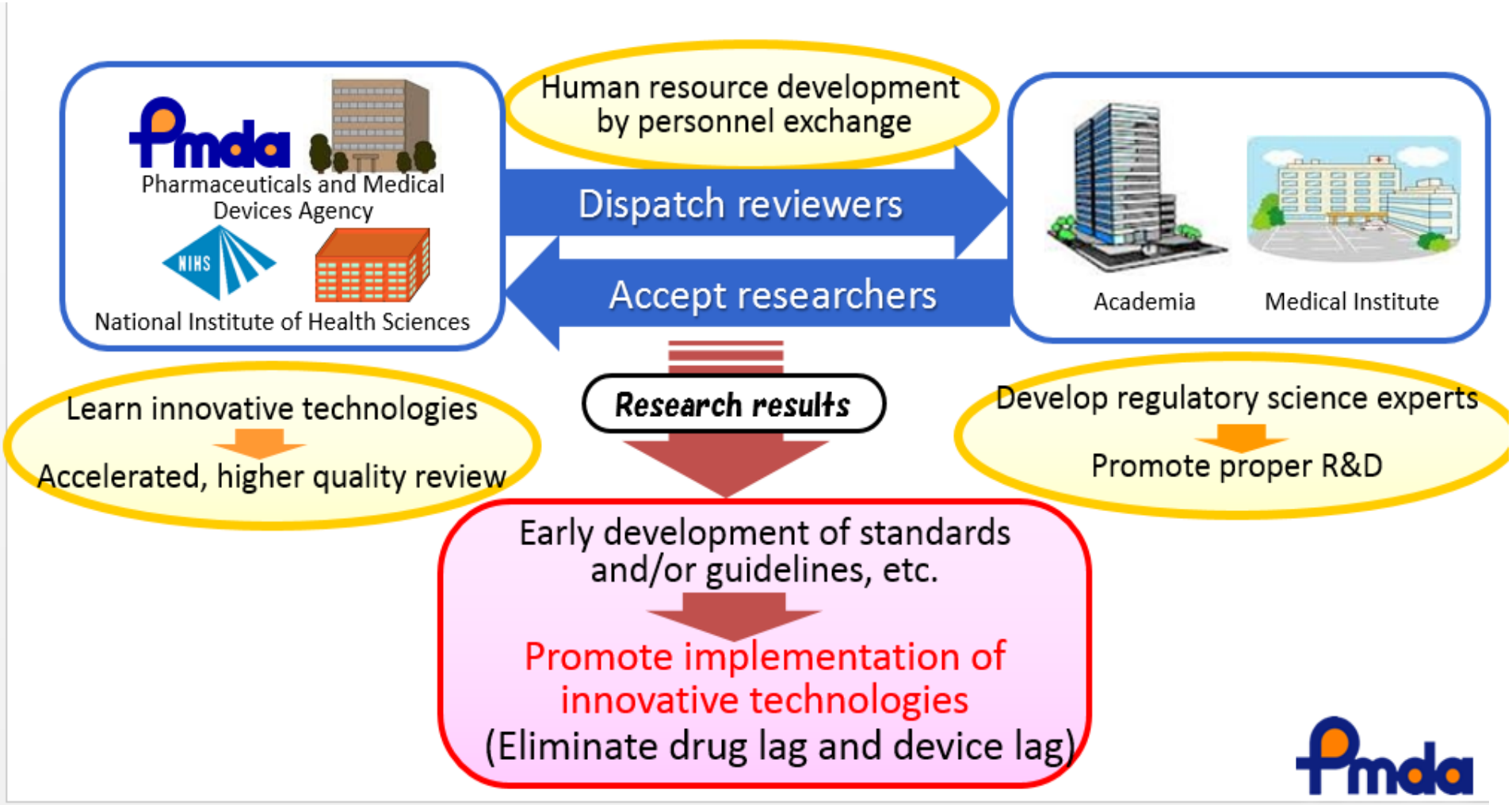
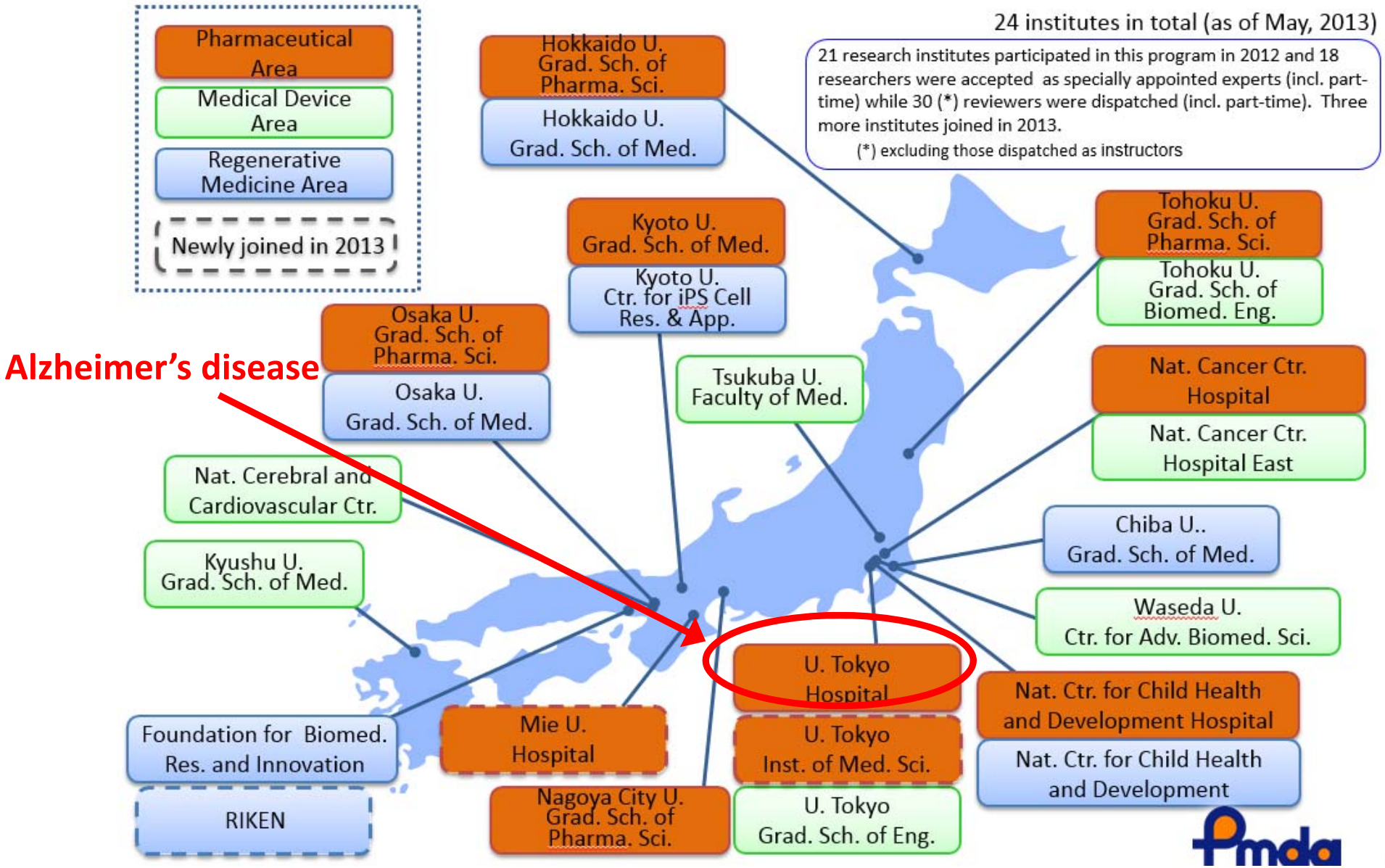
Novel Regulatory Science Research Project in Japan

