Clinical trials of foreign drugs

INTRODUCTION

According to the AT Kearney Country Attractiveness Index for Clinical Trials (1), the People's Republic of China (China) is ranked as number one amongst the fifteen most popular low cost countries in which to conduct clinical trials in. Indeed with an estimated 2/3 of the cost of developing new drugs spent on the clinical trial process, and an estimated 30 to 65 percent saving of expenses associated with the cost of clinical trials in such developing countries, it is small wonder that major multi-national drug companies have taken a keen interest in China (2). In order to streamline operations and improve efficiency, it is necessary for drug companies to select the most suitable low-cost country in which to base their clinical trial operations (3).

CHOOSING CHINA

The most important factors determining the selection of the most suitable countries in which clinical trials can be conducted are:

- operational costs;
- availability of patients;
- accessibility to sites and investigators ; and
- governmental attitude.

The social substrate in China is rapidly evolving with a fast growing middle class that suffer from the same diseases as those of developed western countries (cardiovascular diseases, hypertension, diabetes, cancers). Notwithstanding that there is still a huge difference between rural and urban areas, in particular aspects relating to hygiene and access to good quality medical treatments, it is not surprising to notice remarkable differences in the diseases that affect the rural and urban communities.

Access to over 2.5 million doctors, nurses and technicians that will work for a fraction of the cost of those in developed nations is a factor which is immediately apparent in China. The depth of expertise and economical price required to conduct clinical trials make this a leading factor in why China has become the world's most popular clinical trial destination. Another aspect is the fact that China offers the world's largest urban patient population, making the patient selection process so much easier. Another fundamental factor is the heterogeneity of the patient pool available in China. Despite the fact that the main ethnic group is the Han ethnic group, which constitute approximately 92% of the population, there are many Asian sub-ethnical groups spread around China and even Caucasian populations in the Northern areas of China. Each of these ethic groups possess different genes which provide a rich ground for examining the resistance to drugs and infections of different groups. As a result of China having the world's largest urban population patient recruitment is relatively easy. In the Chinese environment there is less competition for subjects, costs for recruitment are lower, durations are shorter and fewer patients have undergone other clinical trials.

While indeed there are many benefits for selecting China as a clinical trial base, there are also some difficulties relating to the time frame required to gain government approval from the **State Food and Drug Administration (SFDA)**, between 9-12 months, all the material submitted to the SFDA and other government agencies must be in the required official language (Chinese) as well as the costs associated with, translating the data recorded by researchers in Mandarin into English. It is only until a drug has gone through clinical trials and passed evaluation that a New Drug Certificate may be issued when approved by the SFDA (4).

LEGAL ASPECTS OF CLINICAL TRIALS

The procedures and laws relating to clinical trials and drug registration intertwine and are regulated by a number of national laws, regulations, rules and notices issued by the National People's Congress, State Council, State Food and Drug Administration (5). Any drug clinical trial must be approved by the SFDA, which is an organ of the State Council, before it can commence (6).

The SFDA is the government organization responsible for national drug registration, the inspection and authorization of clinical trials and issuing administrative notices for the areas (7). The most important of these administrative notices are the *Drug Registration Management Methods* (Drug Methods) (8) and the *Clinical Drug Trial Quality Management Standards* (Drug Standards) (9) which were issued by the SFDA by virtue of its powers of office (10). The Drug Standards contains thirteen sections regarding the rights and obligations of the applicant, the rights and obligations of the patient, the rights and obligations of the observer, other organizations taking part in the clinical trial, as well as the procedures to be taken in conducting the clinical trial.

Any methods used to conduct clinical trials of drugs must be in accordance with those methods issued by the SFDA (11). The Ministry of Health (MOH) originally controlled clinical trials, but this role was transferred to the SFDA and much of the legislation promulgated in the late 1980s regarding the role of MOH in these areas has now been superseded by new legislation, regulations and other instruments.

