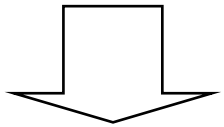
Japan MHLW/PMDA Perspective and Strategy

Yoshiaki Uyama, Ph.D.
Office of New Drug III
Pharmaceuticals & Medical Devices Agency
(PMDA)

Benefit of Pharmacogenomics

- Improving benefit/risk ratio
  - More safe, more effective
- Adjusting Dose
  - Can determine the best dose
- Increasing successful rate of clinical trials
  - Focusing on data in responder



More drug, more appropriately

PGx-based Medicine

There are some examples using pharmacogenomics in approved drugs: e.g.; Herceptine (trasutuzumab)

"PGx-based medicine is *not* a *dream*"

However, to realize it, pharmacogenomics should be appropriately applied in drug development

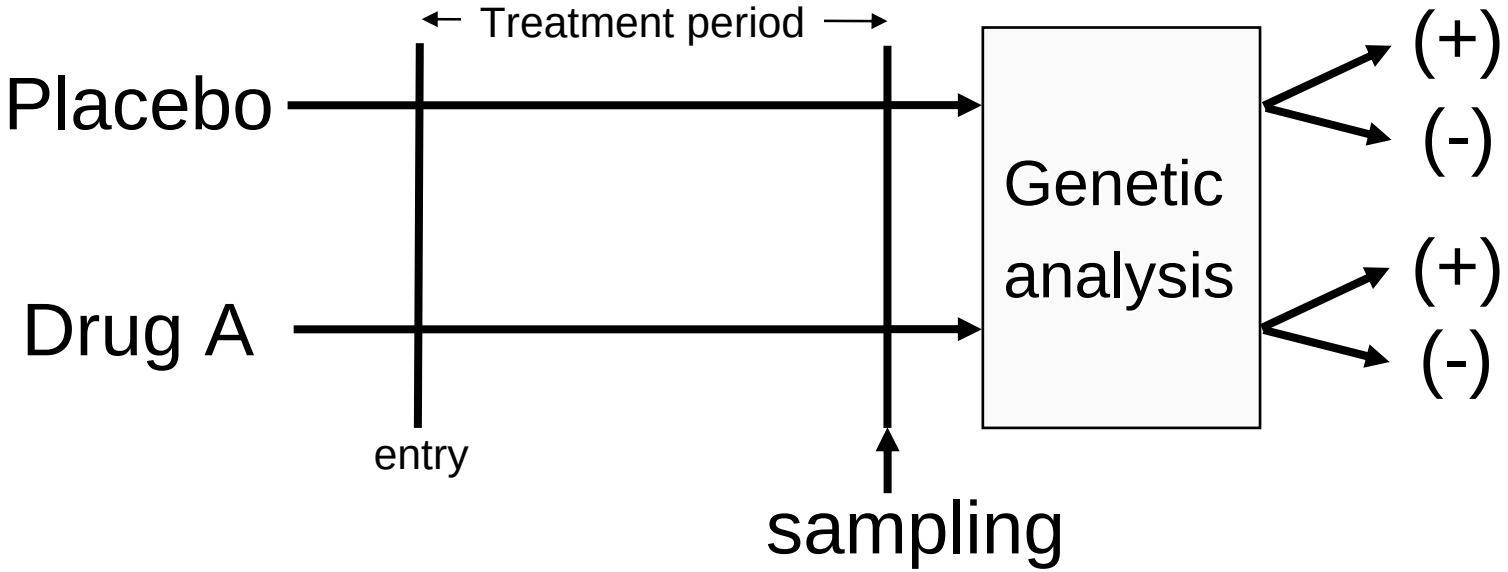
Possible Designs for Pharmacogenomic Clinical Trials

- Retrospective Approach
  - To search a target gene
  - Exploratory Data

- Prospective Approach
  - To confirm a hypothesis
  - To establish clear evidences