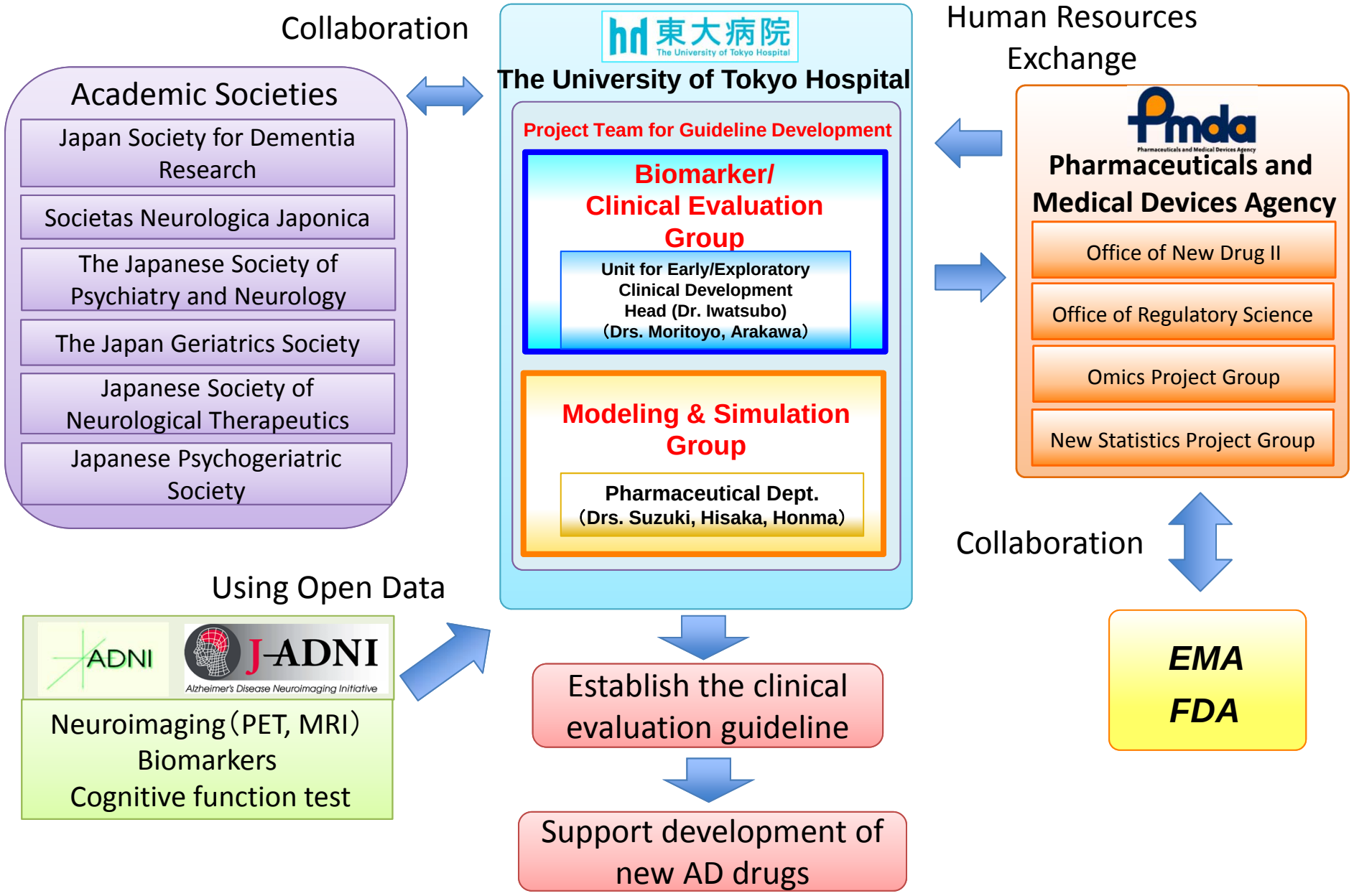
- MHLW launched a project termed "Accelerating regulatory science initiatives" to promote the development of innovative drugs and its approval review



