DIVISION OF BIOLOGICS' PRODUCTION

Taiwan is located in a humid subtropical area where a lot of infectious diseases can easily become prevalent. The most effective way known of today to keep infectious diseases from becoming endemic is to immunize the public through vaccination.

Soon after the Japanese occupation ended in 1945, the Taiwan Provincial Hygiene Laboratory was established for producing antiserums and vaccines. This Laboratory was later renamed the Taiwan Serum and Vaccine Laboratory. The cholera vaccine manufactured by the Laboratory was at one time sent to support Korea, WHO and Ivory Coast, and the small-pox vaccine to UNICEF. However, along with our withdrawal in 1971 from the United Nations, not only were we cut off from the rest of the world in such goodwill exchanges in general, but more seriously we have since been left out of the world's health events and thus lagged behind in vaccine technology in particular.

As people on Taiwan were steadily prospering in the last decades, better quality of everything in life, with biological products being no exception, became the aim of a relentless quest. In order to address our people's wishes and to implement the nation's policy of "good manufacturing practice (GMP)," the Division engaged itself in 1985 in a zealous task of renovating its aged factory to meet the GMP requirements. In spite of severe shortage in funds and the fact that the building was much too old, our unrelenting determination and unfailing efforts did finally prevail over all obstacles, and the very first government owned GMP pharmaceutical plant on Taiwan was completed and certified in May 1988. The plant presented itself for not only being a leader for the rest to follow, but also the landmark unveiling a new era of the Division.

Major Functions

A. Manufacturing Biological Products of GMP Standard:

Biological products currently manufactured by the Division include bacterial and viral vaccines, toxoids, and antiserums as follows:

Bacterial vaccines:	cholera vaccine and freeze-dried BCG vaccine
Viral vaccine:	Japanese encephalitis (JE) vaccine
Toxoids:	tetanus toxoid alum precipitated; tetanus and diphtheria toxoids adsorbed (for adults); diphtheria and tetanus

adsorbed

Antitoxins: lyophilized tetanus antitoxin 4000 I.U.; lyophilized tetanus antitoxin 1500 I.U.; lyophilized diphtheria antitoxin 5000 I.U.

Lyophilized antivenins: antivenin of A. acutus; bivalent antivenin of B. multicinctus and N. naja atra; antivenin of Tr. mucrosquamatus and Tr. gramineus

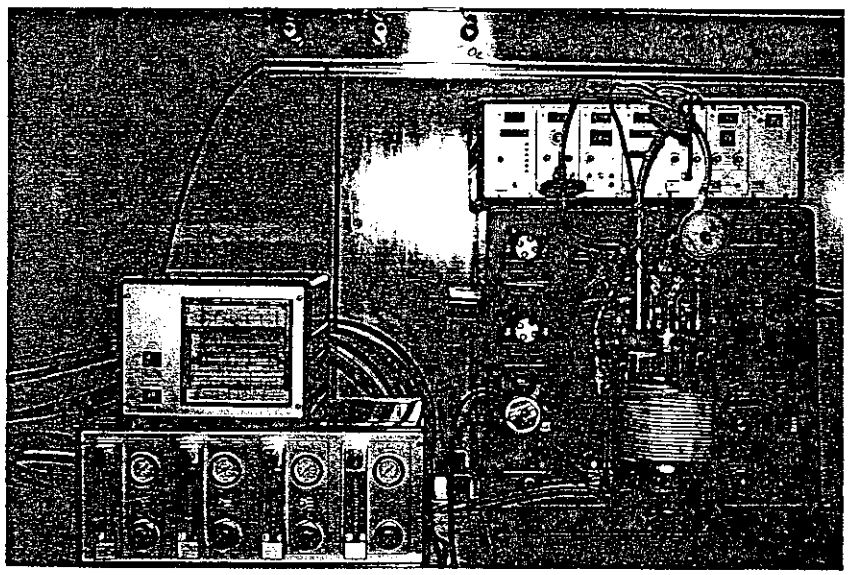
Tuberculin

B. Research and Development on Japanese Encephalitis Vaccine:

To improve the quality of biological products, the Division has lately given top priority to research and development. As the first step, several scientists of high caliber joined the staff in the past year.

The current major focal point in research and development is aiming at a new inactivated cell-culture derived Japanese encephalitis vaccine to replace the conventional one from mouse brain. Besides, each step in the inactivation and purification processes will be looked into and modified if needed to achieve higher antigenicity and lower probability in adverse side-effects.

