Tragedy of TGN1412 case

TGN 1412 is an anti CD28 monoclonal antibody specific to human with super agonistic action.

In the FIH trial, all of 6 healthy volunteer suffered from cytokine storm, 2 of them were critically ill with multiple organ failure.

It was considered that non-clinical data did not show any toxicity to be worried.

Was this case inevitable?

At first, the case was considered to be an exceptional case,

however

we believe we can avoid the 2nd case.

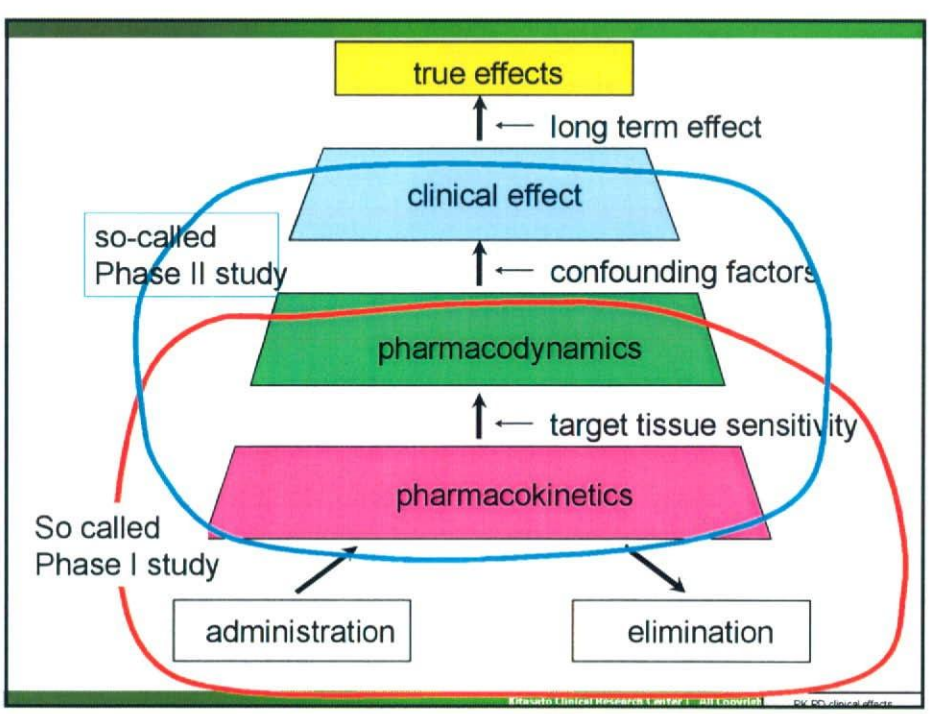
Phase I Trial
(Most typical kind of study: Human Pharmacology)

a) Estimation of Initial Safety and Tolerability

b) Pharmacokinetics

c) Assessment of Pharmacodynamics

d) Early Measurement of Drug Activity



In Planning a Phase I study

Presumption

Little difference in free drug concentration and toxicity according to species

Most toxic reactions is predictable from multiple animal models.

Prepare as many observations and means as possible to minimize possible risks.

Pharmacological and Pharmacokinetic Studies

The basis and direction of the clinical exploration and development rests on the non-clinical pharmacokinetic and pharmacology profile, which includes information such as:

a) Pharmacological basis of principal effects (mechanism of action).
b) Dose-response or concentration-response relationships and duration of action
c) Study of the potential clinical routes of administration
d) Systemic general pharmacology, including pharmacological effects on major organ systems and physiological responses
e) Studies of absorption, distribution, metabolism and excretion

Recommended non-clinical studies before first-in-human trial

1) Safety pharmacology
2) Toxicokinetics and pharmacokinetics
3) Single dose toxicology (2 species)
4) Repeated dose toxicology (>2 weeks)
5) Genotoxixity
6) Carcinogenisity*
7) Reproducive toxicology*

* not needed in initiating human studies.

