

Clinical Trials in Taiwan—
Regulatory Achievement and Current Status

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Abstract

The July 7 Announcement (Double-Seven Announcement) in the year of 1993 marked the beginning of Taiwanese government to devote itself to the establishment of a sound environment for clinical trials. The visible efforts include the international harmonization of Good Clinical Practice (GCP) guidelines (ICH E6), GCP professional training, a Joint Institutional Review Board (JIRB) to facilitate multi-center clinical trials and reviewing efficiency, the set-up of the Center for Drug Evaluation (CDE) to specialize in the reviewing processes and consultation, and the introduction of General Clinical Research Centers (GCRC) to quality conduct of early phase clinical trials. Besides, ICH E5 was introduced since 2001, which aims at bridging studies in order to avoid unnecessary trials and to provide evidence for ethnic concerns in accepting foreign clinical data in a step-by-step manner.

Key words : JIRB, GCRC, bridging study, GCP Inspection

INTRODUCTION

This article describes the current status of clinical trials and related regulations in Taiwan in the following aspects: Clinical trials and Good Clinical Practice (GCP), Guidelines on clinical trials on specialty areas, GCP training, GCP inspection, and the infrastructure of clinical trial which includes GCRC, JIRB, and the CDE. Current status of clinical trials and the application reviewing process are described in details.

DEMOGRAPHICS

Taiwan's total pharmaceutical market value was US\$ 2.4 and 2.6 billion in 2001 and 2002, the fifth largest among Far East countries, ranking only behind China, Korea, India & Australia. The demographics of Taiwan (2001) is shown in Table 1; and the disease structure (10 leading causes of death) of Taiwan (2002) is shown in Table 2.

CLINICAL TRIALS AND GOOD CLINICAL PRACTICE (GCP)

Until its modification in 1986, the patent law of Taiwan protected only the "manufacturing process" of new drugs, but not the end products. In the 1990s, the protection of intellectual property became a major issue in trade negotiations between the United States and Taiwan, hence the registration requirement was modified on July 7, 1993 to meet this new demand. Under this new regulation, it is necessary for the sponsor to conduct a pre-marketing "good local clinical trial" (with at least 40 cases) before approval. After approval, marketing exclusivity will be granted to the sponsor for the 7-year safety monitoring period. Any sponsors applying for a generic drug permit are required to conduct the "same standards" local clinical trials during the first 5 years of the monitoring period.

During this period of time, Taiwan has demonstrated its ability in conducting quality clinical trials designed by multinational pharmaceutical companies. Local pharmaceutical industries were also encouraged by the government to invest in the area of research and development. Integrated effort has been made to actively explore new pharmaceuticals, including biological products. Regulating the increasing number of clinical trials has thus become an ever demanding task for the administrative authority.

GUIDELINES ON CLINICAL TRIALS IN SPECIALTY AREAS

Taiwan's GCP guideline was officially announced first in 1996 and revised in 2002 according to the ICH E6 guidance. In 1999 and 2000, the Department of Health (DOH) in Taiwan announced the guidances for clinical trials of drugs in a variety of medical subspecialties, such as anti-infectious drugs, anti-cancer drugs, cardiovascular drugs, endocrine drugs, and radioactive drugs in 1999, and herbal extracts in 2000.

In 2001 and 2002, the DOH further announced the guidances for clinical trials of drugs in special populations, such as geriatrics, pediatrics, population with impaired hepatic function or impaired renal function; the Guidance for Bridging Studies - Ethnic Factors in the Acceptability of Foreign Clinical Data; and also guidance for the Content and Format of Clinical Trial Report.