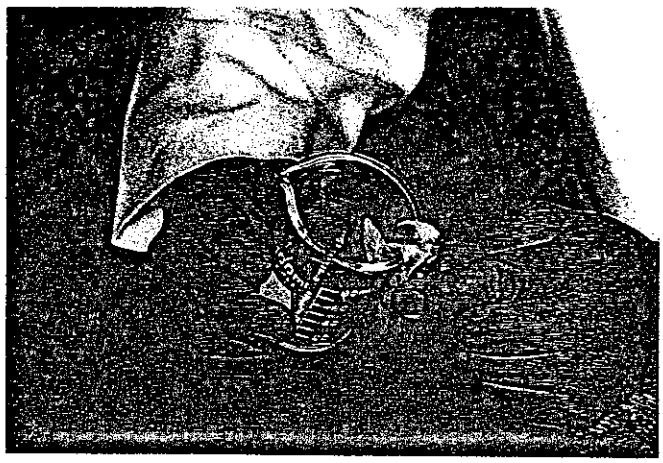
It is predicted that once the project is successfully completed, life of more than half a million mice could be spared annually in the operation alone, and that all the labor, material, and time spent on breeding and rearing those animals being no longer needed will for sure considerably lower the cost of the vaccine product. Also the leaving-out of mouse brain tissue as growing medium would most likely subside the possible ill side-effect derived from protein contamination.



Small scale fermentor for vaccine R & D

The last but by no means the least, the ever rising global animal-right movement will certainly make the mass utilization of any animal tissue in any fashion obsolete before we know it. With this universal recognition, we can appreciate that our attempt to switch over to cell-culture method is rather a "must" than an option in the strict sence and time is really pressing.

Collection of snake venom



C. Study on Local Poisonous Snakes and Their Antivenins:

Antivenins are a rather unique and important group of products we have been making and carrying. To better their quality, in terms of reducing the product's capability to elicit hypersensitive reaction in patients while improving its efficacy, constitutes a part of the unrelenting task of the Division.

Our current undertaking in this regard is to identify and purify some of the effective components in the snake venom through modern biochemistry techniques and animal tests. Hopefully, with the use of purified component in lieu of raw venom in horse immunization, it would lead us to antivenins of more desirable quality.

D. Methodology of Antigenicity Monitoring for JE Vaccine:

Being able to keep track of its antigenicity is one of the most critical features in JE vaccine quality assurance at each step during its production process and product quality control thereafter.

The conventional methods used at the Division in this respect include virus content estimation based on the LD50 on mouse, and the more straight-forward virus population counting in the plaque assay. Unfortunately, both methods mentioned are quite complicated to execute, tedious, time-consuming, yet poor in accuracy.

We are, therefore, working on a project in which we try to develop a more

accurate, sensitive, and above all, much quicker assay out of the popular ELISA technique to replace those cumbersome methods in use.

Our research data gathered so far indicate that the direction is right and the new assay is encouraging. A nice linear correlation exists between results of the ELISA and those of the plaque, and the outcome of ELISA also appears to be parallel to that of the plaque reduction neutralization test (PRNT) in the role as a quality control tool.

E. Study on the Stability of JE Vaccine:

JE virus, a species belonging to the Flaviviridae genus of Arbovirus, is very unstable because of its extreme sensitivity to temperature and the pH. This instability greatly complicates and hampers all endeavors in the research and development work, production, and storage of JE vaccine.

In this study we shall try out a number of likely substitutes for the existing preservatives and stabilizers in order to achieve better stability and safety without sacrificing its efficacy.

F. Administering Laboratory Animals Including Horses, Poisonous Snakes, and Mice:

In addition to the above mentioned research and manufacturing chores, our supporting personnel are responsible for keeping 20 some horses and five kinds of local poisonous snakes for antivenin production, not mentioning the upkeep of mice for the laboratory routines involving them.

Future Prospects

A. In coordination with the national policies on diseases control, to manufacture sufficient in quantity vaccines and antiserums of high quality;

B. To actively bring in modern vaccine technology to quickly bridge the gap we have been left behind with on basic, common vaccine products, while taking steps to strengthen our own research and development capability to develop new vaccines of local interests;

C. To help and encourage the private sector to further invest in biological product industry through technology sharing;

D. To improve the existing vaccine products in the directions of more cost-

effective, more acceptable by the future social standards concerning animal right and environmental issues, safer, more stable, and more effective; to target market efforts not only domestically, but at needy countries in the Southeast Asian region in particular and elsewhere in the world as well.