Academic Institutions Involving in the Project



Structures


Collaboration
Academic Societies
Japan Society for Dementia Research
Societas Neurologica Japonica
The Japanese Society of Psychiatry and Neurology
The Japan Geriatrics Society
Japanese Society of Neurological Therapeutics
Japanese Psychogeriatric Society
東大病院
The University of Tokyo Hospital
The University of Tokyo Hospital
Project Team for Guideline Development
Biomarker/ Clinical Evaluation Group
Unit for Early/Exploratory Clinical Development
Head (Dr. Iwatsubo)
(Drs. Moritoyo, Arakawa)
Modeling & Simulation Group
Pharmaceutical Dept.
(Drs. Suzuki, Hisaka, Honma)
Human Resources Exchange
Pharmaceuticals and Medical Devices Agency
Office of New Drug II
Office of Regulatory Science
Omics Project Group
New Statistics Project Group
Collaboration
EMA
FDA
Using Open Data
ADNI
J-ADNI
Alzheimer's Disease Neuroimaging Initiative
Neuroimaging (PET, MRI)
Biomarkers
Cognitive function test
Establish the clinical evaluation guideline
Support development of new AD drugs

Guideline Development for Drugs for Alzheimer's disease

- Interim Report "Issues to Consider in the Clinical Evaluation and Development of Drugs for Alzheimer's Disease" was released to the public in November 2013.

- Based on the comments submitted from industry and academia in Japan, the interim report is now being revised.

Efficacy Endpoint Required for AD Dementia in Japan

	Donepezil		Rivastigmine (2011)	Galantamine (2011)	Memantine (2011)
	Mild/Mod, (1999)	Severe (2007)			
Cognition	ADAS-J cog	SIB	ADAS-J cog	ADAS-J cog	SIB-J
Global Assessment	Global rating	CIBIC plus	CIBIC plus-J*	CIBIC plus-J *	Modified CIBIC plus-J*

