“Good Review Practice” in Japan

Session B : GRevP Workshop
7 November, 2012 in Chinese Taipei

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Today’s contents

1. “Good Regulation”

2. Japan’s efforts for “Good review”

3. Related area to be considered

4. Summary from our experience

1. “Good Regulation”

“Good Regulation”?

- Efficient: Cost-beneficial
- Effective: Achieve the regulatory outcome
- Transparent
- Clarity: Understandable, practicable
- Equity: fairness
- Harmonization: International Standard
- Consistent
- Flexible: Continuously updated and maintained

2. Japan’s efforts for “Good review”

Two Japanese Regulatory Authorities for Pharmaceuticals and Medical Devices

MHLW

Planning basic policy, enforcement of administrative measures based on the law

- Marketing authorization of pharmaceuticals and medical devices
- Issue emergency safety information and direct product withdrawal
- Safety measures for emergent and significant cases

PMDA

Review, examination and data analysis

- Scientific review, GMP/GLP/GCP inspection and consultation on the development of pharmaceuticals and medical devices for marketing authorization
- Collection, analysis and dissemination of information relating to quality, efficacy and safety of pharmaceuticals and medical devices

“Good Review Practice”

We do not have the word “Good Review Practice” in Japanese regulation, but acknowledge the necessity of “General Review Principles” in PMDA

- To standardize general review policy
- To avoid inconsistent decision making
- To clear minimum check points in the review
- To accelerate review time
- To be Transparent in regulatory review process

- To standardize general review policy
- To avoid inconsistent decision making
- To clear minimum check points in the review
- To accelerate review time

"Points to consider documents" in April, 2008

- To be Transparent in regulatory review process

"Sharing review situation of an individual product" in December, 2010

“Points to Be Considered by the Review Staff Involved in the Evaluation Process of New Drugs”

Contents

Japanese: http://www.pmda.go.jp/topics/h200417kohyo.html
English: http://www.pmda.go.jp/english/services/reviews/file/points.pdf

“Points to Be Considered by the Review Staff Involved in the Evaluation Process of New Drugs”

Purpose:

To promote an understanding

among the review staff involved in the evaluation

- of new drugs
- of the basic principles and major points

that need to be considered in being involved in he drug evaluation process (at the PMDA)

“Points to Be Considered by the Review Staff Involved in the Evaluation Process of New Drugs”

Scope:

- Summarizes basic points to be considered

  during the actual evaluation process after submitting new drug application

- Mainly describes points related to clinical studies

  It has been major issues of discussion for approval in the past

- Many other points which should be judged on a case-by-case basis

  especially, for drugs in the field of orphan diseases, serious diseases which existing therapies have not been yet established

“Points to Be Considered by the Review Staff Involved in the Evaluation Process of New Drugs”

<u>Basic Principles in the Review</u>:

Major Points

- Evaluate data **based on science**, but take into consideration other factors
  (e.g. timing of the study, previous decisions and the patient’s points)
- Present **opinions proactively** for making the best decision at PMDA
- Attempt to **find the appropriate solution for concerns** by having good communication
- Provide **an objective and accurate information** to the patient and healthcare professionals
- Prepare **the review report** with easy understanding

“Points to Be Considered by the Review Staff Involved in the Evaluation Process of New Drugs”

<u>Major Points for consideration</u>:

1.Has the **reliability** of the conducted studies and submitted documents been ensured?

2.Is the efficacy in the study population considered to be **more effective** than placebo according to the results of properly designed clinical studies?

3.Do the obtained results have **clinical significance**?

4.Are there **any unacceptable risks as compared to the benefits**?

5.Can the drug be supplied continuously with **stable efficacy and safety from a quality assurance** standpoint?

“Points to Be Considered by the Review Staff Involved in the Evaluation Process of New Drugs”

Detailed Points to consider(1):

1.Are the development strategy, data package and study designs appropriate in line with the intended indications and usage?

2. Has the data reliability in the submitted documents been ensured?

3.Are there no significant differences in the efficacy and safety caused by ethnic factors (when foreign clinical data are submitted as the pivotal confirmation data)?

4.Has superiority been confirmed against placebo or other doses in the efficacy evaluation?

5.Is the range of the placebo responder rate presumed to be constant in the efficacy evaluation?