LIST OF STAFF

Chief:		
Liau, Ming-Yi	Ph.D.	Biologics R&D, Prodn, Veterinarian
Research Fellow :		
Huang, Reuey-Jen	M.S.	Biologics R&D, Prodn, Veterinarian
Associate Research Fellow:		
Jou, Ruwen	Ph.D.	Biologics R&D, Prodn
Li, Shu-Ying	Ph.D.	Biologics R&D, Prodn
Chang, Polun	Ph.D.	Health Care Policy
Chi, Shu-Jen	B.S.	Biologics R&D, Prodn, Pharmacist
Chen, Shu-Whei	B.S.	Biologics R&D, Prodn, Pharmacist
Huang, Ching	M.S.	Biologics R&D, Prodn
Assistant Research Fellow:		
Lee, Cheng Dow	B.S.	Biologics R&D, Prodn
Chen, Tsun Kang		Biologics production
Yen, Shang-Yung	B.S.	Biologics prodn & QC, Medical technician
Miao, Bor-lin		Horse immunization and venom purification
Kan, Shou-Ru		Biologics prodn & QC, Pharmacist
Chang, Man Ku		Biologics production
Hu, Men-Shing		Lab animal care
Chen, Chii Thuh		Biologics production & lab animal care
Huang, Mei-Tung		Biologics production
Research Assistant:		
Chiou, Aih-Jing	M.S.	Venom purification
Chang, Seng-chin		Biologics prodn & horse immunization
Liu, Chun-Jing		Cell culture & file management
Chou, Kuei		Toxoid production
Technician/Clerk:		
Lai, Yueh Fu		Inoculation of JE virus & lab animal recording
Hsu, Ming-Chang		Horse immunization & blood taking

Ho, Chung-Lin		Poisonous snake breeding & venom collecting

Contract Personnel:

Shih, Min-jwei	Ph. D.	Biologics R&D
Lo, Jun-Chih	M.S.	Biologics R&D
Chen, Yueh-Chun	M.S.	Biochemistry
Tsai Chia-Rong	B.S.	Entomology
Liao, May-Heuy	B.S.	Cell culture
Chen, Chin-Hsiu		Word Processing

LIST OF PUBLICATIONS

Journals:

1. Chang SY,Yu DS, Ma CP,Liau MY: Safety and immunoresponse study of intravesical instillation of Taipei-NIPM Bacillus Calmette-Guerin. Eur.Urol. 1992;21:52-57.

Conference papers:

1. Jou R,Yen SY, Huang C, Kang S, Liau MY: Determination of antigen content of Japanese encephalitis virus by ELISA method. The joint meeting of the Chinese Society of Microbiology & Immunology. 1994, September issue.

Books and Technical Reports:

1. Liau MY:Studies on the toxoids and antivenins of Formosan venomous snakes. NTU PhD Dissertation, 1991.

DIVISION OF BIOLOGICS' QUALITY CONTROL (DBQC)

Biological products like vaccines, toxoids and antisera, can be used effectively to prevent various infectious diseases. Most of the biological products are derived from animals or microorganisms and are thus potentially toxic to the human beings. Therefore, those issues pertaining to the product safety and efficacy are of special concerns to both the users and the manufacturers and should be under strict quality controls and regulations.

DBQC originated from the fifth division of the "Taiwan Provincial Serum and Vaccine Laboratory" and is responsible for the quality control of biological products manufactured by NIPM. Consequently, the major missions are focused on the following aspects, (1) monitoring the quality of biologics produced by NIPM with special attentions on the product effectiveness and safety; (2) executing GMP regulations in NIPM; (3) improving and updating the assay methods routinely used in the quality control efforts; and (4) employing modern biotechnologies to perform research and development efforts and to set up new assay systems for better quality control.

Animal tests on the presence of pyrogens in vaccine preparation.

Major Functions:

1. Performing Chemical and Biological Tests to Materials Used for Production and to Final Products for Safety and Effectiveness Assurance:

DBQC is equipped with well-defined assay systems for the quality control of biologics production procedures starting from raw materials to the final products. As general routines, tests are regularly performed to ensure purity, stability, effectiveness, and safety of materials used for production and of final products. These include biological tests like sterility, pyrogen, safety, toxicity, potency and chemical assays like protein content, stabilizers, aluminum contents, pH value and mamy others. All products manufactured by the Division of Biological Production, NIPM, should pass the tests of the DBQC before they can be transferred to the National Laboratories of Foods and Drugs (NBFD) for final evaluation and subsequently, for marketing.

2. Executing GMP Regulations in NIPM:

DBQC is also responsible to supervise the actual execution of GMP regulations in NIPM. Everything related to the final products (product quality, containers, labels, packings and others) is subjected to strict monitoring. All matters pertaining to the production efforts (production environment, production procedures, master file of quality control and Standard Operation Procedures, and others) are routinely placed under strict inspections. To ensure optimal technical performance of DBQC, training programs are organized regularly for maintaining or even upgrading technical arsenals of colleagues in the Division. DBQC's efforts on supervising the execution of GMP regulations in NIPM are under DOH's inspection every year. Further improvement of the techniques of modern GMP regulations and establishment of minimum requirements for biologics are performed to cope with DOH's recommendations.