CLINICAL TRIALS IN CHINA

There must be an appropriate scientific reason to conduct the clinical drug trial, in which the problem that needs to be resolved is weighed against the risk to the patient (12). In China there are three types of clinical trials:

1) Drugs which have been clinically tested but not registered in the applicant's country as a new drug and for the purposes of registration in China a clinical trial is conducted;
2) Drugs which the applicant has already applied for registration in their country, but has not been imported for use in China and for the purpose of obtaining a **Pharmaceutical Import License** (13) a clinical trial is conducted. Following the up to date Provision for Drug Registration "A New Drug" is defined as a drug that has never been marketed in Chinese territory, diverging from the former Regulation that identified New Drugs as those produced in China for the first time;
3) Drugs for which the applicant already in their country has obtained approval to conduct a clinical trial or to register the drug, for the purpose of obtaining the caseload data of that medicine in China a clinical trial is conducted (14).

PRE-CLINICAL TRIAL PROCESS

Before a clinical trial is conducted pharmacological and toxicological results for the drug should be submitted to SFDA before the clinical trial can be commenced (15). SFDA's Department of Drug Registration meticulously reviews the completeness of the submitted materials, records the qualified applications and transmits all the materials of qualified applications to the Center for Drug Evaluation directly to SFDA. For foreign applicants seeking to conduct pre-clinical trial research to assess the safety of the drug should be according to the standards set out in the *Non-Clinical Drug Trial Research Management Standards* (16). Pre-clinical drug trial research for the purpose of drug registration is to determine, amongst other things, the toxicity and safety of the drug to be used in the clinical trial (17). If the applicant provides false data relating to the drug production procedures or false pharmacological and

toxicological results the SFDA may issue a warning, or if the circumstances are serious not accept an application from the same applicant for the same drug for three years (18).
Both the non-clinical evaluation and the clinical trial institutions, when undertaking their respective roles, must implement the **Good Laboratory Practice for Non-Clinical Laboratory Study (GLP)** and **Good Clinical Practice (GCP)**, standards which are formulated by the State Council and help to quality of data and protection of trial subjects (19). Any institution which does not follow the abovementioned standards and/or conducts a clinical trial without authorization is liable to be fined up to 20,000 RMB (20). Foreign applicants applying for drug registration must follow the drug importation procedures and requirements (21).

CLINICAL TRIAL PHASES: I, II, III, IV

When applying for registration of a new drug a clinical trial must be conducted. The clinical trial is divided into four phases (22). Before the new drug may be put on the market it must have successfully passed through the first three phases of the clinical trial, it is only until the fourth phase (post licensing phase) can it be put onto the market. Generally the SFDA requires each phase of the clinical phase to be completed, however **in some circumstances the SFDA may authorize an applicant to only conduct phase II and phase III, or only phase III. This is an important factor for European and American clinical trial companies that are interested in conducting the latter phases in China.**
Phase I of the clinical trial is an assessment of the clinical pharmacology and human safety tests. Phase I trials aim to ascertain dosing, to provide evidence how a drug is metabolized and excreted, and identify acute side effects. Usually Phase 1 trials involve only a small number of healthy volunteers (between 20 and 50). The first cohort to take part will be given a very small dose of the drug; if and if only the outcome of first tests are positive, the dosage of the drug provided to the next group will be increased. This stage provides a basis for formulating a drug plan for the next stages of the clinical trial as well as observing the tolerance levels of the new drug and pharmokinetics (doses and side effects).
Phase II of the clinical trial is an initial assessment of the therapeutic action of the drug. This stage is a preliminary assessment of the drug for the target group for therapeutic efficacy and safety. Phase 2 trials include a higher number of participants (about 100-300) who exhibit the disease or else, states that could be potentially treated with the drug. The design of this stage of the clinical trial can take a number of forms including random blind trials and provides a foundation for the design of the third phase of the clinical trial and the drug dosage plan.
Phase III of the clinical trial is the stage in which corroboration of the therapeutic action is determined. A larger number of people manifesting the disease (approximately 1,000-3,000) is involved in drug study during Phase III. Number are larger than in Phase I and II, because the differences in success rates may be too small and the smaller the figures the higher the influence of an inherent deviation of the outcomes. Moreover to render the data as independent from local conditions as possible, clinical trials in phase III are usually carried out in different hospitals designated by the SFDA. This stage is to corroborate whether the therapeutic use is suitable for the patients and safety, assess the relationship between benefits and risks, and to provide a foundation for the drug registration application examination. In many clinical trials, while one group of patients will be given an experimental medicine or treatment, a control group is given either an existing standard treatment (comparator) for the illness or a placebo.
Phase IV of the clinical trial is research of the drug once it has

been shown to work, granted a licence and has gone on the market. The objective of this stage is to investigate the efficacy and adverse reactions of the drug, the long term risks and benefits, as well as to evaluate the usage in common or special groups, so dosage can be improved.

