[Workshop] [10/10/2003(Fri) 13:00-14:00/ Grand Ballroom 101]

Current Status and Strategies of the Efficacy and Safety Evaluation in Drug Approval Process

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This presentation briefly will be introduced on new drug approval process and the review of safety and efficacy of drugs in Korea. First, we will present the regulation related to new drug registration [Regulation of the Efficacy and Safety Evaluation of Drugs, etc (Notification No. 2003-17), Standards for Toxicity Test of Drugs, etc(Notification 1999-61) and GLP Regulation for Nonclinical Laboratory Studies (Notification No. 2000-63)] and the regulation related to clinical trial [Guidelines to Clinical Study Authorization for Drugs (Notification No. 2002-65)] and [Korean Good Clinical Practice(KGCP, Notification No. 1999-67) Regulation]. These regulations include detail informations on new drug application(NDA) and clinical trials for investigational new drug(IND). In 1999, the Korea Food and Drug Administration(KFDA) adopted bridging study for evaluation new drugs that have been developed in other countires and eliminated obligatory local phase III study. In 2002, KFDA revised the related regulation for distinguish IND and NDA process and promotion development of oriental drugs. The new KGCP is adopted for protection rights, safety and well-being of trials subjects and assurance of the quality of clinical trials.

Application Dossier for IND were data defined in the "guide for the approval for the IND of medicine" announced by KFDA including protocol or protocol amendment. Categories of data should be submitted for new drug applications, were as follows ;

1. Data related to origin, details of discovery, and background of development,
2. Data (including in-house specification and test methods) related to determination of structure, physicochemical and biological properties,
3. Data related to stability ; long-term storage test or accelerated stability test, stress test
4. Data related to toxicity.
5. Data related to pharmacology ; efficacy, general pharmacology, absorption, distribution, metabolism and excretion tests
6. Data related to clinical trials results ; clinical trial data package, bridging data
7. Data related to registration status or usage in foreign countries,
8. Data related to comparison with similar drugs that are currently available in Korea and other

special features of the drug,

Since the adoption of bridging study, it has been faced with many issues related to its clinical trial design methods, appropriate sample size and evaluation method. The basic purpose of ICH E5 guideline and the Korean regulations of Efficacy and Safety Evaluation of drugs is to extrapolate foreign clinical trials in Korea. There are several ways of evaluating bridging data. From 2002, pharmaceutical companies may join early phase of clinical trials to get Korean clinical trial data. It may be considered an ideal method to prove ethnic difference or similarity of drugs.

It is important to assess not only drug efficacy but also safety for the approval of new drugs and clinical trials.

Data related to toxicity contain single dose toxicity, repeated dose toxicity, reproductive· developmental toxicity, genotoxicity, immunotoxicity, carcinogenicity, dependency and local toxicity study. All the toxicity data which submitted to the KFDA for the application of new drug approval should be conducted by GLP testing laboratories from 2003. Among toxicity studies, immunological toxicity, carcinogenicity, dependency and local toxicity studies can be exempt according to case-by-case. The required immunological toxicity data, falling under one of the following categories, may be exempted: a)Antigenecity data, in the case of a drug with an oral route of administration except for polymer materials, protein drugs or other drugs with residual protein materials. b) Other immunological toxicity test data, in case where there was no abnormality in the immune system as a result of repeated-dose toxicity test. The carcinogencity test data shall be submitted in the following cases: a) Potential carcinogens: Drugs (or its metabolite) which have similar chemical structure or biological activity with already known carcinogens and whose repeated-dose toxicity test results or genotoxicity test results indicate potential carcinogenicity. b) Drugs being used clinically over a long period of time: Drugs whose clinical administration period are generally longer than 6 months (e.g.: analgesic/anti-inflammatory agent for chronic rheumatoid arthritis, antihypertensives for essential hypertension, etc.). Dependency test data shall be submitted for drugs having pharmacological actions on the central nervous system, or drugs acting primarily on the peripheral but having side effects on the central nervous system. However, compounds belonging to Phenothiazines, butyrophenones, reserpine, Tricyclic antidepressants, Aspirin, aminophylline, Indomethacin, flufenamic acid, Camphor, picrotoxin, pentylenetetrazol, strychnine, which are known to be free from inducing dependency may be exempted from the test if they are deemed homogeneous to the group with regard to their chemical structure, pharmacology an purpose of use. In the case where a drug is directly applied to a skin or mucosa, or may easily be contacted without direct application, the local toxicity test data shall be submitted. However,

other toxicity tests may include the local toxicity test.

In case of investigational new drug application for clinical trial, submission timing of toxicity studies (Repeated dose toxicity according to duration of clinical trial, reproductive toxicity and carcinogenicity study) differ according to clinical phase (phase I, II, III) and NDA registration. Repeated dose toxicity data shall be what is applicable to the minimum treatment duration depending upon the clinical trial phase, as provided in "Standards of a Toxicity Test on Drugs, etc." stipulated by Commissioner of Korea Food and Drug Administration. In case a male reproductive organ has been examined in the repeated dose toxicity study, phase 1 and phase 2 clinical trials on males may be conducted before the test data on the male reproductive toxicity is submitted, but the test data on the male reproductive toxicity shall be submitted before the phase 3 clinical trial is started. In case a female reproductive organ has been properly examined and evaluated in the repeated dose toxicity study, the clinical trial may be conducted on women under life-long birth control or incapable of pregnancy after menopause without reproductive toxicity data, but the test data on the female reproductive toxicity shall be submitted before the phase 3 clinical trial is started. Among the genetic toxicity studies, the test data on in vitro mutation and chromosomal aberration shall be submitted before the phase 1 clinical trial, and in case the test result appears to be quasi-positive or positive, the in vivo assay on micronucleus shall be submitted before the phase 1 clinical trial. However, in case the test result appears to be negative, the data on in vivo micronucleus assay shall be submitted before the phase 2 clinical trail. If the special concern on subject dose not exist, the clinical trial may be conducted without carcinogenecity data.

When reviewing toxicity study data in NDA phase, we have to consider many matters such as scope of data needed, requirements of data, dose level, toxicity parameters, toxicity results, statement of "Precaution on Use", comparison of toxic dose and clinical dose etc. In case of IND, we also have to consider following items ; 1. Determination of Scope of data needed according to clinical phases 2. Establishment of safe starting dose base on NOAEL of Toxicity Data, 3. Restriction of Subject, 4. Addition of toxicological parameters 5. Providing of information on toxicity in "Precaution on Use or Report for subject" 6. Information of timing of toxicity study according to clinical phase or NDA.

Biologics contain vaccine, antitoxin, blood products, DNA recombinant protein drugs, monoclonal antibody, cell therapy and gene therapy. There are general differences between conventional drug and biologics. Point to consider for toxicity studies of Biologics were as follows ; 1. characteristics of biologics (various nature of each products), 2.selection of appropriate animal species, 3. selection of dose, 4. route of administration, 5. regimen.