Retrospective Design

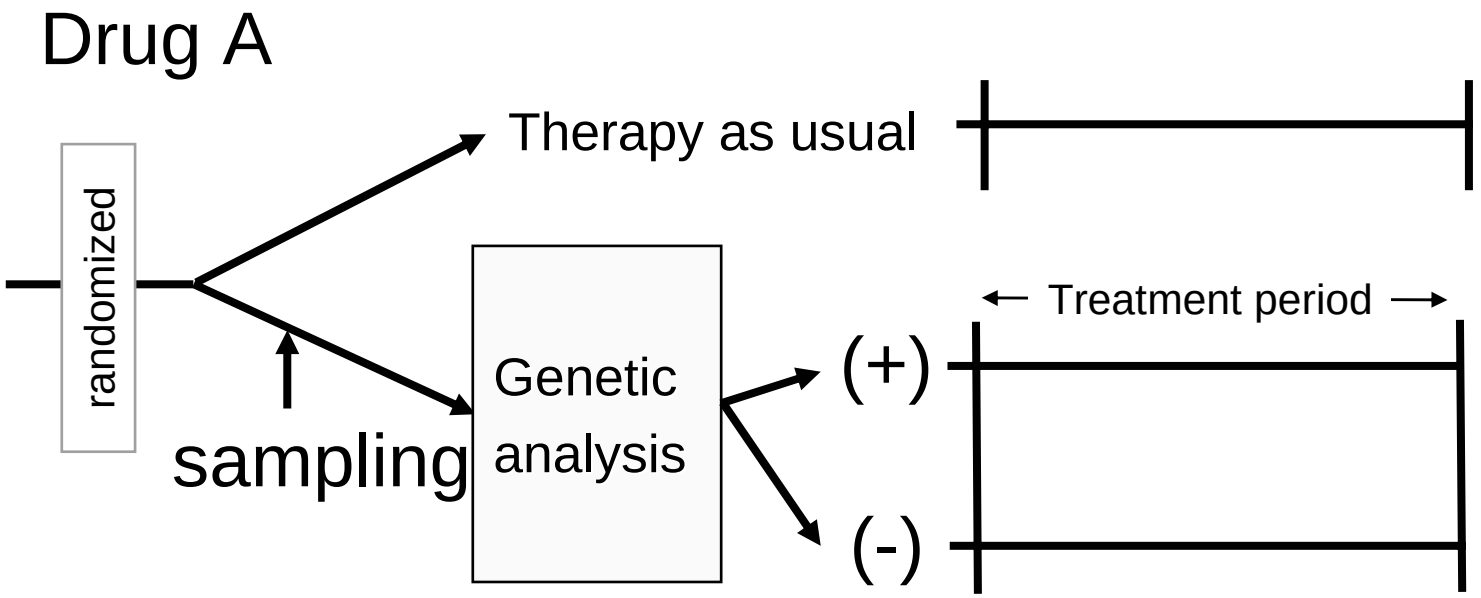
Randomized, Double Blind, Placebo-controlled Trial



- Patient numbers for genetic test maybe unbalanced in two arms?
- Sampling maybe limited in some patients?
- Results are not confirmative?