“Points to Be Considered by the Review Staff Involved in the Evaluation Process of New Drugs”

Detailed Points to consider(2):

6. Has non-inferiority/superiority against an active control been confirmed in the efficacy evaluation?
7. Has the efficacy been confirmed sufficiently even in a unblinded study without a control?
8. Are there any discrepancies among the pivotal study results?
9. Can the recognized risks be controlled and the risks acceptable when considering the benefits?
10. Are there any points of concern in regard to the non-clinical study results in the submitted application documents?
11. Have the appropriate processes and strategies been provided for assuring the quality of the product that would allow continuous manufacture of a drug which shows efficacy and safety equivalent to those suggested by the data in the submitted application document?

“Points to Be Considered by the Review Staff Involved in the Evaluation Process of New Drugs”

Supplementary Note:

(Requisite clinical study)

- In Principle, recommend to confirm drug efficacy in “two or more randomized controlled studies”
  - “two or more randomized controlled studies”
    - an exploratory dose-finding study + a confirmatory study
    - a domestic bridging study + overseas confirmatory studies

- The superiority of a drug to placebo is generally sufficient evidence for approval

- In a disease area where placebo responder rate is presumed to be constant, non-inferiority results or objective results in a study without a control maybe sufficient for evaluation

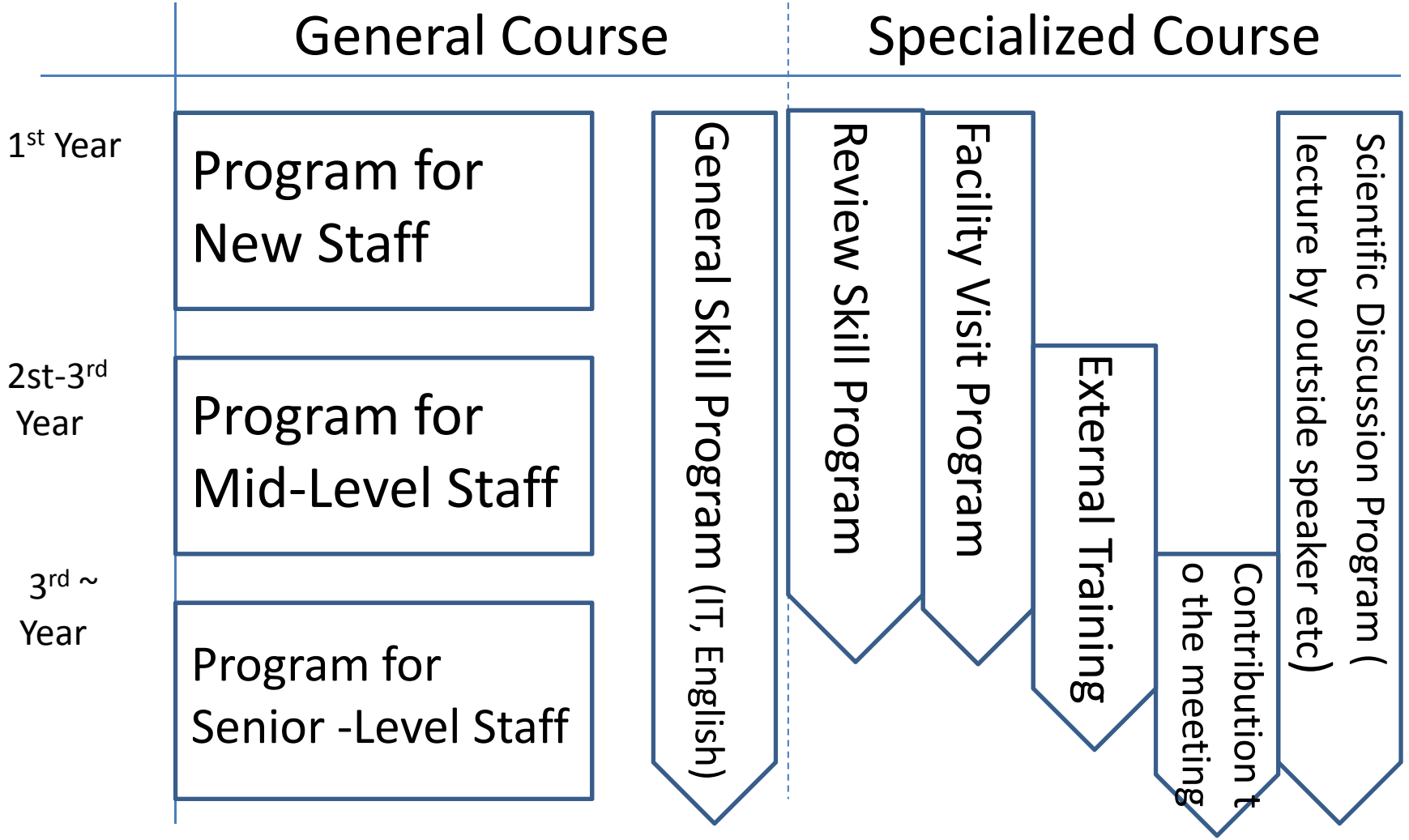
3. Related area to be considered

To enhance the ability of “Good Review”