CLINICAL TRIAL APPLICATION PROCESS

After a drug clinical study has been approved by the SFDA the applicant must select an institution that is qualified to conduct drug clinical trials as well as the main researchers as well as other entities participating in the study (23). The applicant is required to sign a clinical study contract with the clinical trial work unit, provide manuals to the researchers, as well as file a copy of the clinical trial plan with the ethics committee (24). Medicine free of charge should be provided to the clinical trial work unit for use in the clinical trial, which should meet the standards provided in the **Clinical Drug Trial Quality Management Standards** (25). Inspection of the drugs to be used in the clinical trial must be carried out by an institute that has been accredited by the SFDA, such as the **National Institute for the Control of Pharmaceutical and Biological Products**, before they can be used as clinical trial drugs (26).
Before the clinical trial is conducted the applicant must submit a clinical study plan, the names of the principle researchers of the clinical trial work unit, list of organizations taking part in the clinical trial, a sample informed letter of consent with information concerning the trial for patients. All these documents must be submitted to the SFDA offices where the clinical trial study entity is located (27).

RIGHTS AND OBLIGATIONS OF THE APPLICANT

The applicant is responsible for submitting the application to the SFDA for the clinical trial, selecting the clinical trial work unit to conduct the trial and must pay the associated trial expenses (28). They also have to provide the researcher with a manual which contains data and information relating to toxicology and scientific results (29). Before the clinical trial commences the applicant is legally required to fully inform the patient attending the clinical trial about the clinical trial, as well as obtain a signed informed letter of consent from the patient (30).
The applicant must guarantee the researcher for any legal and economic ramifications related to the clinical trial (31). Furthermore, the applicant has a duty to provide insurance for the patient attending the clinical trial and is responsible for any medical fees and related economic compensation for injury or death resulting from the clinical trial (32). Although the clinical trial work unit is responsible for the safety of the patient, in the event that an adverse reaction occurs the applicant takes responsibility and is legally liable to pay compensation to the patient. Only until the applicant receives the approval of the SFDA can the clinical trial be organized (33).

RIGHTS AND OBLIGATIONS OF THE PATIENT

An informed letter of consent must be obtained from the patient after satisfactory and comprehensive information of the circumstances of the clinical trial have been communicated to the patient(34). The patient or their legal representative, as well as the researcher administering the informed consent process must sign and date the letter of informed consent (35). The researcher or their appointed representative must make the patient aware that the clinical trial is voluntary and that they can choose to leave the clinical trial and will not be discriminated against or suffer reprisals if they make the decision to leave (36). When the situation arises the SFDA, the ethics committee or the applicant, according to the rules can refer to the patients' information (37).

RIGHTS AND OBLIGATIONS OF THE RESEARCHER

The researcher and the applicant have a joint responsibility to design and implement the clinical trial plan (38). Certain qualifications must be possessed by a candidate before they can become a researcher including; working in a related post or possessing proper qualifications from a medical institution, possessing specialized knowledge and experience of the trial plan, familiar with the clinical trial data, having power to allocate and use the technology used in the trial (39). The researcher also has other responsibilities in Chapter Five of the *Clinical Drug Trial Quality Management Standards*, one of the more important is to provide a detailed explanation that was agreed to by the ethics committee to the patient, as well as to obtain a signed informed letter of consent from the patient (40).