→Confirmative trial will be necessary

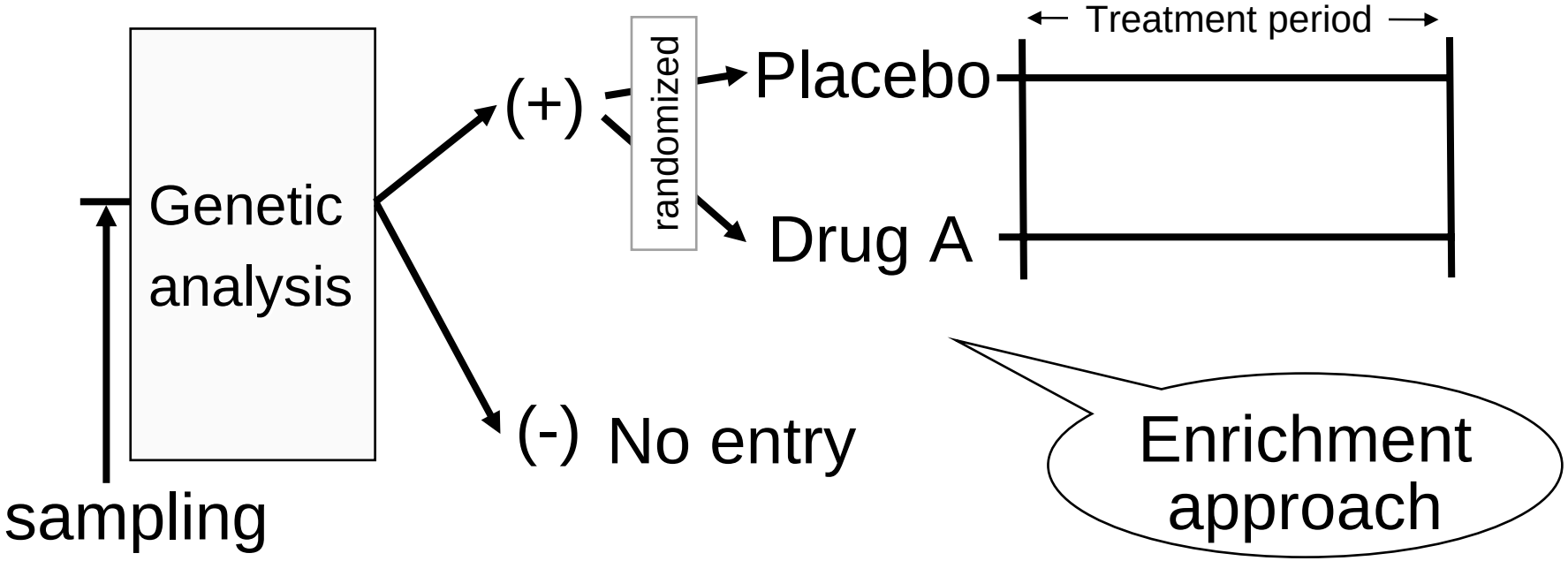
Prospective Design 1



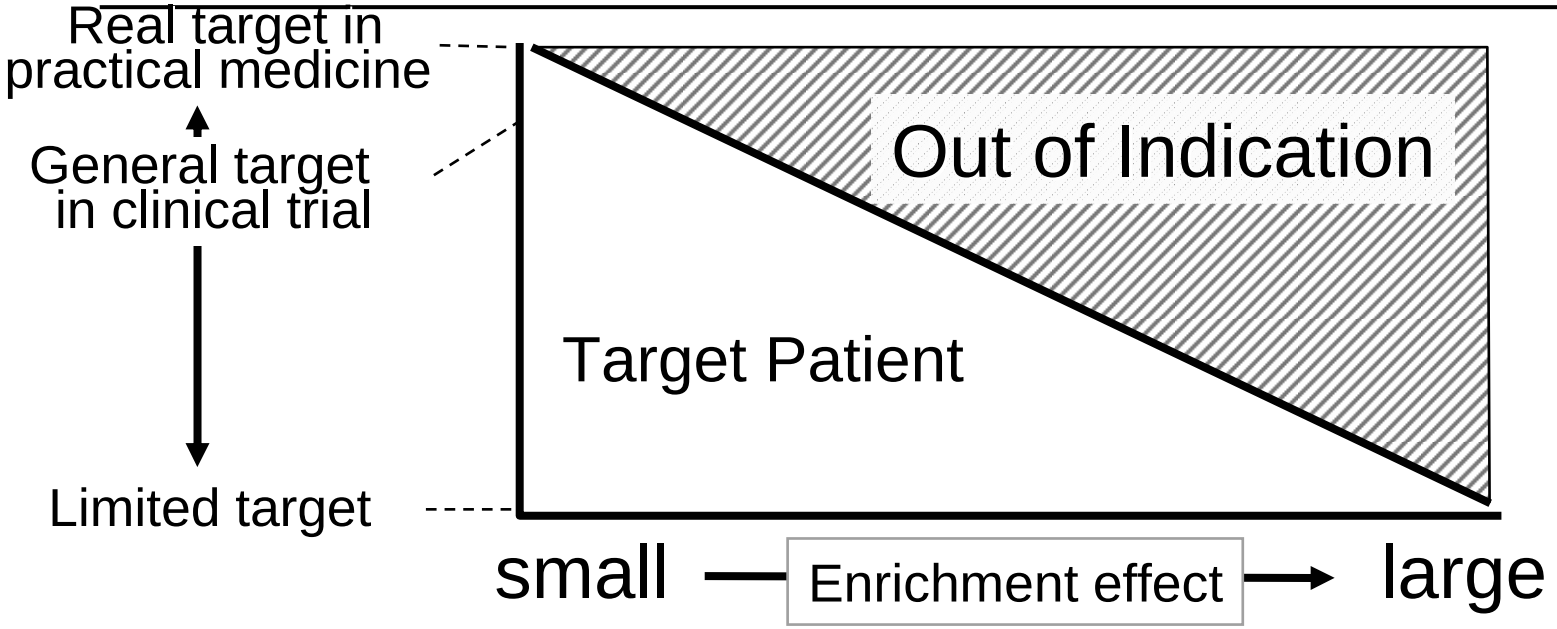
- To test clinical utility
  - PGx test is really necessary?
  - Cost-benefit relationship
- Results are confirmative

