Strategies and challenges for innovative drug development

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Drug Evaluation Committee
Japan Pharmaceutical Manufactures Association
Vision of Drug Evaluation Committee

**Innovative Information & Methodologies**
- Real World Evidence
- Clinical Innovation Network
- Adjustable Clinical Trial

**Innovative Legislation**
- Conditional early approval
- RMP/Optimum Use GL
- PMD Act/Clinical Study Act

Pursue Regulatory Science
- GCP Renovation/PMD Act

Invent Innovative Medicine
- Higher productive/Earlier patient access

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Countries of origin of top 100 sales of pharmaceutical products for medical use (2017)

- USA: 50
- Japan: 12
- Switzerland: 11
- UK: 7
- Germany: 7
- Denmark: 5
- France: 3
- Sweden: 2
- Belgium: 1
- Israel: 1
- Luxembourg: 1

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Drug Development: challenging

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<tr>
<th>Target Disease</th>
<th>Oncology</th>
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<td>Rare Disease</td>
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<th>Clinical Trials</th>
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<td>Non-traditional trial</td>
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<td>RWD/RWE</td>
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How can we improve productivity, probability, and predictability?
Multi Regional Clinical Trial  mid 2000～now

North America
EU
South America
Africa
Asia
Japan
MRCTs in Clinical trial notification in Japan

First Notification
2nd or further notification

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<th>Year</th>
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Clinical trials in Asia managed from Japan - Approved drugs in 2006-2019 -

229 trials in Asia/498 trials in Global (Phase 1-Phase 3)

↓

235 Products approved
Clinical trials in Asia managing from Japan
- Ongoing trials in 2019 -

Total: 272 (Phase 1-Phase 3)

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<th>Country</th>
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<th>Gastro-intestinal</th>
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Comparison of data queries

Drug Information Journal
- 26 multinational studies
- 10 therapeutic areas
- 4,721 enrolling sites
- 63,871 patients
- 7 global CROs
- From 2005 to 2010

→ No statistically significant differences in the query rate
ICH-GCP renovation

- ICH-E8(R1), ICH-E6(R3), ICH-E17, ICH-E19

- Diversity
  Conventional Clinical Trial ~ Observational study (using RWD)

- Flexibility / Adjustability
  - Master Protocol (Basket/ Umbrella)
  - Adaptive Design (ICH-E20)
  - Registry-based RCT : Pragmatic Clinical Trial
E6(R3)-Reconstruction of GCP

• GCP Renovation: step wise reconstruction of achievable process to “Fit-for-purpose Quality”

E6(R3): 2nd step of GCP renovation – critical step for fundamentals

Revised E6: Overarching principles

Fit-for-purpose

Critical-to-Quality factors

fundamental

Study objectives

Data source

E6 Annex 1: For traditional interventional trials

E6 Annex 2: For non-traditional interventional trials

New Drug Registration

Evidence generation for reg review of approved drugs

Traditional CRFs

Real world data source

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Innovative Methodologies for Clinical Trials

-Adjustable clinical trials-

- Master Protocol
  - Basket trial design: single investigational drug or investigational drug combination across multiple cancer population
  - Umbrella trial design: investigational drugs or investigational drug combinations in single cancer type

- Adaptive Design: allows for prospectively planned modifications to one or more aspects of the design based on accumulating data from subjects in the trial
Possible Utilization of Real World Data

**Objectives for RWD Utilization**
- **A) Market Research**: feasibility for clinical development
- **B) Pts recruitment**: Recruit the registered Pts
- **C) Control arm**: Possible for “Single Arm” trial
- **D) PMS**: Survey for SAE frequency after marketing
- **E) Conditional Approval**: Confirm the predefined condition
- **F) Off-label use**: new population, change in dose
- **G) HTA**

**Utilization timing in drug development process**

- **Preclinical**
- **Ph 1**
- **Ph 2**
- **Ph 3**
- **Registration**
- **Launch**
- **Post Market**

A) Market Research

B) Patient recruitment

C) Control Arm

D) PMS

Conditional Approval

Launch

E) Confirm in RWD/RWE
RWD with off-label use supported the FDA’s label expansion

- Palbociclib for Male Patients with metastatic breast cancer
- CD4/6 Inhibitor for HR+, HER2-, metastatic breast cancer
- Men: <1% of breast cancer
- FDA approved based on RWD in Apr. 2019
- Three data bases;
  i. IQVIA Insurance database
  ii. Flatiron Health breast cancer data base
  iii. Pfizer global safety database

- Example of RWD for a change in dose, dose regimen, or route of administration, new population, etc

Edited from presentation by T.Yamanaka
Possible Utilization of Real World Data

◆ Objectives for RWD Utilization
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  E) Conditional Approval : Confirm the predefined condition
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  G) HTA

◆ Utilization timing in drug development process
To make our business more productive

- Multi Regional Clinical Trial
- GCP renovation
- Utilize RWD