



Clinical Research in Taiwan, South Korea and Malaysia

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Introduction

Taiwan, South Korea and Malaysia are fertile ground for clinical research to support global drug development. All three countries offer large patient populations and qualified pools of medical facilities and practitioners. Their regulatory environments are evolving as they emerge into the global clinical research picture.

Taiwan

In July 2006 Taiwan had a population recorded at 23 million, with a GDP per capita of \$27,500 (2005 est.). There are 19 major medical centers or hospitals where Phase II or III (IND) studies are generally conducted. The country has a pool of almost 500 accredited hospitals with more than 20,000 physicians and almost three times as many registered professional nurses.

The Taiwan Joint Commission on Hospital Accreditation (www.tjcha.org.tw/english/english.asp) is entrusted by the Department of Health-Taiwan (DOH-Taiwan) to conduct regulatory inspections every three years at all 500 medical facilities for (re)certification purposes. It also qualifies medical facilities as medical centers, regional hospitals, community hospitals or clinics. Clinical research studies are approved for conduct at a total of 121 teaching institutions.

Clinical investigations are practiced only in Taiwan's government-approved medical facilities. Investigators who work there are generally considered "employees" and thus insured under their employers' policies, which may or may not cover clinical research procedures. The government does not mandate that MDs or clinical investigators purchase malpractice insurance and, to date, no domestic insurance company offers such insurance to individual practitioners. Out of the 19 major clinical development sites, five require the sponsor to bear the liabilities for any loss. At the remaining sites, the sponsor needs only to signify indemnification for any loss when investigators follow protocol and do not practice with negligence or commit willful acts. Sponsors may consider purchasing malpractice insurance for some of the investigators, although most have opted to accept the liabilities.

In November 1996, the first edition of Good Clinical Practice Guidance, translated according to the guidance of EU, WHO and Japan, was enacted by the DOH-Taiwan. The implementation of GCP started in July 1997. Since then clinical trials conducted for IND must comply with GCP guidance, and nearly all clinical trials are inspected by the health authority at end of each study (Phase I, II or III) and during/after NDA. US Food and Drug Administration (FDA) GCP compliance inspections,



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which took place twice in Taiwan at National ChenGung University Hospital and Tri-Service General Hospital in the early 2000s, cited no major deficiencies.

In Taiwan, clinical trial protocols must be approved by an Institutional Review Board (IRB) and the Department of Health (DOH) before trials are started. The time for IRB review process depends on the individual hospital IRB. To simplify the application and review process for multicenter trials, a joint IRB (JIRB) (www.jirb.org.tw/English_Version/eng-index.asp) was established by DOH in 1997 to ensure the quality and efficiency for the protocols review. Presently, 44 hospitals have authorized JIRB to review clinical trial protocols for them. The average JIRB review time for each protocol is around 25 working days. To save time, parallel submissions to IRB and DOH may be made.

In April 2006, Taiwan announced it had reduced the approval time for INDs to 42 days. Two years earlier, the DOH issued new regulations on post-marketing surveillance that mandate the submission of Product Safety Update Reports within five years of a drug's approval. The improvement in IND approval time and the increased emphasis on safety in Taiwan make it a more attractive locale for conducting clinical research.

In most of the multinational trials involving Taiwan, Taiwan does not represent a major contributor of participating subjects. However, according to the International Research-Based Pharmaceutical Manufacturers Association (IRPMA), clinical trials data conducted in Taiwan have been accepted by the FDA as part of pivotal trial data sets, such as for Lamivudin (Glaxo) and Cialis (Eli Lilly).

New drug clinical trials for registration approval conducted in Taiwan will be granted conditional market protection according to the scale of the trial. Five years after a drug is approved, a licensing application for a generic version of the drug may be submitted, but only after clinical trials are conducted on the same scale as for the novel drug. Another benefit of conducting global trials in Taiwan, for local market, will be the early submission of an NDA package, which may shorten the time to product launch by at least four to five months.

Taiwan Clinical Trial Approval Process/Timeline

Regulatory body	Approval	Time
DOH	Average regulatory approval for study conduct	10 to 12 weeks
IRB/ EC	IRB/EC approval by the various study sites	8 to 12 weeks
DOH	DOH approval also represents IMP Import License approval	N/A
Total		10 to 12 weeks

South Korea

South Korea's population reached 49 million in July 2006, and the country, which has a GDP per capita of about \$22,600 (2005 est.), has the world's 10th largest economy. The genetic polymorphic make-up of the Koreans and the Chinese and Japanese is very close, making South Korea a good precursor to moving trials to those countries. There are nearly 225 well-equipped



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hospitals accredited as clinical institutes in a nation that has a pool of 83,000 nurses and 75,000 physicians. The country's health systems and regulatory infrastructure have undergone a progressive modernization over the past 20 years.