3. Improving and Updating the Assay systems Used in Quality Control Efforts:

In addition to the routine works with the quality control of biological products manufactured in NIPM, DBQC has recently made several progresses in the improvement of assay systems used in regular quality control routines. The most important one is "The Establishment of Plaque Reduction-Neutralization Assay" to replace the traditional "Mouse Brain Challenging Assay" in the evaluation of effectiveness of JE vaccine. A comparative study on the virulence enhancing agents has also been completed to facilitate the toxicity test for bacteria and potency test for bacterial vaccines. Both systems have been incorporated in "the Minimum Requirement of Biologics" published by DOH.

Test of JE vaccine potency by "Plaque Reduction-Neutralization Assay"

4. Developing Efforts on Acellular Pertussis Vaccine:

Whooping Cough is one of the most important infectious diseases in children. Traditional whole-cell pertussis vaccine can efficiently prevent over 80% of disease incidence. However, adverse reactions have been reported in the past decades. Therefore, new generation of vaccines using protective antigens as sources of immunogens have been developed by Japan and the US. NIPM has been funded by the provisional National Health Research Institutes for an "Integrated Project on Vaccine Research and Development" since 1993. Efforts on acellular pertussis vaccine are among the three sub-projects, and DBQC is responsible for this task.

Thus far, several assay systems (eg. ELISA, CHO Cell Aggregation Assay and Histamine Sensitizing Assay) have been set up for assaying the biological activities of pertussis vaccine.

In addition, efforts have been made to develop fermentation systems suitable for mass-production of B. pertussis with high yields of toxin products. Optimization of the toxin production and related purification procedures are also underway. As a long term goal, the detoxified toxin will be combined with diphtheria toxoid and tetanus toxoid as 3 in 1 vaccine for domestic use.

5. Research on Japanese Encephalitis (JE) Vaccine:

JE is one of the most important endemic diseases in Taiwan. Although effective vaccines are available for disease prevention, some clinical cases have been reported these years, indicating the need for vaccine improvement. DBQC has recently developed a column chromatography-based procedure for high purity of JE virus

preparation and its extension to mass production is now under intensive investigation. Research on basic properties of JE virus is also ongoing. Extensive epitope mapping is performed with a hope to identify immunologically important epitope(s) for peptide vaccine development. Cross protection with different strains of JE virus on JE infection is also systemically evaluated with an aim to find out suitable local virus strain(s) for better JE vaccine.

Future Prospects:

Improvements on medicine and pharmaceutics have been called for more urgent demands on the quality, effectiveness and safety of pharmaceuticals. DBQC feels strongly that not only her technical capacities should be properly expanded, but her every step employed in laboratory practices should be highly regulated and controlled. Consequently, the establishment of GLP and CGMP management system for improving assay results and production process control are aims for self-upgrading in the near future.

For technical capacity expansion, DBQC will further strengthen her ability on immunological assays and techniques in molecular biology for both practical utilization and research tasks. In the next few years, JE and acellular pertussis vaccines are targets for intensive investigation. Further extension of these research results obtained in the next few years will be the development of multivalent vaccines and systemic studies on the immunological effects of individual and combined vaccines.

LIST OF STAFF

Chief:

Lu, Cheng-Hsiung	Ph.D.	Microbiology, Immunology, Pharmacology

Assistant Research Fellow:

Chou, Feng-Yuan		Assay of biological products
Chang, Shu-Nien	B.S.	Assay of biological products
Kao, Mei-Chuan	M.S.	Microbiological assay
Hsu, Tung-Chien	B.S.	Cell Biology research
Sheu, Gwo-Chang	M.S.	Biochemistry
Ju, Chi-Liang Chu	M.S.	Biochemistry
Chen, Tzy-Yin	M.S.	Assay of biologic produces

Research Assistant:

Wu, Pao		Assay of biological products

Cheng, Ya-Fen	M.S.	Cell Pathology
Liu, Liahng-Yirn	M.S.	Endocrinology & Cell Physiology
Chang, Jui-Hsien	B.S.	Biochemistry