Safety Pharmacology

includes the assessment of effects on vital functions,such as

cardiovascular system
central nervous system
respiratory system

should be evaluated prior to human exposure.

The data are used for determining extent, frequency, and timing of checkup including CV and CNS.

TOXICOKINETIC AND PHARMACOKINETIC STUDIES

Before human studies, information on absorption, distribution, metabolism and excretion in animals should be made available to compare human and animal metabolic pathways, although prediction of pharmacokinetics in human is difficult*.

Practically, investigators rely on toxicokinetic data more than pharmacokinetic data.

*Microdose clinical study is expected.

Single dose Toxicity

should be evaluated in two mammalian species prior to the first human exposure.

The data are extrapolated to the prediction of accidental over dosage.

In revised M3, the study may not be essential for initiating human studies.

Repeated dose toxicity

Check points are;
Evident toxicity (anatomical, histological)
Surrogate markers (laboratory testing)
Excessive pharmacological action

To avoid unacceptable adverse effects in human, lethal dose and NOAEL are important.

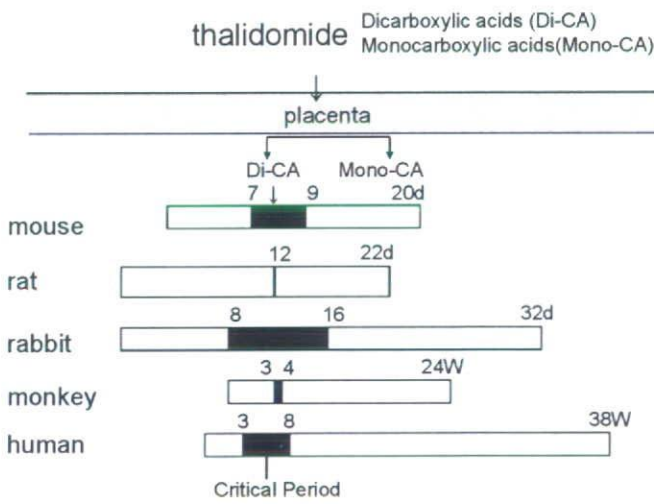
A repeated dose toxicity study in two species (one non-rodent) for a minimum duration of 2 weeks would support Phase I .

GENOTOXICITY STUDIES

In vitro tests for the evaluation of mutations and chromosomal damage are generally needed.

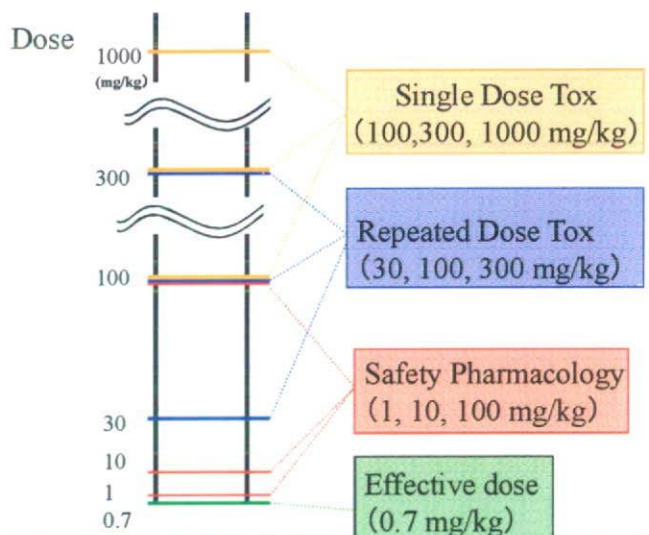
This is the most difficult part for extrapolating and we don't have a good tool to detect signals before the damage is reversible.