RIGHTS AND OBLIGATIONS OF THE OBSERVER

The purpose of the observer is to guarantee the rights of the patient who is taking part in the clinical trial and the accuracy of the trial records and report data, as well as confirming that the trial follows the approved plan and conforms with the related legislation (41). For the purpose of the trial, the observer is the most important contact person for both the applicant and the researcher (42).
The observer plays a very important role in the clinical trial as they must guarantee that the clinical trial is conducted in accordance with the plan including; before the clinical trial is conducted that everything conforms with the plan requirements, confirms that an informed letter of consent has been obtained from the patient, confirm that all the adverse reactions have been written in the records, and other essential steps to ensure that correct procedures are adhered to in the clinical trial(43).

ETHICS COMMITTEE

Only when the ethics committee has agreed and signed the approval opinion can the applicant implement the clinical trial (44). The decision whether the clinical trial will be approved is determined by ballot, and from which those committee members should abstain from voting (45). After receiving the application the ethics committee should promptly convene a meeting, read and discuss the application, sign the written opinion and attach a name list of those members attending the ethics committee meeting, including their speciality and personal signatures (46). The written opinion of the ethics committee will either be one of four opinions:

1) Agreeing to the clinical trial;
2) Not agreeing to the clinical trial;
3) Agreeing to the clinical trial after necessary amendments have been made; or
4) Terminate or suspend the already approved clinical trial.

The ethics committee will discuss a number of factors in deciding whether to agree to the clinical trial, paramount amongst these is the rights of the patients (47). Several of the relevant factors that will be discussed by the ethics committee include: the qualifications of the researchers, their experience, whether they have sufficient time to attend the clinical trial, whether the equipment or technology accords with the clinical trial requirements, whether the clinical trial plan has sufficiently considered the ethics committees principles which are the research objective, patient and other possible risks caused to the attending patient, and numerous other factors (48).

CLINICAL TRIAL TIME RESTRAINTS & SAFETY REPORTS

The applicant has within three years from the day of approval to carry out the clinical trial and has associated rights, and responsibilities to the SFDA, patients and other entities involved in the clinical trial (49). However if the clinical trial itself takes longer than one year, a progress report must be submitted to the SFDA and the local office of the SFDA where the clinical trial is being conducted (50). Of particular importance is the responsibility of the selected clinical trial work unit to take necessary measures to

guarantee the safety of the patient, and report any serious adverse reaction to the SFDA within 24 hours, as well as promptly report to the Ethics Committee (51).

SUSPENSION OR TERMINATION OF CLINICAL TRIAL

In the event that serious adverse reactions occur in the clinical trial then the SFDA or local offices of the SFDA have the power to suspend or terminate the clinical trial immediately (52).

MULTI-CENTER CLINICAL TRIALS

A multi-center clinical trial is a trial where a number of researchers according to an identical plan, in different places and work units, conduct a clinical trial at the same time (53). The multi-center clinical trial has proved to be a popular amongst clinical trail companies from the European Union and the United States. In the multi-center clinical trials each center must conduct the same clinical trial following an identical plan, starting and finishing at the same time, the trial being managed by one main researcher who coordinates the work (54). Foreign applicants wishing to conduct an international multi-centre clinical trial of drugs must file an application with the SFDA and should be aware of the following:

1) The drugs for clinical study must have been registered overseas or have entered Phase II of the clinical trial phase (if a new drug has not been registered overseas the SFDA will not accept the application for an international multi-centre study of the vaccine);
2) The SFDA may require that Phase I be carried out in China;
3) If during a multi-centre international clinical trial any serious adverse reactions are reported in any country this must be promptly reported to the SFDA; and
4) The applicant must submit a final report to the SFDA when the clinical trial has concluded (55).

THE PROTECTION OF THE UNDISCLOSED TRIAL DATA

As stated by the law, it is prohibited to use the undisclosed trial and other proprietary data for illegitimate commercial purposes. The state protects the undisclosed trial and other data obtained by the producer or distributor who have been granted the production or distribution license of the drugs containing a new chemical entity. Within six years after the drug manufacturer or distributor is granted the production or distribution license of the drug which contains a new chemical entity, the drug regulatory authorities will not approve use of the above-mentioned proprietary data for any other organization to apply for the production and distribution of the new chemical entity unless with the permission of the rights holder (56) .

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