LIST OF PUBLICATIONS

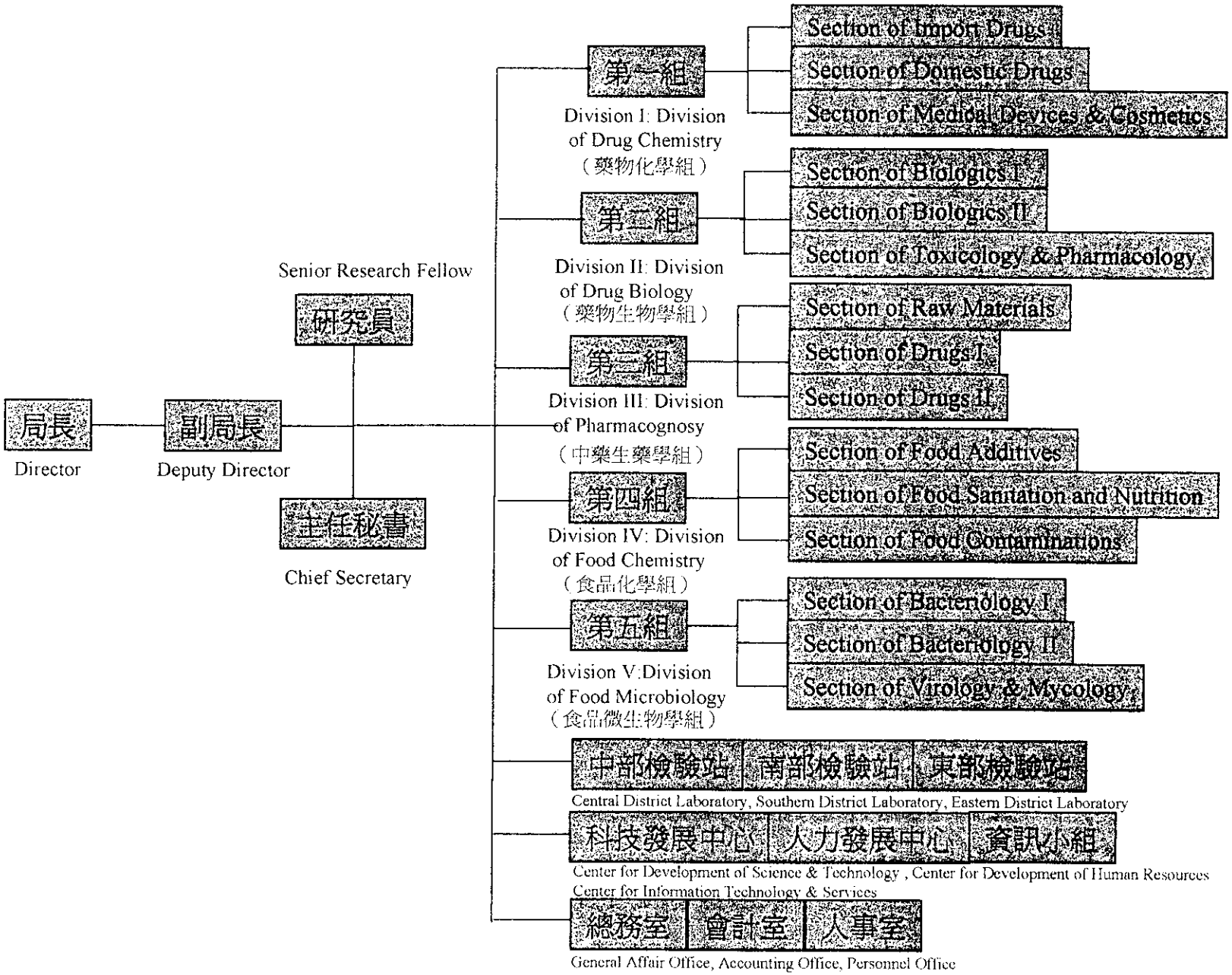
Journal

1. Kao MC, Lu CH: 1992. Comparison of assay methods for determining the protein content of Japanese encephalitis vaccine. Annual Reports of the National Institute of Preventive Medicine, ROC, 1992;6:255-263.
2. Hsu TC, Yen SY, Lee JD, Yu TS, Chou FY, Lu CH: A column chromatography based method for purification of Japanese encephalitis. Annual Reports of the National Institute of Preventive Medicine, ROC, 1992;6:264-271.
3. Sheu GC, Chou FY, Lu CH: Comparison of different methods for purification of Bordetella pertussis endotoxin. Annual Reports of the National Institute of Preventive Medicine, ROC, 1993;7:123-131.
4. Lu CH, Kind Phyllis, Lee CJ: Immune response of neonates to Streptococcus pneumoniae type 9V polysaccharide-tetanus toxoid conjugate. Infect. Immunity 1994;62:2754-2760.