Species difference of critical period of thalidomide



 P179

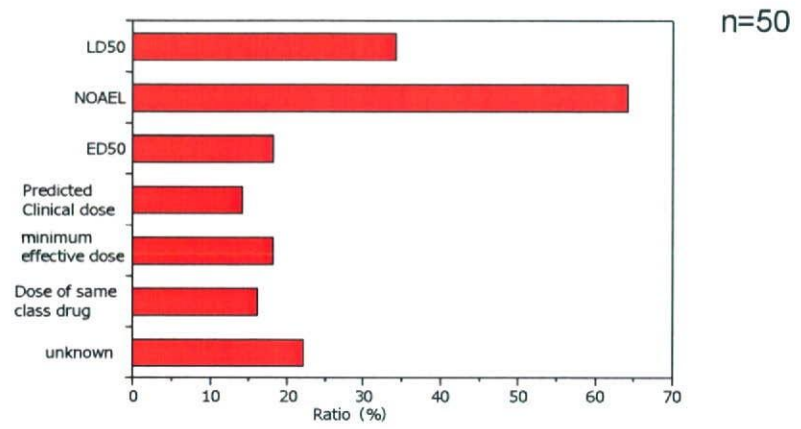
Example of Dose Range of Non-Clinical Study



 P180

Rationale for the first dose

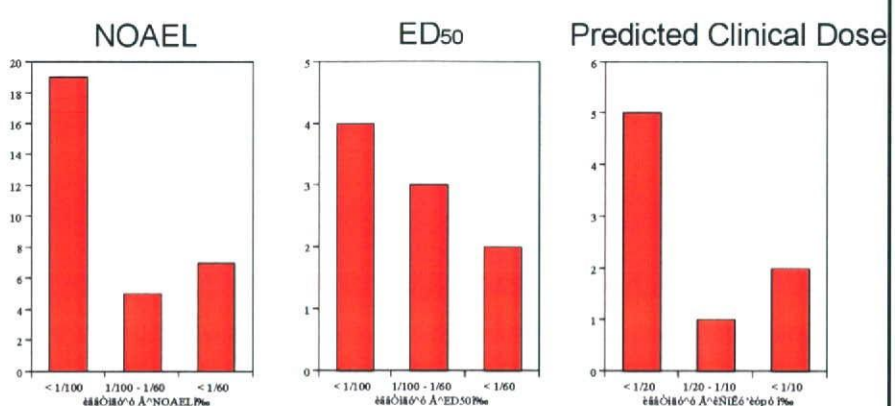
(Ozaki et al 2006)



 P181

Ratio of First dose / calculated dose

(Ozaki et al, 2006)



 P182

Change Paradigms

From OFF TARGET to ON TARGET

Toxicities are "off target" of the drug.

TGN case was owing to pharmacological action.

We should turn to another side.

ON TARGET approach to select a starting dose is being interested in.

MHRA ESG recommendation

A broader approach to dose calculation, beyond reliance on 'No Observable Effect Level' or 'No Observable Adverse Effect Level' in animal studies, should be taken. The calculation of starting dose should utilise all relevant information. Factors to be taken into account include the **novelty** of the agent, its **biological potency** and its **mechanism of action**, the degree of **species-specificity** of the agent, the **dose-response curves** of biological effects in human and animal cells, dose-response data from *in vivo* animal studies, pharmacokinetic and pharmacodynamic modelling, the calculation of the **target occupancy** versus concentration and the calculated exposure of targets or target cells in humans *in vivo*.

MABEL (Minimum anticipated biological effect level)

Case study of TGN1412
NOAEL and MABEL

MRSD(maximum recommended starting dose)

NOAEL in monkey was 50mg/Kg.
⇒1.6mg/Kg

MABEL
In vitro T cell effects 0.1mcg/mL
⇒ 0.001mg/Kg
In vivo rat arthritis
=> 0.005mg/Kg

Starting dose was 0.1mg/Kg

Check points in human study
- consideration from tox findings-

Are there any non-invasive measures to detect the toxicological events in human?

Can the measure decrease risk of subjects? That is if we can get rid of toxicity before it turns to irreversible.