Prospective Design

Randomized, Double Blind, Placebo-control Trial



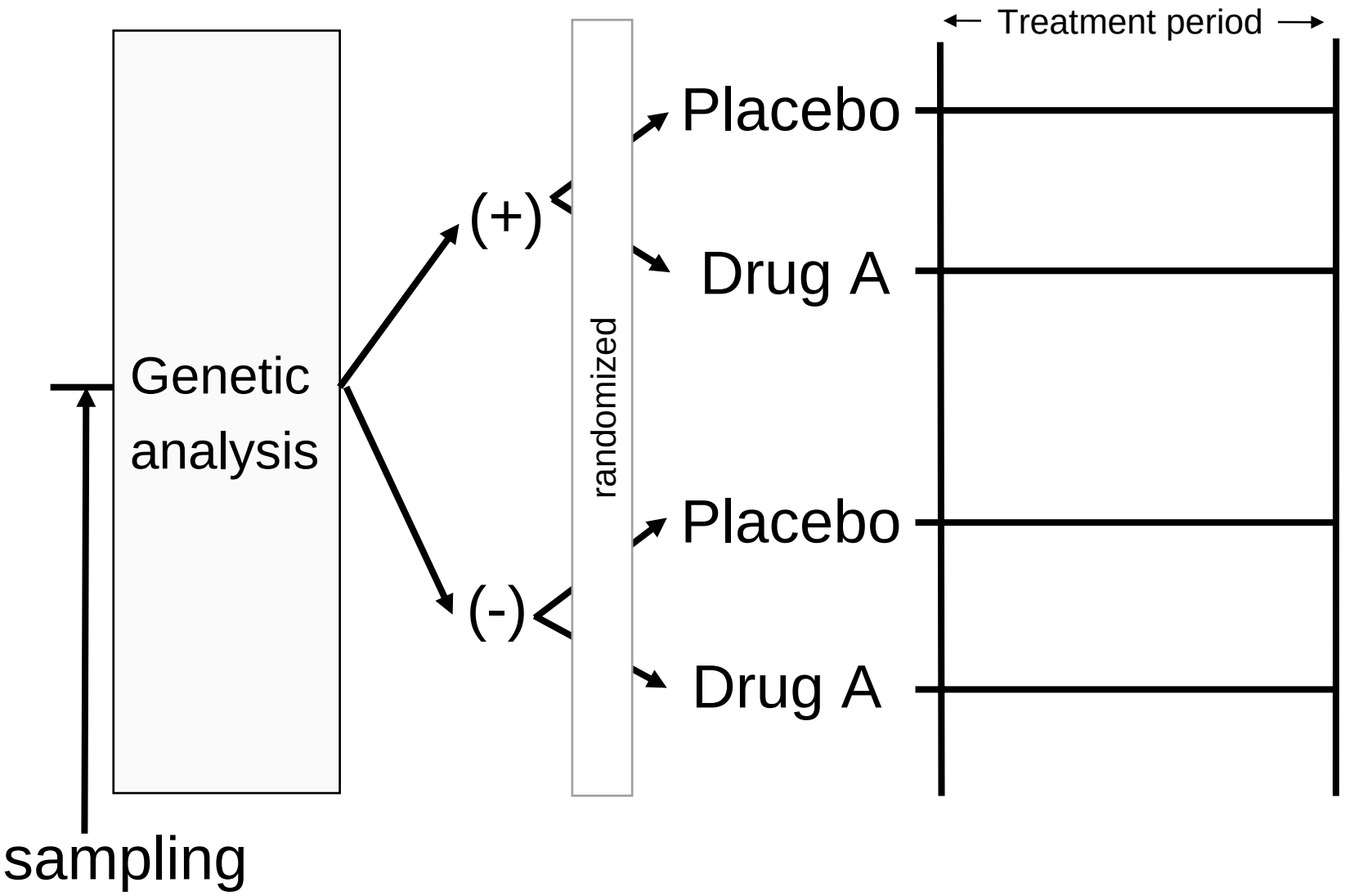
- Increase analytical power of trial
- Results are confirmative
- But, data in gene(-) patients can not be obtained
- May lose a chance of treatment for (-) patients