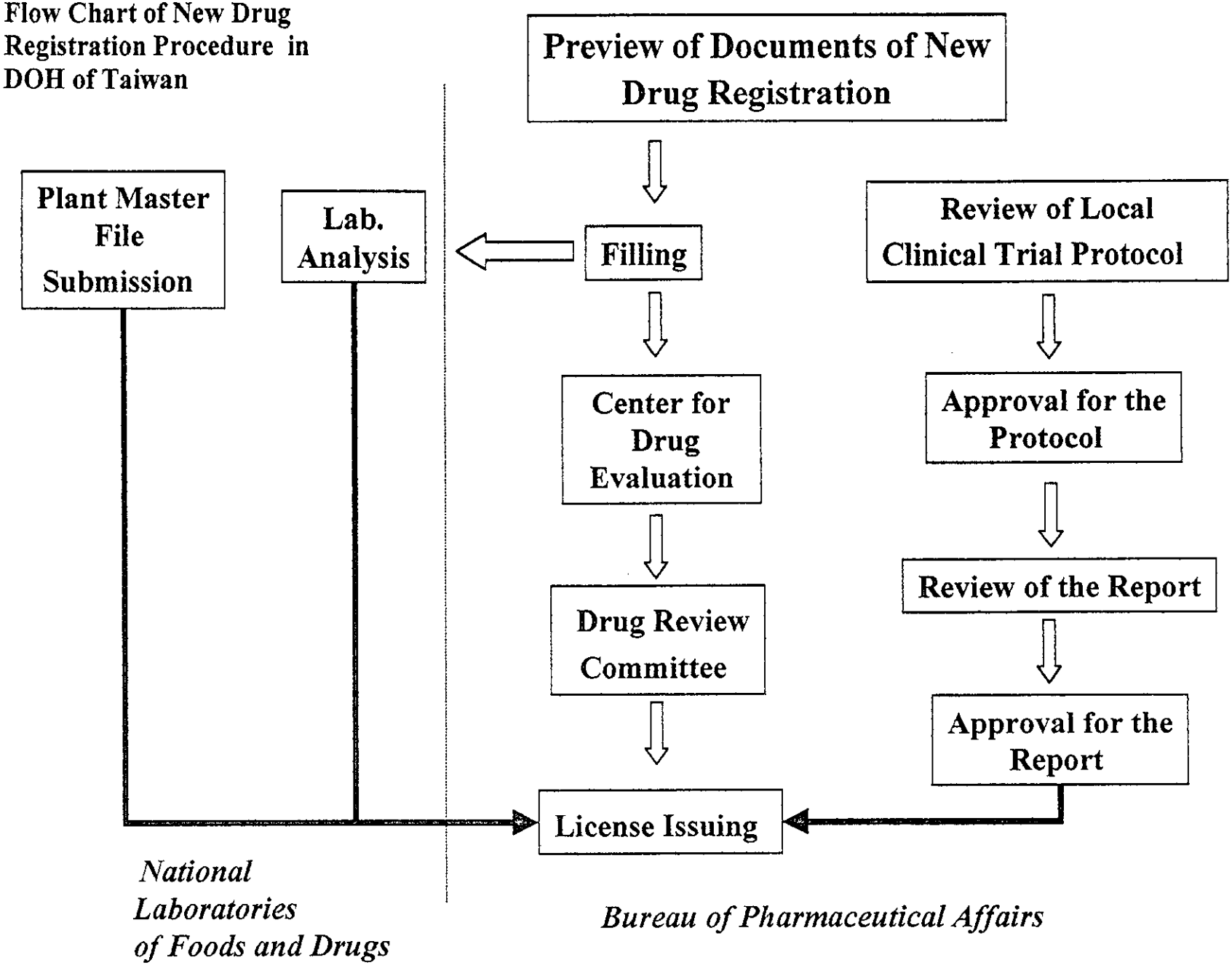
Symposium Papers

1. Hsu TC, Yen SY, Lee JD, Yu TS, Chou FY, Lu CH: A column chromatography based method for purification of Japanese encephalitis virus. The 26th annual meeting, Chinese Society of Microbiology. Taipei, R.O.C. 1992.
2. Hsu KC, Chou HY, Lu CH: 1993. The new method of purification of the lipopolysaccharide of B. pertussis. The 27th annual meeting, Chinese Society of Microbiology. Taipei, R.O.C. 1993
3. Hsu KC, Lu CH: Comparison of the toxicity of B. pertussis lipopolysaccharide and pertussis toxin in mice. The 1994 joint meeting of the Chinese Society of Microbiology & the Chinese Society of Immunology. Taipei, R.O.C. 1994.
4. Lee YS, Chiu SY, Ju CL, Pan TM, Lu CH, Horng CB: Antimicrobial susceptibility and pertussis toxin productivity of B. pertussis isolated in Taiwan. The 1994 joint meeting of the Chinese Society of Microbiology & the Chinese Society of Immunology. Taipei, R.O.C. 1994.