GCP TRAINING

To meet the increasing demand of domestic clinical trials, it is necessary that most clinicians well understand the importance of clinical trials & related methodology, and make up the infrastructure together with other supportive disciplines (e.g. nurses, pharmacists, statisticians). It is for this reason that since 1995, under the aegis of DOH, "The Foundation of Medical Professionals Alliance in Taiwan" has cooperated with medical centers and professional medical associations to hold a series of training courses of clinical trials. The topics included clinical trials in heart and vascular diseases, oncology, infectious diseases, endocrine & metabolic diseases, gastroenterology, clinical trial inspection, neurology, anti-inflammatory & analgesics, the statistics in clinical trials & GCP Issues, the assessment of drug safety, respiratory diseases, research subjects protection - ethics regulations & responsibilities, GCP inspection & ethnic factors, developing new therapies of alternative sources, clinical trials for radiological agents, pharmacokinetics, case study and bridging study in oncology, anti-infective and cardiovascular trials, and safety evaluation for biological products, etc. These training courses were well received with good feedback by physicians, pharmacists, nurses and other participants. As of the end of 2001, 1,942 clinicians, 1,073 pharmacists, 151 nurses, and 1,732 researchers have participated in these courses.

GCP INSPECTION

To assure the quality and credibility of clinical trials, the DOH performed GCP inspection on all registration trials done in Taiwan. In 2002, 37 trials were inspected and the results (case numbers in parenthesis) were categorized as: *Accepted* (5),

Accepted upon further clarification (12), *Re-inspection* (4), *Case dismissed* (2) and *Pending supplement from trial companies (sponsors)* (14). Among these inspected trials, those concerned with drugs acting on the nervous system (13) ranked the first, followed by immunologic agents (4), antineoplastics (3), and cardiovascular and renal drugs (3) and others .

GENERAL CLINICAL RESEARCH CENTERS (GCRC)

For the purpose of strengthening the infrastructure of clinical trials and monitoring the conduction of early phase clinical trials, the DOH has sponsored a number of medical centers in Taiwan to establish centers for clinical trials, so called the general clinical research centers (GCRC). The strategy was to create an environment conducive to research and development of new drugs in Taiwan. At present there are 6 GCRCs for the conduction of Phase I, Phase II & Pharmacokinetics studies of new drugs and Chinese herbal medicine (Table 3). Another 3 GCRCs (Lin-Kou Chang Gung Memorial Hospital, Show Chwan Hospital, and Chimei Hospital) are used exclusively for clinical trials of Chinese herbal medicine..

The GCRCs provide services for the execution and follow up of clinical trials, including randomization of study subjects, storage and dispensing of investigational drugs, monitoring of pharmacokinetic parameters, biostatistical consultation, key-in of research data, and analysis of research data,. A clinical trial regulatory committee is established to manage and audit the performance of clinical trials in each GCRC .

To integrate the resources of clinical trials, the DOH held five regular meetings with GCRC in 2002 to report the progress, share experiences, build up cooperation model to effectively integrate the resources and solve problems.

JOINT INSTITUTIONAL REVIEW BOARD (JIRB)

To provide an efficient and high quality IRB review for multi-center trials, a Joint IRB (JIRB) was established in Taiwan in March, 1997. This new JIRB has improved Taiwan's competitiveness in successfully attracting multi-center trials, including Phase IIIa global trials, to Taiwan..

The missions of the JIRB are :

1. to improve the safety of study subjects in human clinical trials
2. to shorten the time required to obtain the permission for clinical trials
3. to avoid repetition of trial application and the variability of application formats

4. to encourage pre-marketing clinical trials in Taiwan
5. to further Taiwan's competitiveness and international reputation in IRB-related issues
6. to establish the communication network in regional IRB-related issues
7. to review the multi-center clinical trials, the phase I-III studies of new drugs, and the cases entrusted by medical institutions without a Clinical Trials Regulation Committee.

At present, 44 hospitals have participated in JIRB, among them are 17 medical centers, 23 regional hospitals, and 4 specialized clinics. JIRB has completed the review of 5 phase II studies and 13 Phase III multinational studies in 2002.

CENTER FOR DRUG EVALUATION (CDE)

In order to facilitate both the protection of public health and the development of pharmaceutical industry, to overcome the restriction imposed by a rigid administrative system, and to solve the problem of manpower deficiency in the professional review, DOH established Center for Drug Evaluation (CDE) in July 1998. Through an open and transparent mechanism, CDE reviews all the clinical trial protocols entrusted by DOH, by holding sponsor meetings to clarify any review concerns, shorten the protocol review time and elevates the legitimate approval rate for the trials. In principle, it takes about 1.5 month to approve a protocol.

