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SCREENING CENTRE FOR PHARMACEUTICALS

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REPUBLIC OF KOREA

Technical report: Development of cardiovascular pharmacology screening unit*

Prepared for the Government of the Republic of Korea
by the United Nations Industrial Development Organization,
acting as executing agency for the United Nations Development Programme

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1. INTRODUCTION

Pharmaceutical industry in Korea has been traditionally limited to dispensing of imported raw materials for domestic market in most of the pharmaceutical items. However, the future of the industry in Korea heavily depends on successful development and marketing of new drugs for the world. Competitiveness of Korean products in heavy industry and a steady improvement of economic growth in Korea awoke this country to see the direction of the world industry. In fine chemicals, particularly in the pharmaceutical industry, the Korean government and private industry can no longer ignore international pressure from developed countries on the development of new drugs due to the acceptance of so-called substance law in Korea.

2. OBJECTIVES

Unfortunately, neither Korean government, industry, nor academia is in a position to carry out the big task of new drug development at this time. Scientific institute such as Korean Research Institute of Chemical Technology (KRICT) has sufficient professionals who can synthesize potential new drugs rapidly and efficiently. However, Korea lacks experienced pharmacologists, facilities, and practical knowledge in the field of bioactivity evaluation of new pharmaceuticals. All these elements needed for that project are available internally or externally, although it might take time, depending on the nature of problems. The cold reality is the inhibitive cost that is usually involved in bioactivity screening procedures with living animal experimentations.

The primary objectives of this report were: 1) to lay out fundamental ground work for a cardiovascular drug screening center; 2) to introduce briefly basic methods for bioactivity evaluation procedure; and finally, to provide general and specific recommendations for rapid establishment of the center in terms of personnel, facilities, and instrumentations.

3. CARDIOVASCULAR BIOACTIVITY EVALUATION

a. Evaluation of drug efficacy and potency

Efficacy or intrinsic activity of a drug as a potential new drug must be determined first, because if it has no efficacy, no further bioactivity evaluation is needed. The potency of the drug should be determined simultaneously with a test of drug efficacy, compared to known standard drug.

b. Determination of adverse action for safety evaluation

Efforts should be directed to search for the potential adverse actions of a drug at the dose that produces therapeutic effects.

c. Evaluation of drug toxicity

Unwanted acute and/or chronic toxicity of a drug, including drug lethality should be studied in laboratory animals.

4. BASIC METHODS OF BIOACTIVITY EVALUATION

a. Whole animal test (ref. 1)

b. Spinal animal model

c. Noninvasive radiotelemetry for conscious animals

d. Isolated organ model such as Langendorff heart preparation (ref. 2)

e. Experiments with isolated tissues

   1) Papillary muscle

   2) Purkinje fiber

   3) Atrial and/or ventricular muscles

   4) Isolated blood vessel such as arterial ring preparation (ref. 3)

f. Cellular experimentation

   1) Cell culture of cardiac myocytes (ref. 4)

   2) Nerve activity such sympathetic efferent nerve activity (ref. 5)

   3) Cluster of neuron or specific nuclei of brain tissue

g. Intracellular test

   1) Electrophysiology of cardiac cells: cardiac action potential with or without drug; action potential configuration and its phases with intracellular ionic fluxes.

   2) Drug and receptor binding: Radioactive ligands binding study to their specific receptors in vitro; competition and displacement studies (ref. 6 and 7).

h. Enzymatic drug bioactivity evaluation

   1) Angiotension converting enzyme

   2) Sodium and potassium activated ATPase (ref. 8)

   3) Cardiac sarcoplasmic reticulum or sarcolemmal preparation (ref. 9).

5. PHARMACOKINETIC STUDY OF CARDIOVASCULAR DRUGS

a. Absorption

b. Distribution and compartmentalization

c. Metabolism

d. Elimination

e. Methods of drug delivery

6. STUDIES ON MECHANISM OF DRUG ACTIONS

Mechanism - of cardiovascular drugs may not be directly relevant to their bioactivity evaluation. It is evident, however, that a healthy progress in mechanistic aspects of drug actions will provide useful, fundamental knowledge not only for effective drug evaluation, but for the development of new superior pharmaceuticals. In this report, I will not attempt to document methods, even general guidelines, for the studies of drug mechanisms due to technical complexity of individual drugs. Please review recent relevant publications as indicated under references.