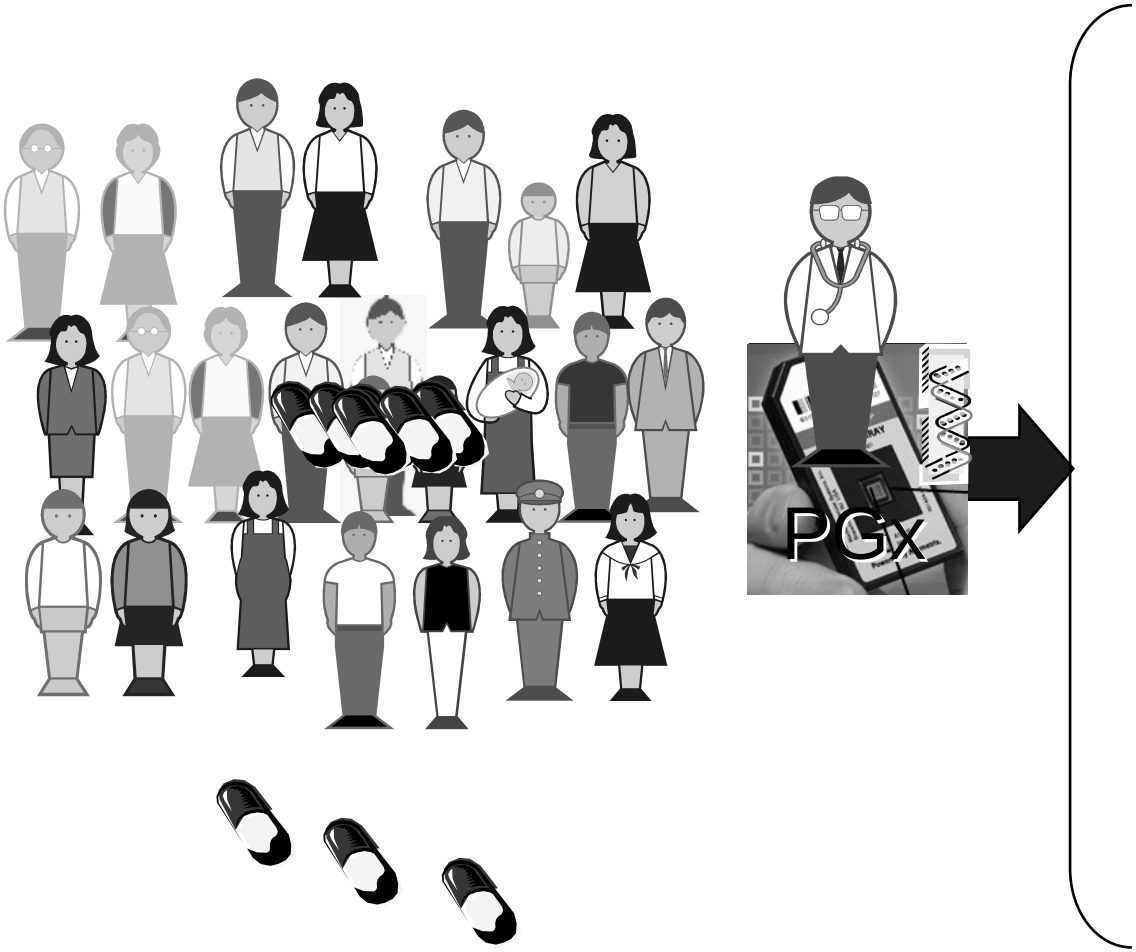
- Too much enrichment may limit target patients/Indication
  - Enriched population may not represent a real population in a practical medicine
  - Enriched approach may limit the indication for approval and increase off label use
- How much enrichment effect is useful and reasonable?