Organization of National Laboratories of Foods and Drugs



Flow Chart of New Drug Registration Procedure in DOH of Taiwan



OVERVIEW

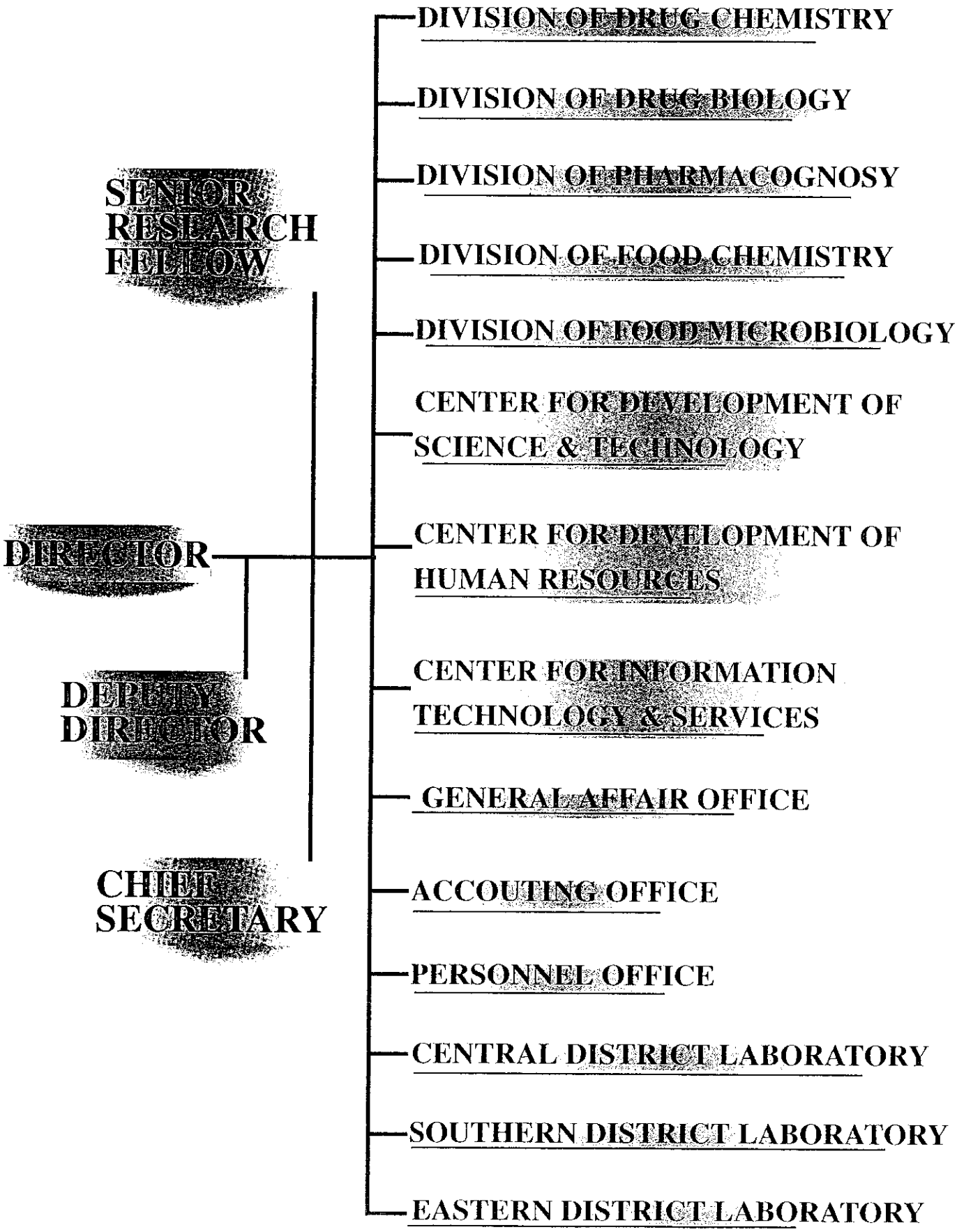
■ **The National Laboratories of Foods and Drugs (NLFD)** was founded on September 20, 1978. The former Taiwan Provincial Hygienic Laboratory, originally established in 1946, was then reorganized and established under the auspices of Department of Health as the NLFD. In its 32 years of operation, the Laboratory has established an excellent foundation for testing and inspection procedures and techniques.

