The Impact of Critical Path Initiative on R&D in Japan

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Outline

- The Critical Path Innovation
- The Indication of CPI to R&D in Japan
- Future Trends
The Critical Path Innovation

Facts:
- Recent bloom of biomedical science and discovery of innovative products can provide prevention, treatment, and cure of serious disease to our society

BUT
- The number of submissions to FDA has been decreasing
- Biomedical spending has been increasing
  - The cost of critical path becomes very expensive
The Critical Path Innovation

Possible Reasons:

- Still applying "the tools and concepts of the last century" for the evaluation of the "century's candidates"

  Success rate is decreasing

  "Currently one out of every two phase III trials fails"
  (Dr. Janet Woodcock, Keynote at FDA and Industry Workshop, 2004)

  "The path to the market for successful candidates is long, costly, and inefficient, due in large part to the cumbersome assessment methods"
  (FDA Critical Path Whitepaper, 2004)
The Critical Path Innovation

- Goal:
  “is to develop new, publicly available scientific and technical tools – including assays, standards, computer modeling techniques, biomarkers, and clinical trial endpoints – that make the development process itself more efficient and effective and more likely to result in safe products that benefit patients” (FDA Critical Path Whitepaper, 2004).
10 Year Trends in Biomedical Spending

Figure 1: 10-Year Trends in Biomedical Research Spending

Source: FDA, Critical Path Whitepaper, 2004
10-Year Trends in the Number of Submissions to FDA

Figure 2: 10-Year Trends in Major Drug and Biological Product Submissions to FDA

Source: FDA, Critical Path Whitepaper, 2004
Investment Escalation per Successful Compound

Figure 3: Investment Escalation per Successful Compound


Source: FDA, Critical Path Whitepaper, 2004
Current Situation in Japan

- Clinical Trial Costs: Very High
- Numbers of Clinical Trials: Diminishing
Location of Clinical Trials conducted by Japanese Companies

Even Japanese companies conduct clinical trials in foreign countries
Speed of Clinical Trials in Japan

[Comparison of Speed of Clinical Trials in Japan and Other Countries by Selected Companies]

(Area I)

(Area II)
Hollowing out of Clinical Trials

- High cost to conduct clinical trials
- Domestic companies conduct their clinical trials outside of Japan
- Slow speed of clinical trials
Comparison between US and Japan (Number of Clinical Trials)
Comparison between US and Japan (Cost)

Figure 3: Investment Escalation per Successful Compound

Investment required for one successful drug launch (discovery through launch)

Future Direction

- Methodologies
  - Clinical Trial Design
  - Evaluation tools
- Safety Network
Future Direction (Methodology)

Critical Path

- Preclinical
- Phase 1
  - PK/PD
- Phase 2
  - Dose Finding
- Phase 3
  - Confirmatory Assessment

"Cumbersome assessment methods"

"last century tools"
Future Direction (Methodology)

Adaptive Design

Phase 3

Stage I

1st assessment

Go/Stop - Decision
Sample size recalculation
Computer based Simulation
(Bayse, or empirical Bayse approach)
Surrogate marker evaluation
(validate within a study)

Stage II

Monitoring patients

High prob. of Success of Phase 3 Trial
Future Direction (Methodology)

Adaptive Design: Combination of Phase 2 and Phase 3

**Phase 2**
- **1st Assessment**
  - Futility Assessment
  - Biomarker, surrogate
  - Computer modeling (Bayes, Emp.Bayses)

**Phase 3**
- **Final Assessment for Phase 3**
  - Utilizing all pts. Participated in SGCT
- Extensive data monitoring for homogeneous pts.

- **2nd Assessment**
  - Recalculation of SS
  - Computer modeling (success prob.)
  - Biomarker, surrogate (validation)
Future Direction (Endpoints)

Ex: Neuropharm Disease Area

Characteristics of Clinical Trials

- Heterogeneity of Patients → Large Variability of response
- Hi Placebo Response Rate → Seek minimum efficacy
- Old Type of Primary Endpoint → Less Sensitive Evaluation of up-dated Products

HELP!

NEED science based objective evaluation tools
Finger movement Monitor

Quantitative evaluation of finger movement by using simple magnetic

Healthy volunteer

Distance (mm)

Time (秒)

Patient with Parkinson’s disease
70 yrs · male · left hand

## Optical Topography for Mental Disorder Diagnosis

Pattern of brain activity is dependent on

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<th>Pre</th>
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<th>Post</th>
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**WFT***

*Word Fluency Task*

### Performance
No significant between depression and bipolar

### brain activity shows big deference (depression state)

- Monopolar
- Bipolar

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Safety Issues

- Network system between Hospitals
- Research Grant from MHLW
  - EDC Network system within hospitals to monitor patients
  - Detection of unexpected AEs
  - Build data base regarding patients' background for signal detection and pharmacoepidemiology
Overall Picture

Medical Facility 1

Medical Facility 2

Medical Facility 3

Medical Facility 4

Medical Facility 5

Medical Facility N

Data Center

Step 1

Step 2
Step 1: Within a Medical Facility

Connect Necessary Medical Records per Patient

Unification of Medical Records regarding:
- Patient's background
- Dosage and duration
- Efficacy
- Safety
Step 2: Among Medical Facilities

(i) Unification of database from different MFs and establishment of Patients’ data base at Data Center

(ii) Detect unexpected AEs and analyze safety profile according to actual dosage and duration
Conclusion

- Our mission in Japan is the same as CPI
  - Need new methodologies
- Safety network
- Team work
  - Clinical trial specialists
  - IT, Computer scientists
  - Statisticians
Back up Slides
Costs of Clinical Trials in Japan

Average cost per patient per year

Relative cost per patient

Presentation by Dr. Uden at 3rd Kitasato-Harvard Symposium, 2002
Figure 7: Industry – FDA Interactions During Drug Development

Source: FDA, Critical Path Whitepaper, 2004