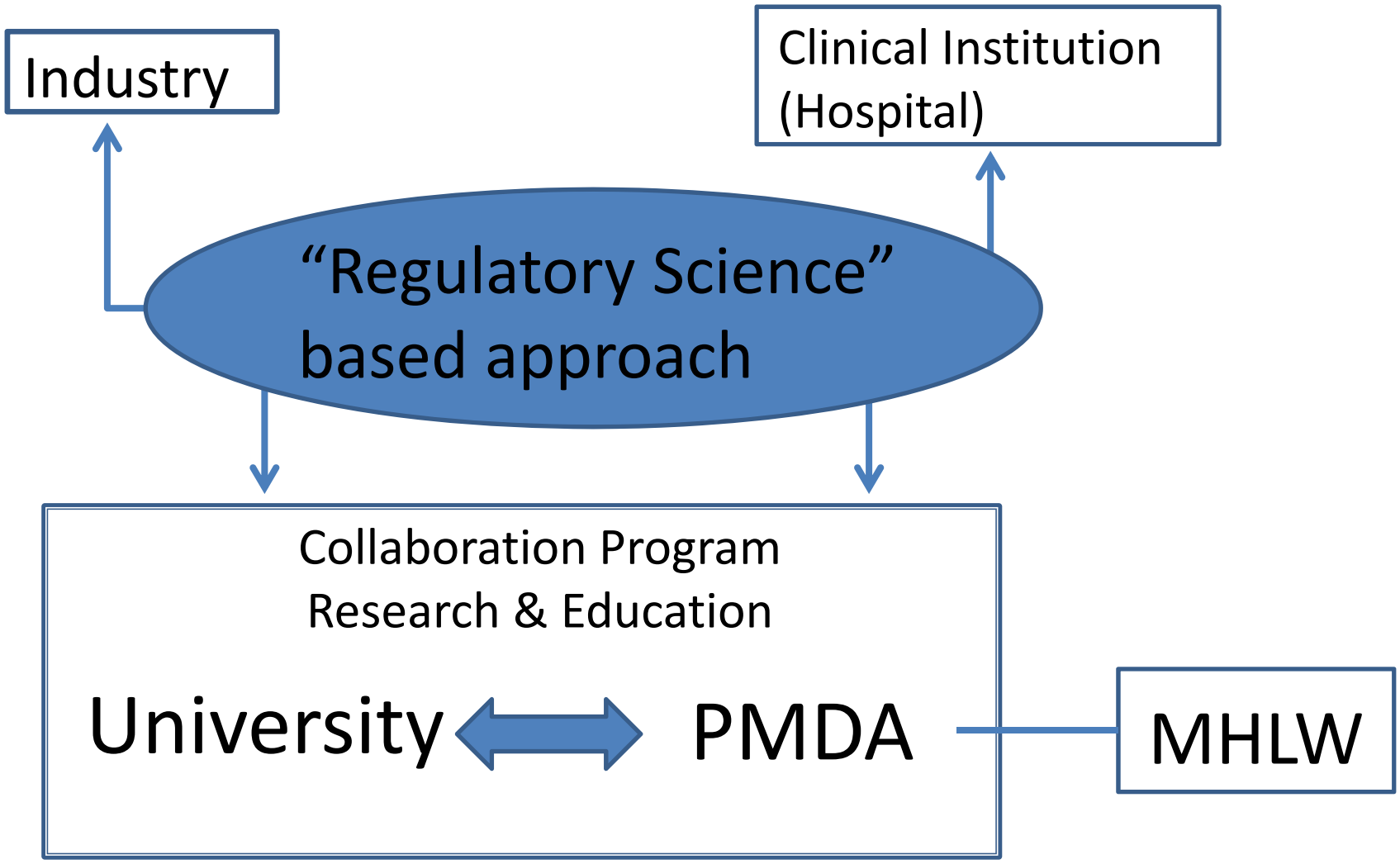
1. Human Resource Training and Development

2. Advancing “Regulatory Science”

Human Resource Training & Development



Advancing “Regulatory Science”



4. Summary from our experience

Summary

From Japanese experience

1.Good review system needs clear principle of organization as well as individual reviewer and to outside regulators understanding

2. In addition,
   (1) the enhancement of the ability of reviewer through the training
   (2) collaboration with outside entities to improve his/her ability for new scientific issues