We should make every effort to avoid subjects' permanent dysfunction.

Cases of Toxicity in reproductive organs

Histological check is out of discussion.
Sperm counts are not reliable enough.

In rats, pathological change in epididymis was found and hypertrophy of testis was also found.

→ Volume of testis were assessed in HVs.

In rats, pathological atrophy of epididymis was found without apparent changes of testis.

→ Exclude young male from subjects.

When renal toxicity is concerned,

Exclude subjects with possible risks
Check Past history and family history,
Measure Ccr*, urinalysis, urinary proteins.

During studies, check parameters such as
Ccr, urinalysis, micro albumin,
NAG, beta-microgloblin etc.

*Note that calculating formulae of Ccr is not reliable in healthy volunteer.

When QT prolongation is concerned

Exclude subjects with possible risks
Check family history of sudden death and LQT, serum electrolytes and ECG findings.

During studies, subjects should be monitored by telemetry and recorded by Holter ECG.
Normal ECG assessment and blood chemistry are also needed.

Note that QT prolongation is mainly caused by pharmacological action of drugs.

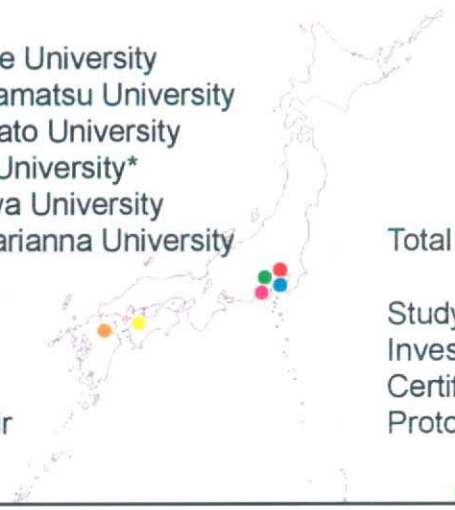
Can we extrapolate findings in animal studies?

1. An animal can't speak.
   We can miss common symptoms.
2. Special caution to findings in multiple species
   However don't forget SMON etc.
3. Special attention to dose response

4. Caution to irreversible findings
   You will administer healthy people with future.
5. Drug concentrations is useful than doses.
   Clearance may vary according to species.

J-CLIPNET
Member Sites

- Ehime University
- Hamamatsu University
- Kitasato University
- Oita University*
- Showa University
- St.Marianna University



*Chair

Total Scale of J-CLIPNET

Study beds	93
Investigators	31
Certified CRC	
Protocols/yr	300

 P181

REVIEW ARTICLE

The Significance of Adaptive Design in R&D in Japan

*Masahiro Takeuchi**

In the past decade, the number of drug and biological product submissions to the United States Food and Drug Administration has been slowly declining, while biomedical research spending has increased. A similar situation can also be seen in Japan: the number of domestic clinical trials is diminishing, and the cost of conducting a trial is rising. To prevent further decreases in the number of clinical trials, there is a need for an innovative strategy such as an adaptive design in research and development. Integrative celerity research aims to combine critical path and translational research, and seek update and participation in global clinical research. Participation in global studies through an adaptive design raises statistical concerns, which can be dealt with by adapting bridging studies. As a result of the restricted number of patients before approval in the adaptive design, safety issues must be guaranteed. Thus, establishing an effective and strong safety network between medical facilities is crucial. Japan's mission is to develop better drugs more efficiently and to investigate new drug methodologies for participation in global/Asian studies. Team work between clinical trial specialists, computer scientists, medical doctors, and statisticians is important for the success of both adaptive design and construction of a safety network between medical facilities in Japanese research and development. [*J Formos Med Assoc* 2008;107(12 Suppl):S9–S13]

Key Words: adaptive design, critical path initiative, safety network

In the past decade, the number of drug and biological product submissions to the United States Food and Drug Administration (FDA) has been slowly declining, while biomedical research spending has increased. Investment in the discovery phase per successful drug was the same between 1995–2000 and 2000–2002. On the other hand, investment in critical path initiatives almost doubled in 2000–2002 compared with 1995–2000. The increased focus on biomedical research allows for possible discovery of innovative products that may provide prevention, treatment and cure of serious diseases that affect contemporary society. Scientific knowledge is advancing, yet using this knowledge to help society is at a standstill. Increased biomedical spending, combined with fewer drug submissions, leads to critical paths becoming very expensive and the cost of success of a compound is greatly escalated.