Prospective Design

Randomized, Double Blind, Placebo-control Trial



How to use PGx in drug development

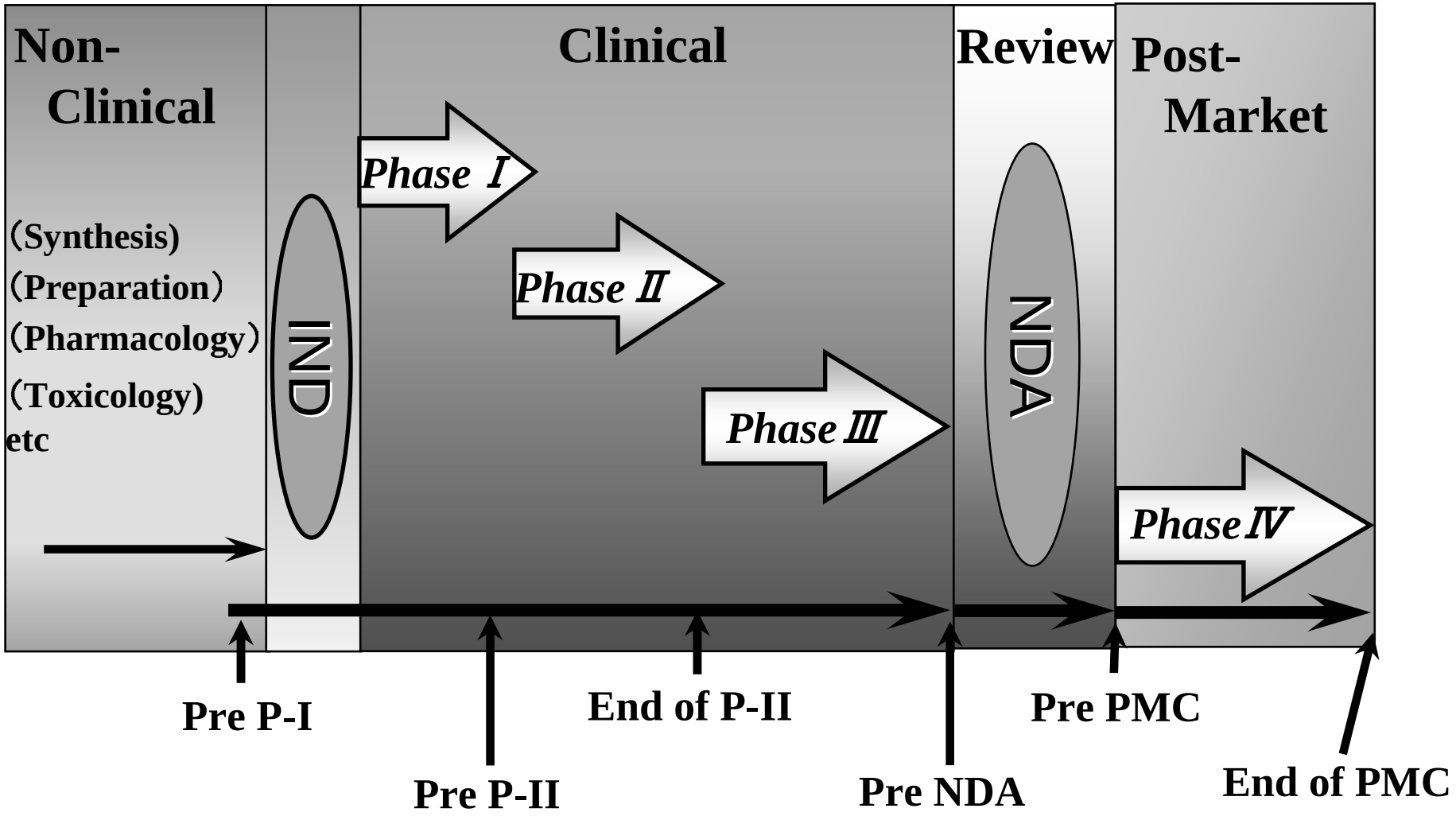


How many capsules are appropriate?