7. ALLIED PHARMACOLOGY THAT SUPPORTS CARDIOVASCULAR BIOACTIVITY EVALUATION

Good bioactivity evaluation of cardiovascular drugs depends on the firm establishment and operation of allied pharmacology for obvious reasons. It is also true that an efficient bioactivity evaluation of non-cardiovascular drugs requires directly or indirectly an involvement of cardiovascular system. Important major allied pharmacology for the proposed Pharmaceutical Screening Center would be:

a. Neuropharmacology

b. Endocrine Pharmacology

c. Renal Pharmacology

d. Pharmacogenetics

e. Psychopharmacology

f. Immunopharmacology

g. Nutrition and modification of life style

h. Cardiovascular demography and epidemiology

8. RECOMMENDATION

a. General

As a scientist who has considerable experience in both Korean and U.S. pharmaceutical industry, a few words to Korean government, pharmaceutical industry, and academia may be appropriate. The fate of Korean pharmaceutical private industry is shared with the future of Korean governmental performance in international competition. Korean pharmaceutical private industry needs a special protective measure, for the time being, to compete with every aspect of its foreign counterpart. Korean government should allow the private industry a tax incentive for the amount that it contributes to basic research and development yearly. The more they (drug companies) set aside fund for research and development, the better screening center or research facilities they might have. Using this tax incentive, Korean private pharmaceutical industry should establish a specific, but bold long-range plan, which requires massive hemorrhagic investment for a long period of time. In line with the supportive movement, Korean academia should provide eventually a state-of-the-art technique and knowledge including qualified experts in every aspect of pharmaceutical sciences.

Korean government, private industry, and academia should hold or sponsor more specific national and international scientific conferences instead of merely providing a meeting place. Only through quality scientific meetings state-of-the-art information can be exchanged naturally. Non-essential and non-informative formality disserves real purpose of a particular scientific gathering. Korea is not in a position to attack every frontline of pharmaceutical industry. Priority must be established depending on national needs or industrial feasibilities,

etc. It is also recommended that administrative business should be done by an administrator rather than by a professional. The cost of a scientific professional is too expensive to allow to perform an ordinary business administration, which can be done efficiently by a business student.

b. Physical facilities

1) A large (10 x 12) surgical suite for various acute and chronic preparations of various species of animals. This suite must be equipped with all surgical and life-saving instruments such as a cardiac defibrillator, respirators and so forth. Several isolated electrical inlets should serve the power of physiographic recorder and other vital instruments from the center of the ceiling.

2) Two small (10 x 6) monitoring and observation rooms after survival surgery for acute or chronic conscious animal experimentation.

3) At least 10 bench-top spaces for studies of heart perfusion and isolated tissues with several water sinks.

4) A large (10 x 12) culture room for the evaluation of potential direct action of drugs on cardiac myocytes. An excellent air-flow device with positive air pressure is needed for the operation of this type of work.

5) An electrically insulated room (10 x 12) for intracellular studies with modern electrophysiological instruments.

6) A large (10 x 12) laboratory with sufficient bench-top space for radioligand binding and biochemical enzymatic studies.

7) An instrument room (10 x 12) for centrifuges, beta- and gamma-counters, etc., must be available near to the biochemical laboratory.

8) Sufficient office space, space for secretary, room for reproduction and word processing instruments should also be available.

9) Library with recent Pharmacology periodicals and books.

c. Personnel

A senior pharmacologist (M.D. and/or Ph.D.) who is responsible for the entire operation of cardiovascular drug evaluation. He must be able to communicate with organic chemists and pharmacologists in charge of allied pharmacology for an efficient management of a cardiovascular evaluation center. An extensive academic and/or industrial experience in research and development for at least 10 years is strongly recommended for the post. One pharmacologist (at least two years postdoctoral training) each for 1) systemic animal evaluation including isolated heart and tissue study; 2) for cell culture laboratory; 3) for intracellular electrophysiology; and 4) for radioligand and receptor binding and biochemical studies. Each professional pharmacologist should be assisted by at least three or four supporting research staves who have either M.S. or B.S. degrees.

d. Equipment

1) Animal experimentation in a surgical suite requires several small and larger operation tables, various sizes of respirators, a blood flow meter and probes, electro-cautery system, recorder with various amplifiers and transducers

2) Device for the indirect determination of blood pressure such as radiotelemetry system with various transmitters and attached IBM personal computer.

3) Langendorff perfused heart apparatus and muscle bath with necessary recording system.

4) Microelectrode puller, high fidelity oscilloscope, force-displacement transducers, and light sensitive recording system for electrophysiological studies.

5) A coulter counter, a phase microscope, recording and analysis systems for isolated cardiac myocytes.

6) Preparatory centrifuges with various heads, ultracentrifuge liquid scintillation and gamma counters, a spectrophotometer, gel electrophoresis system, and catecholamine assay system.

9. CONCLUSIONS

My overall reaction to the proposed screening center for pharmaceuticals in Korea is favorable. From my brief interaction with Korean scientists from academia and industry, including the government sector, I could read their positive determination to establish the first class bioactivity screening center in Korea. The most valuable asset that Korea has for such an ambitious project is unquestionable human resource. Korean scientists' commitment for such a project is real and they have good basic scientific education. They are willing to educate themselves. It seems to me that they are ready to meet any challenge or hardship to achieve their goal. The only stumbling block that they have to overcome is the fact that administrators in government and/or industry do not anticipate the inhibitive cost of bioactivity evaluation procedures. The gap between the administrators who usually control funds and scientists is getting closer rapidly day by day. I am confident that a fund drive for the establishment of the modern screening center for pharmaceuticals in Korea will be successful, and I also do not have any doubt that the center will be in operation in the near future, if the valuable assistance from UNIDO and UNDP is continuous for a while.

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