Possible reasons and explanations for this phenomenon of decreased success are that the tools and concepts of the last century are being used to evaluate this century's drug candidates. This indicates that recently discovered innovative drugs are still evaluated by ordinary endpoints, which cannot measure the proper profile of the innovative drugs. In a 2004 FDA and industry workshop, Dr Janet Woodcock noted that "currently, one out of every two phase III trials fails", which means that the success rate of clinical trials is

Department of Biostatistics and Pharmaceutical Medicine, School of Pharmaceutical Sciences, Kitasato University, Japan.

Received: September 19, 2008
Revised: September 23, 2008
Accepted: October 13, 2008

***Correspondence to:** Professor Masahiro Takeuchi, Department of Biostatistics and Pharmaceutical Medicine, School of Pharmaceutical Sciences, Kitasato University, Japan.
E-mail: takeuchim@pharm.kitasato-u.ac.jp

decreasing to < 50% in the United States. To combat this decrease, FDA's Critical Path Initiative (CPI) believes that it is necessary 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".[1] Therefore, a new approach to develop and evaluate the efficiency and effectiveness of promising innovative drug candidates is required.

A similar situation can be seen in Japan: the number of domestic clinical trials is diminishing, and the cost of conducting a trial is rising. For example, in 1992, only 18.3% of compounds were first developed outside of Japan by Japanese domestic companies, but in 2000, 43.2% of the compounds were developed outside of Japan. It is also known that the speed of conducting clinical trials in Japan is very slow. The three factors of high cost, slow speed, and foreign conduct of clinical trials by Japanese domestic companies comprises the phenomenon called "hollowing out of clinical trials" in Japan. To prevent further decrease in the number of clinical trials in Japan, we need a new approach to clinical research. A possible solution is an adaptive design in research and development, which borrows accumulated clinical information, thus modifying the trial design in terms of required sample size and/or dropping one or two arms of a phase III trial, for confirmation of the efficacy/safety of the treatment being tested.

Concept of Integrative Celerity Research in Japan

Integrative celerity research (ICR), proposed by Imura, aims to combine both critical path research and translational research.[2] Figure 1 shows the concept of ICR. In Japan, translational research activity has been growing, and the results of the research have been published in leading journals such as *Science*. Unfortunately, clinical research activity in Japan has not increased and is not recognized when compared with translational research. Therefore, the purpose of ICR is to unite the achievements of basic science with the activity of clinical research. Not only does ICR aim to combine critical and translational research, new perspectives on clinical research can be formulated by the introduction of bridging studies and the participation of Japan in Asian and global studies. In 1998, the E5 guideline, which allows extrapolation of the results of foreign clinical trials to Japan for the approval of new drugs, was adopted. More than 40 compounds have been approved through