Current status and statistics on clinical trials

The clinical trials reviewed by the DOH in 2002 were shown in Table 4. The proportion of multinational trials in Taiwan is 49.79% (71/143) in 2002. Taiwan has demonstrated its ability to conduct increasing number of early phase clinical trials and to participate in multi-national clinical trials. These efforts are essential in creating a favorable environment for domestic research and development of new pharmaceuticals.

On December 12, 2000 DOH issued the Bridging Study Announcement (the Double-Twelve Announcement) to substitute for the Double-Seven Announcement. It was for the purpose of fulfilling the spirit of ICH-E5 to reduce the waste of the resources in new drug R&D, and to improve the quality of clinical trials. Beginning January 1, 2001 but with a two-year transition period in implementation, a bridging

study evaluation would be required before submitting the application for new drug review. A set of intrinsic and extrinsic factors are used in the evaluation of the impact of ethnical differences on the efficacy and safety of the new drug. Results from the bridging study evaluation would determine whether foreign clinical trial data could be extrapolated to Taiwanese populations and whether further clinical trials in Taiwan could be waived. From March, 2001 to December, 2002, 46 applications have been evaluated and in 33 cases (72%) bridging studies were waived. Before the end of 2003, if a bridging study may not be waived, the sponsor has the options of either doing a 40-case clinical trial (following the Double-Seven Announcement) or a required bridging study. After January 1, 2004, however, the 40-case trial will no longer be accepted and the sponsor will have to do a required bridging study if not waived.

DOH also issued 5 announcements between 1998 and 2000, which provided other pathways of clinical trial waiver for specific drug products governed by each announcement. From June 2001 to Dec. 2002, 44 applications have been evaluated and in 28 cases (63.6%) clinical trials were waived.

CONCLUSION

The demand of domestic clinical trials has given an impetus not only to the promotion of domestic clinical research activities, but also to the upgrading of domestic pharmaceutical industry.

Table 1 Demographics in Taiwan (2001)

Population size:	22.52 million
Population pyramid:	Younger population (under 15 years) 20.8% Productive age (15 – 64 years) 70.4% Aged population (65 years and over) 8.8%
Life expectancy :	Female 78.48 years

	Male 72.80 years
Infant mortality rate:	5.99 /1000 live birth
Adult literacy rate:	96%
Per capita GNP:	US \$12,900
Population covered by National Health Insurance	96.15%

Table 2 Leading causes of death in Taiwan (2002)

Cause of death	% of All deaths	Mortality per 100,000
All causes	100.00	565.08
1. Malignancy	27.05	152.88
2. Cerebrovascular diseases	9.46	53.46
3. Heart disease	9.01	50.93
4. Diabetes mellitus	6.95	39.26
5. Accident and Adverse Effects	6.69	37.79
6. Chronic liver diseases and cirrhosis	3.78	21.35
7. Pneumonia	3.57	20.17
8. Nephritis, Nephrotic syndrome, and Nephrosis	3.28	18.55
9. Suicide	2.41	13.59
10. Hypertensive disease	1.53	8.67

Table 3 Clinical trials conducted in GCRCs (2002)

	Phase I	Phase II	Phase III	Phase IV	Total
National Taiwan University Hospital	4	4	3	0	11
National Cheng-Kung University Hospital	1	2	4	0	7
Tri-service General Hospital	2	2	1	0	5
Taipei Veterans General Hospital	0	0	1	2	3

China Medical College Hospital	0	10	3	0	13
Taichung Veterans General Hospital	0	0	3	2	5
Total	7	18	15	4	44

Table 4 Clinical trials reviewed by DOH in 2002

	Multinational trials	Domestic trials	Total
Phase I	0	4	4
Phase II	12	14	26
Phase III	52	49	101
Phase IV	7	5	12
Total	71	72	143