- Pharmacogenomics can be applicable in clinical trial for regulatory submission, if
  - Genetic assay is available and reliable/validated
  - Results are prospectively confirmed
  - Benefit/Risk can be evaluated even in gene (-) patients
  - Enrichment effect is reasonable and acceptable

etc.

R&D stage and clinical trial consultation



Many chances to discuss about PGx issues

Establishment of guidance for appropriate Pharmacogenomic approach in Clinical Trial & Review in Japan

“Submission of Information to Regulatory Authorities for Preparation of Guidance for the Use of Pharmacogenomics in Clinical Trials”

- June 8, 2004

  Official announcement was made for inviting the comments

- July 9, 2004 Comment submission was closed

- March 18, 2005 Final version was notified

Final Version of the Notification

- Purpose
  - Correctly understand situations of pharmacogenomic activities
  - Establish reasonable & appropriate guidance focusing on Pharmacogenomic Clinical Trial
- Contents
  - Recommend to submit information (List) about Pharmacogenomic Clinical Trial under conducting, conducted in the past or planning
  - Information includes a target disease, a target gene, sample size, purpose of a study and so on.

Remark in the Notification

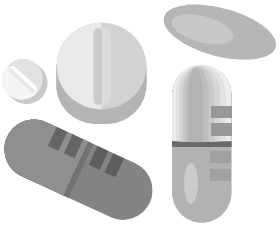
- 1st deadline for submission
  - September 30, 2005
  - Even after this period, data submission are also appreciated
- MHLW/PMDA may ask to provide more data after submission of the list
- The information is protected to disclose to the public
- The submitted information is not used for regulatory decision for approval
- Data having direct impact to indication, dosage or safety should be submitted in accordance with requirement of the law (Pharmaceutical Affair Law)

PMDA PDG (Pharmacogenomics Discussion Group)

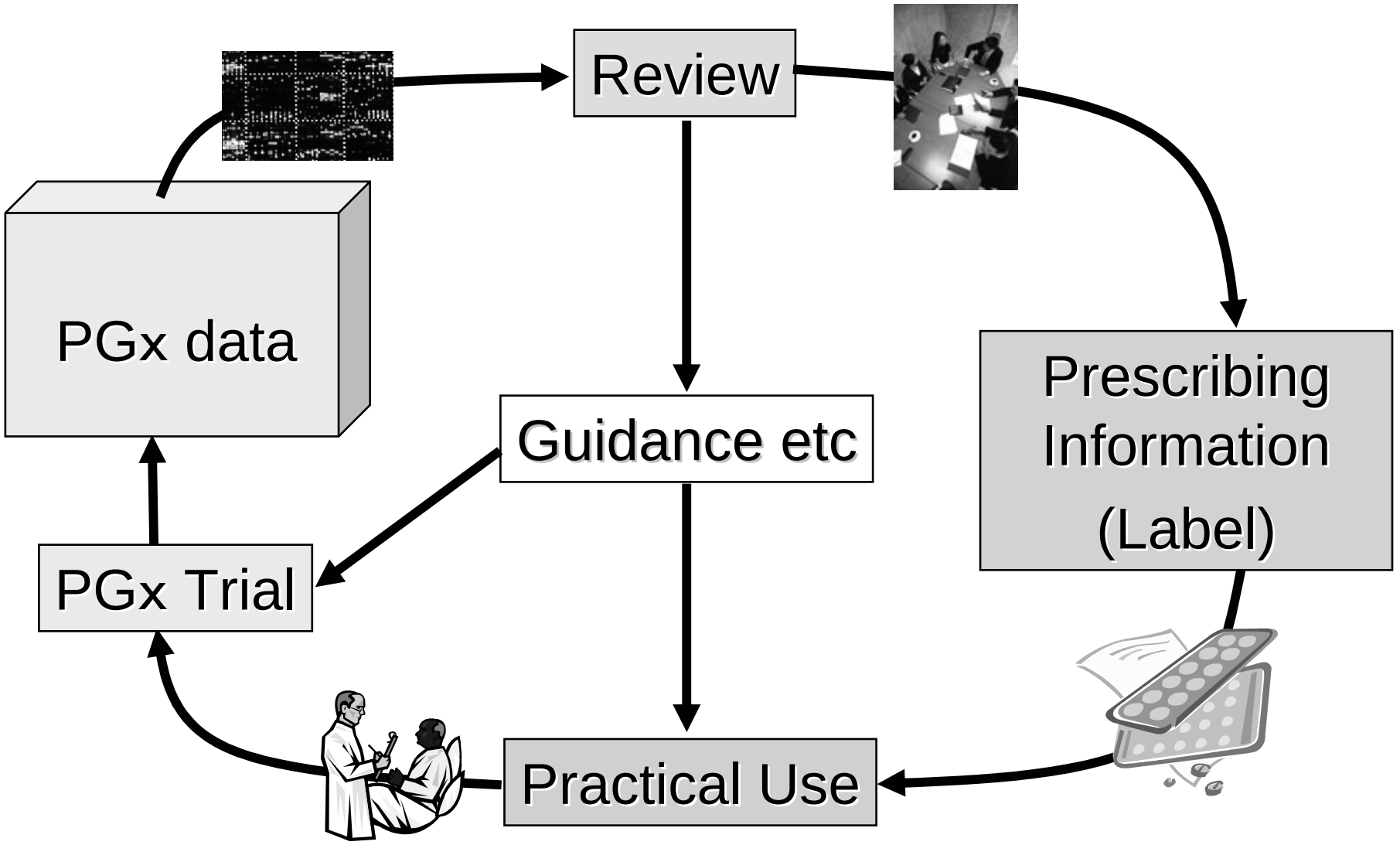
- 16 members from Review Offices (New Drug, Safety & Devices)