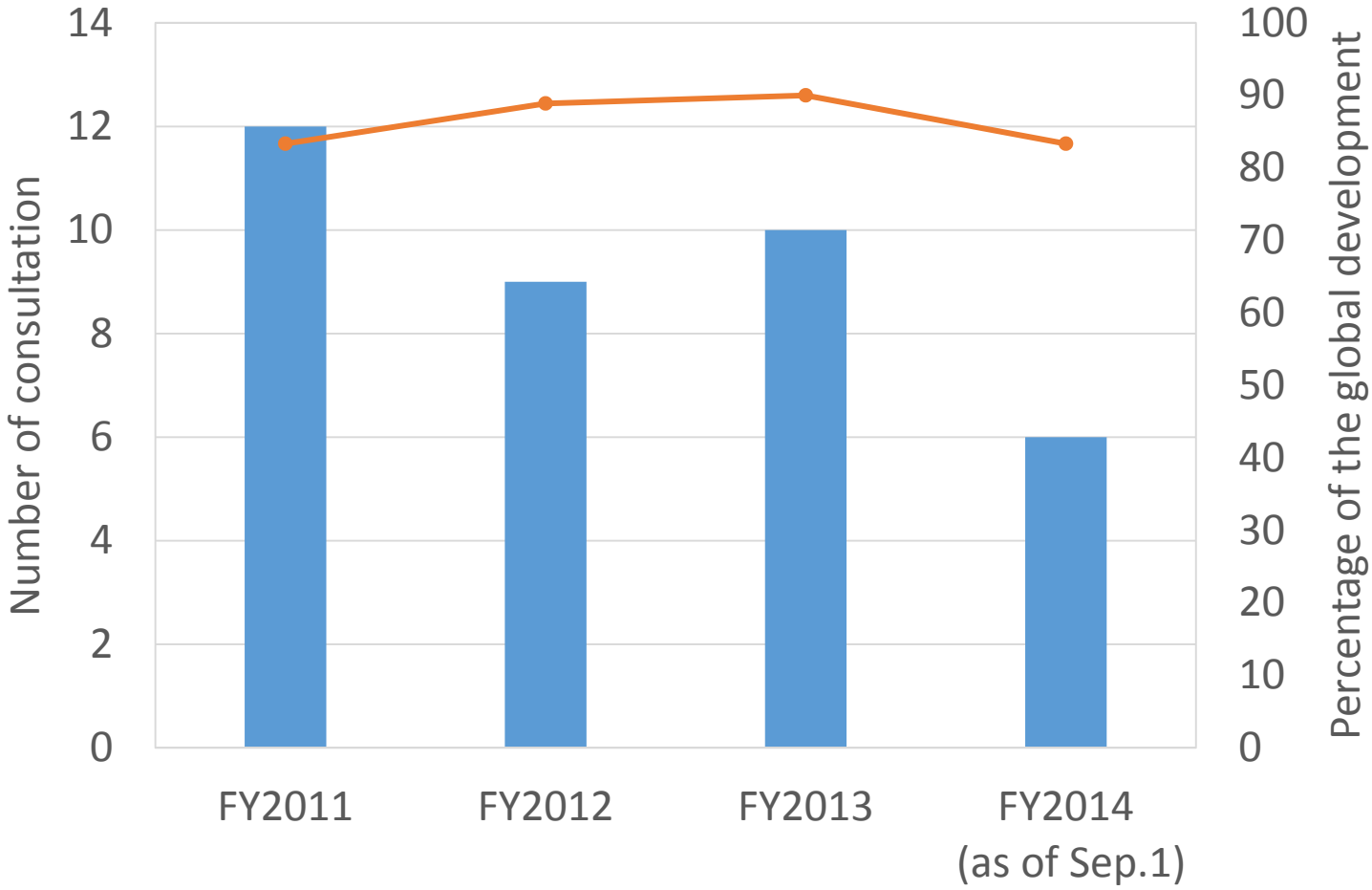
* No significant result

- The Cause of the failure is unclear (prevalence of nursing-service, insufficient observation of patient by their informant, etc.)
- In principle, efficacy in both cognitive and functional or global endpoint are required.

Efficacy Endpoint Required for Predementia Stage of AD in Japan

- Predementia stage of AD
  - Time to a diagnosis of dementia
  - Composite scale of cognition and function
    - CDR-SB
    - New composite scale
      - Publicly available and widely applicable scale is preferable.
      - Appropriateness could be discussed in PMDA's qualification system or clinical trial consultation in each drug.

Scientific Consultation of Drugs for Dementia in PMDA



New Composite Scale of Cognition and Function

1. Characteristic features impaired in Predementia stage of AD should be covered.
2. The relationship between longitudinal change of the score and the progression of the disease including conversion to dementia should be investigated.
3. Validation in Japanese patient is required before Ph3.
   - Careful consideration should be taken in terms of difference in language, culture and healthcare environment, etc.
   - J-ADNI's clinical / neuropsychological data may be used to investigate longitudinal change of each component (except AVLT).

Clinical Data Required in Japan in global development

- Phase 1 study to investigate safety and PK is basically required in Japanese.
- Phase 2 study to compare dose-response relationship between Japanese and other population is required.
  - Simultaneous development of Japan and foreign countries is recommended.
  - Appropriateness of the new composite scale should be examined from Phase 2 study.
- Phase 3 study: Consistency of results (patient characteristic, efficacy, safety) between Japanese and entire population need to be evaluated.

Points to be Considered in Drug Development in Japan

1. Investigation of ethnic differences
   - The differences of the natural history of AD are not well understood at present.
2. Differences in clinical trial circumstances
   - Prevalence of nursing care services.
   - Large number of institutions may be needed.
3. Differences in healthcare environment
   - Difference of doses and dose regimen of ChEIs
   - Universal health care system may cause decrease of patient's incentive to participate in the trial, and increase of concomitant therapy or dropout.

Conclusion

- Participation in global clinical trial would be necessary for pre-dementia stage of AD.

  However, though there are some issues to be considered to conduct clinical trials in Japan.

  (e.g. differences in healthcare environment, the amount of available data regarding natural course)

- We would like to encourage participation in global study from early stage of drug development by addressing regional issues through continuous discussion.

Reference

- Clinical trial Consultation
  - Overview of Consultation System in Japan

    http://www.pmda.go.jp/kokusai/2012_sympo_j/file/2012_sympo-9.pdf
  - Consultation for Qualification (Only in Japanese)

    http://www.pmda.go.jp/operations/shonin/info/consult/m03_pharma.html

- Guideline development for Alzheimer's disease
  - Interim report "Issues to Consider in the Clinical Evaluation and Development of Drugs for Alzheimer's Disease"

    (Only in Japanese)

    http://www.pmda.go.jp/regulatory/promotion_p/file/h_u-tokyo/h_u-tokyo_h25-01.pdf
  - The University of Tokyo Hospital website

    https://plaza.umin.ac.jp/~ueecd/en/jigyo2_2.html