An emerging nation in the global medical arena, South Korea boasts highly trained, experienced and enthusiastic investigators with strong academic and medical backgrounds. The number of global clinical trials grew substantially from only five in 2000 to 95 in 2005. Support services meet international standards, including the pharmacy, radiology and clinical pathology laboratories. Labs are currently certified by the Korean Society for Laboratory Medicine and increasingly by the College of American Pathologists. For Phase I trials, there are 32 accredited clinical institutes, with 84 for Phase II and 107 for Phase III. In the country's urban centers, where the majority of clinical investigational sites are located, most hospitals and other medical facilities have English-speaking physicians. About 15% of the sites are public. All sites are required to assign pharmacists to studies, and each site has its own IRB, since South Korea has no central IRB. The resources and technical infrastructure are in place to support electronic data capture and transfer.

In 1995, South Korea adopted GCP and then ICH-GCP in 2001. The following year the country's Food and Drug Administration (KFDA) (<http://www.kfda.go.kr/>) separated the IND and NDA processes, which opened the door to South Korea's participation in international studies. Since then the review period has shortened to 30 days and pre-IND consultation programs have been activated. Regulation of manufacturing and importation of clinical supplies is considered to be flexible.

In order to conduct a study in South Korea, the KFDA must approve the protocol and the drug must be investigational. Clinical studies may be conducted only at accredited sites by qualified investigators. To be accredited, a site needs to demonstrate it has appropriate facilities and equipment as well as personnel trained in GCP. An IRB is also required. It is imperative that the rights and safety of subjects are protected, with informed consent mandatory prior to enrolling patients.

The KFDA plans to revise its regulations further to harmonize with international ICH guidelines with the goal of encouraging sponsors to bring their global trials there.

South Korean Clinical Trial Approval Process/Timeline

Regulatory Body	Approval Process	Time
Korean Food & Drug Administration (KFDA)	<ol style="list-style-type: none"> Examines Protocol, CMC, Pre-clinical data & IB Issues clinical trial approval In parallel with IRB/EC 	12 to 16 weeks
IRB/EC	<ol style="list-style-type: none"> Examines Protocol, ICF, CRF, IB & CV Issues clinical trial approval IRB/EC & regulatory submissions in parallel 	12 to 16 weeks
Korean Food & Drug Administration	KFDA CTA approval also represents IMP import license approval	
Total		12 to 16 weeks



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Malaysia

Malaysia, divided into two land areas by the South China Sea, is a multi-ethnic country of more than 26.6 million people with a relatively low per capita income of \$12,700 (2006 est.). Major diseases prevalent in Malaysia include diabetes, cancer and heart disease as well as bacterial diarrhea, hepatitis A, B and C, and typhoid fever. Dengue fever and malaria are found in some regions of the country.

Clinical trials are conducted in Malaysia mostly in 14 of the country's government and university hospitals. There are 352 hospitals in Malaysia, however, and 121 of them are government run. Private hospitals generally do not participate. Overall, Malaysia has more than 17,000 qualified physicians, most of whom are English literate and working in modern medical facilities. Clinical investigators are required to be GCP certified. For clinical trials, the leading therapeutic areas are cardiovascular, endocrinology, oncology, hepatology, infectious disease, psychiatry and pediatric. In 2005, nearly 20 Phase I and II studies and 50 Phase III studies were conducted in Malaysia.

Government hospitals use a Central IRB, whereas university hospitals, which are considered semi-governmental institutions, use their own IRBs and ECs. In order to conduct clinical studies in Malaysia, the drug developer or sponsor must first apply to the Ministry of Health (MOH) (<http://www.moh.gov.my/MohPortal/index.jsp?lang=en>) and the IRB or Ethics Committee for permission to run the trial, applications which can be made simultaneously. Application also has to be made by the Principal Investigator or a person authorized by a locally incorporated pharmaceutical company or sponsor with a permanent Malaysian address to the National Pharmaceutical Control Bureau for a Clinical Trial Import License.

In line with the global harmonization of clinical trial practice, Malaysia adopted the ICH-GCP Guidelines in 2004, with some modifications to suit local requirements, in order to provide public assurance that the rights, safety and well being of trial subjects are protected.

Malaysian Clinical Trial Application Process/Timeline

Regulatory Body	Approval Process	Time
Ministry of Health (MOH)	<ol style="list-style-type: none"> Examines Protocol, IB, GMP, Pharmaceutical data, etc. Issues clinical trial approval in parallel with IRB/EC 	12 to 14 weeks
IRB/EC	<ol style="list-style-type: none"> Examines Protocol, ICF, CRF, IB and CV Issues clinical trial approval IRB/EC and regulatory submissions can be in parallel 	12 weeks
Import License	Concurrent with regulatory/MOH submissions	
Total		12 to 14 weeks

FOR MORE INFORMATION ON CONDUCTING CLINICAL TRIALS IN ASIA, PLEASE CONTACT EDWARD IAN, DIRECTOR OF OPERATIONS – ASIA AT IANEDWARD@PRAINTL.COM OR KENT THOELKE, VICE PRESIDENT & HEAD, THERAPEUTIC EXPERTISE AT THOELKEKENT@PRAINTL.COM.