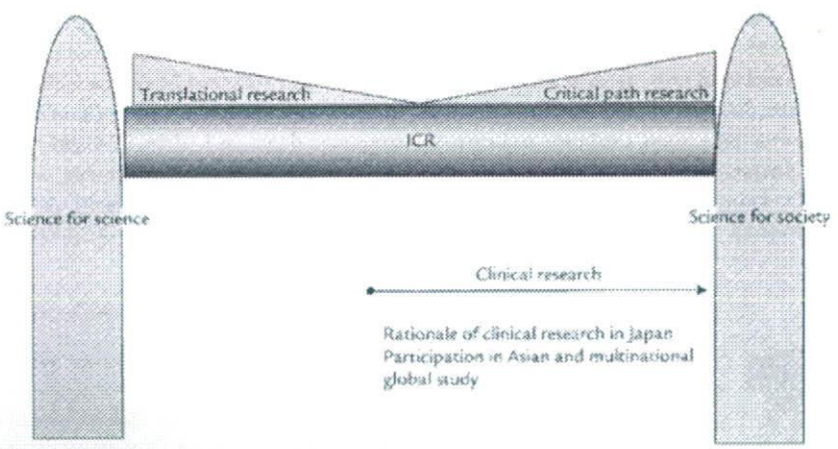


Figure 1. Concept of integrative celerity research in Japan.

extrapolation of foreign clinical trial results by conducting a small study, known as a bridging study.[3,4] Bridging studies provide the necessary information regarding differences in ethnic, intrinsic and extrinsic factors among foreign and Japanese subjects. We can apply the concept of bridging studies to simultaneous ongoing global studies with further extensive experience. The key factor in both bridging and global studies is to recognize an appropriate dosage in Japanese patients.

Adaptive Design in Japan

Currently, adaptive design in the US and EU combine phase II and III with a single assessment in each phase. In order for Japan to participate in global studies, Japan will also have to apply the concept of adaptive design to combine phase II and III. Since dosage determination is a key, adaptive design must be modified. The modified adaptive design is much more complex than the designs used in the US and EU. Figure 2 summarizes the main idea of adaptive design in Japan. In phase II trials, a new dosage such as a low-low dosage may be introduced to investigate intrinsic factors in Japanese patients. As part of translational research in Japanese trials, a futility assessment using surrogate/biomarkers, computer modeling and pharmacogenomics is needed as a primary assessment in phase II trials to determine the dose–response curve. Thus, in the Japanese design, two assessments in phase II will be required. The second assessment of phase II will investigate the probability of success by modeling, validation of surrogate/biomarkers, and patient variability through pharmacogenomic information.

This approach raises statistical concerns and issues. The small sample size in Japanese trials compared with that in other countries raises the concern of evaluating efficacy and producing adequate power in the trial. To combat this concern, the concept in bridging studies of applying similarity of efficacy among countries in the same clinical trial may be used. Determination of an appropriate dosage range for the Japanese population is another issue that has to be addressed. An additional dosage must be introduced as must the application of the concept of similarity to determine whether or not the new dosage is appropriate for a Japanese population. To implement the suggested adaptive design in Japan, there is a need for the accumulation of clinical data such as efficacy and dosage through an electronic data capture (EDC) system. Currently, there are two types of good clinical practice (GCP) in Japan, J-GCP and ICH-GCP.[5,6] The different GCPs prevent implementing an EDC system in Japan. To conduct and evaluate the clinical data results in a timely fashion, professional clinical specialists in regulatory agencies, academia and industry are needed. Training these professionals demands adequate

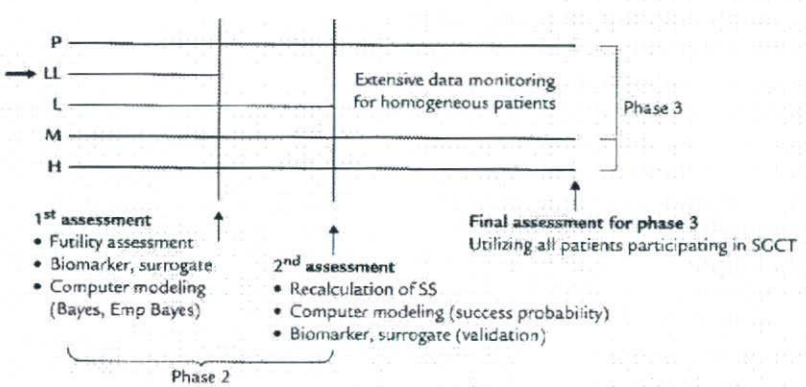


Figure 2. Application of possible approach.

educational programs, not only for biostatisticians, but also for clinicians.