－Mission－

- Share information regarding PGx issues
- Exchange & Discuss a view of PGx regulation
- Keep consistency in PMDA consultation & review on PGx
- Promote appropriate PGx Clinical Trial



Steps for PGx-based medicine



Future

- Discussions for Harmonization of Regulatory Approaches have already been started
  - DIA 3rd workshop on Pharmacogenomics (April 11-13, 2005)
  - ICH Brussels meeting (May 9-12, 2005)
  - OECD workshop (Oct 17-19, 2005)
  - ICH Chicago meeting (Nov 7-10, 2005)

- Possible Area for Harmonization

For example

- Terminology
- Format & Contents of reports for Regulatory submission
- General Principles of pharmacogenomic clinical trial
- General Standard of Ethical issue (incl. Banking)

Backup slides

Format of list for submission (1)

Drug Code/ name	Category (types of drug)	IND No.	Phase	Trial Period	Country (Race)	Target	Size (genetic test)
AAA	232 Gastric Ulcer	AA0011	IV	1998.1～ 1998.12 (complete)	Japan (Japanese)	Healthy	20 (20)
BBB	H^+ pump inhibitor	-BBB-JPN-22 (PPPP)	III	1999.1～ 2001.12 (complete)	Japan (Japanese)	GERD	250 (250)
CCC	CCC Antagonist	CCC-123-456	II	2003.10～ 2005.3 (on going)	UK, NL, DE and other 3 countries in EU (multi-race including Japanese)	RA	200 (200)
DDD	TTT Inhibitor	DDD-778899	II	2005.4～ 2006.3 (planning)	Japan (Japanese)	Gastric Cancer	45 (20)

Format of list for submission (2)

Target Gene/ Marker	Purpose	Method	Banking (year)	Schedule for Analysis	Impact on label	IC	Co-dev. of device
CYP 2C19	(Exploratory) PK/PD difference	PCR	None	Complete	None	Y	N
CYP 2C19	(Exploratory) Responder rate/Randomized by genotype	PCR	None	Complete	None	Y	N
Unk	(Exploratory) Genetic influence on SAE	DNA Banking (unknown)	Yes (15 y)	Not done (unknown)	None	Y	N
Unk	(Exploratory) Detect genetic biomarker	Microarray	Yes (10 y)	Not done (after trial completion)	None	Y	N