DUTIES AND ORGANIZATION

The duties and responsibilities of the **NLFD** are set down as follows:

1. Testing of all food and medicaments (including drugs and medical devices), food additives, utensils, containers, packaging, and cosmetics.
2. Establishment of analytical methods for all medicaments and food additives.
3. Establishment of analytical methods to maintain sanitary standards for all foods; food utensils, containers, packaging; and cosmetics.
4. Evaluation of investigative research, experimentation, and sanitary safety of foods and medicaments; food additives, utensils, containers, and packaging; and cosmetics.
5. Supply of reference standards to be used for comparison purposes in the inspection of drugs and food additives.
6. Technical training and guidance as well as supervision of all district foods, drug, and cosmetic sanitation inspection personnel.
7. All other related aspects of the testing of drugs; foods, food additives, utensils, containers, packaging; and cosmetics.

ORGANIZATION



Message of Director-General

Since the early inception of National Laboratories of Foods and Drugs(NLFD), the role and the duties of this Institute has been the safeguard of hygiene standards for foods, drugs and cosmetics. In addition, offering training courses, assisting local health authority are also very important duties. These functions help enhance the quality of inspection and testing which foster the effectiveness of manpower and avoid wasting of precious resources. Due to the fast development of technology and the vast increase of product varieties NLFD made proper adjustments on her mission through three different phases. The first phase began in 1978, last till 1985. During this time, budgets were allocated, laboratories were built, equipment procured and talented professionals were recruited to initiate the analytical testing work. Subsequently, the second phase started from 1985 to 1994, the duties of the Institute changed to sample testing and enact survey research plans which provide the regulatory agency critical information and allow it to effectively understand and solve administrative problems. It also conducted studies to establish new methodology for testing. The third phase started from 1994. After the promulgation of consumer protection act in that year, the proper public announcement of product testing results and the additional testing procedures are both implement as major directions of NLFD. The information provided to the consumer can also help educate and provide effective protection of health to the public.

The field and knowledge of food and drug testing is enormously wide and profound, especially in the area of Biotechnology and new products' development. There are numerous tasks such as establishment of specifications and standards, quality assurance in the laboratory, Good Laboratory Practice (GLP) and the active participation of proficiency

testing etc, these activities are intended to upgrade the quality of testing procedures to the highest international standard, and to provide reliable testing results to win the public trust. Furthermore, to assist the promulgation of "drug abuse hazard prevention act", accreditation of laboratories in the private sector has been conducted. In order to provide good quality services in drug abuse testing and help the judicial system, ten laboratories have been certified by NLFD according to the "drug abuse urine testing management procedure".

To carry out the "reinvent government"(REGO) policy, the spirit of enterpreneurship and business administration are introduced implemented and "excellent efficiency" and "customer service satisfaction oriented" ideas are emphasized. NLFD adopt this in our laboratory to further advance in such areas like "consolidation of regulatory administration and testing system", "development of accreditation and assist local health lab. to establish GLP", "international cooperation and mutual recognition" and "improvement of research on new testing technology" etc. These are the important subjects and goals of NLFD. The purpose is to enhance administrative effectiveness, enhance quality and efficiency of analysis and increase competitiveness of the Institute internationally.

Finally, the coming 21st century and the new era brings new challenges of high technology, high quality task in the field of drug, food testing. I believe that one of the important links of improving the quality of life as well as high quality medical service is the testing and analysis. I further believe that under the leadership of minister of Department of Health and excellent supervision provided together with the dedication and professionalism of our staff members, we certainly reach our goals and the expectation of our citizens will not be disappointed.

Chun-Heng Liao

Director-General

疾病管制局

An Overview of Center for Disease Control

Ming-Yi Liau, Ph.D.

Vaccine Center

2001, Jan. 11

CDC

疾病管制局

機動化、資訊化、專業化、全民化、國際化

衛生署疾病管制局 Center for Disease Control

快速專業作防疫、全民運動保健康

CDC

疾病管制局

About CDC

The goal is to prevent diseases through active involvement, sound healthcare networks, expertise and proficiency, the full participation of all people, and participation in international activities; and to implement prevention and control measures against communicable diseases, and thus to promote national health.

CDC

疾病管制局

Development

To deal with the changing patterns of communicable diseases, to consolidate disease control resources, and to establish a disease control system to face the challenges of the 21st century, the Center for Disease Control of the Department of Health was established on July 1,1999 under the Organization Law of the Center for Disease Control, the Department of Health, promulgated on February 3, 1999. The Center was established by merging the Bureau of Communicable Disease Control, the National Institute of Preventive Medicine, and the National Quarantine Service of the Department of Health.

CDC

疾病管制局

Legal basis

- Law on the Control of Communicable Diseases (promulgated on June 23,1999);
- Law on the Prevention and Control of AIDS (promulgated in 1999); and Some ten regulations relevant to the above laws.

CDC

疾病管制局

Visions

To prevent diseases promptly and professionally; and to mobilize all people for health promotion.

CDC