Construction of a Safety Network System

Application of this new approach causes major concerns regarding safety, because the number of exposed patients will decrease through possible extrapolation of foreign clinical data for evaluation of efficacy. A large database to detect severe and regionally oriented adverse events will be required. A possible solution is to build a strong safety network between hospitals to construct and evaluate the data from all patients who are prescribed the drug after approval. The Ministry of Health, Labor and Welfare has established a research grant to focus on implementing a network between hospitals. This system aims to develop a strong and validated EDC system to collect clinical data, monitor patients, and detect unexpected adverse events, as well as building a database of patient background details for signal detection and pharmacoepidemiology.

Overall, there are two main steps in creating an efficient and safe networking system in Japan. Figure 3 shows the construction of a network system in Japan. A safety data capturing system within a medical facility must be developed. Within each medical facility, unification of patient medical records regarding patient background, dosage, efficacy and safety of the patients is essential. In most cases, medical records exist in several different departments of the medical facility. Data about each patient must be unified within each medical facility, followed by the unification of the databases from all the medical facilities into one main data center. Compiling patient data into one center allows for a simultaneous monitoring system, which will help to detect unexpected adverse events and analyze safety profiles according to actual drug dosage and duration of treatment.

Similar to the FDA's CPI, Japan's mission is to develop better drugs more efficiently, with new drug development methodologies, by participating mainly in global/Asian studies. Although developing better drugs in a time-efficient manner is important, patient safety must be a priority. The importance of pharmacovigilance by monitoring patients, developing a patient database through a safety network, and a unified EDC system between Japan and other Asian countries are all factors that will help maintain patient safety. Finally, team work between clinical trial specialists, computer scientists, medical doctors, and statisticians is important for the success of adaptive design in Japanese research and development.

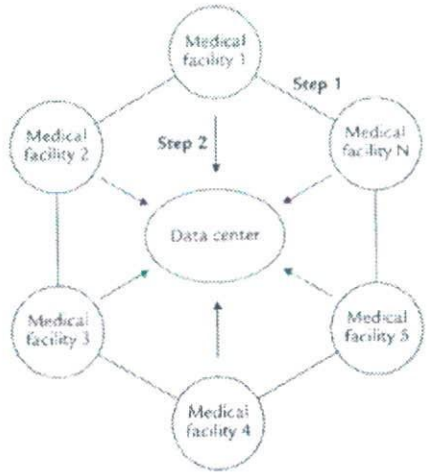


Figure 3. Construction of a safety network system in Japan.

References

1. US Food and Drug Administration. *FDA White Paper. Challenge and Opportunity on the Critical Path to New Medical Products*. Rockville, MD: FDA, March 2004.
2. Imura H. *Strategic Initiative, Promotion of Integrative Celerity Research (ICR), Innovation in Health and Medicine*. Tokyo, Japan: Center for Research and Development Strategy, Japan Science and Technology Agency, 2006 (CRDS-FY2006-SP-18-E).
3. Center For Drug Evaluation, Department of Health, Executive Yuan, Taiwan, R.O.C. *Bridging Studies*. Available from: www.cde.org.tw/bse_website/index.html
4. *The 1st, 2nd, 3rd Kitasato–Harvard Symposium, Japan*. Available from: www.pharm.kitasato-u.ac.jp/biostatis/

5. Ministry of Health, Labor and Welfare, Japan. *Comporison and Summary of Difference of J-GCP and ICH-GCP*. [In Japanese] Available from: www.mhlw.go.jp/shingi/2007/02/dl/s0228-8u.pdf

6. International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use. *Guideline for Good Clinical Practice E6(R1)*. Available from: www.ich.org/LOB/media/MEDIA482.pdf