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ESTABLISHMENT OF A PHARMACOLOGICAL INSTITUTE IN ISRAEL*

DP/ISR/73/010

ISRAEL

Terminal report

Prepared for the Government of Israel by the
United Nations Industrial Development Organization,
executing agency for the United Nations Development Programme

Based on the work of Nathan Back, senior pharmacologist

United Nations Industrial Development Organization
Vienna

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I. INTRODUCTION

A modern and successful pharmaceutical industry is based on a sound Research and Development programme which enables the development and introduction of new and more effective drugs of clinical importance. These developments can be achieved only by the fully integrated and cooperative efforts of medicinal chemists and biochemists who isolate and/or synthesize de novo chemical structures, and the biologists, pharmacologists, and medical personnel who evaluate their potential effectiveness in a wide variety of pre-clinical and clinical settings.

The pharmaceutical industry of a developing country has a direct effect on the health of its people. Most developing countries depend heavily on the importation of drugs. While this fulfills their drug requirements, it tends to supress the development of a country's drug industry, and the many scientific and technological activities directly related to and supporting the industry.

The dependency of a drug industry on licensing arrangements with foreign companies, apart from placing a drain on its foreign currency balance, inhibits the entry and training of scientists into the important applied art of drug design and testing. Bio-medically trained technicians also are deprived of the opportunity to apply their knowledge in this field as well as to enhance their scientific skills. Chemical scientists involved in the synthesis of agents for the treatment of human and animal diseases are required to rely on out-of-country testing services thereby losing the advantage of an immediate feedback of biologic information regarding new chemical compounds. This arrangement has a serious inhibitory effect on the medicinal chemistry synthesis program. The absence of an applied drug research institute also diminishes significantly the discovery and development of drugs directed against diseases indigenous to that country.

Thus, the presence of a drug research institute that has the capability of bringing new therapeutic agents from the chemists'bench to the clinical setting and ultimately to the market place, potentially would benefit a country in many ways. It would accomplish the following:

1. facilitate the overall development of the pharmaceutical industry,
2. expand the employment and training of scientists, technicians, and many other ancilary personnel involved in all phases of drug research and production,
3. focus on the development of drugs of specific benefit to the country's health needs,
4. provide important counsel to the health-related federal regulatory agencies, and
5. benefit the economic and health welfare of the country.

The establishment of an applied pharmacology drug research institute involves the appropriate interdisciplinary scientific and managerial personnel, capital commitment and investment, and advanced technology. All these components are available or can be mobilized. Efforts to mobilize the ingredients necessary to establish such an institute will be more than justified as the pharmaceutical industry expands and new drugs of therapeutic importance emerge.

II. BACKGROUND

The Government of Israel submitted a proposal for the establishment of a Pharmacological Institute as a vital infra-structure to support research and development within the pharmaceutical industry in the country. As pointed out in the background scenario contained in the Report on the Preparatory Mission for the Pharmacology Institute Project undertaken by this Advisor in December, 1975, the Israel Government, as early as 1963, recognized the pivotal role of an in-country pharmacological testing programme to the development and expansion of the pharmaceutical industry. A pharmacology institute, established in 1966 under the aegis of the National Council for Research and Development, was closed in 1971, and attempts since then to organize a collaborative pharmacology institute project with industry, government, and university participation did not meet with success for a variety of reasons.

The Government arrived at the conclusion that the optimal setting for a pharmacology screening activity was directly within an existing pharmaceutical company. Such a company should be capable to develop and expand the activities of such a pharmacology center if provided with the initial appropriate scientific guidance, advice, and support. This conclusion found support amongst the various agencies of the Government interested in the expansion of applied pharmaceutical industrial research, and was consistant with the philosophy of a newly-established Ministerial Committee for Science and Technology organized to consider country problems of Research and Development.

In accord with these objectives, the pharmaceutical comapny ASSIA-TEVA indicated its willingness to make the necessary commitment in both effort and finances to establish a Pharmacology Institute within its recently established Research and Development Division. ASSIA-TEVA was the only pharmaceutical company amongst those polled that agreed to participate in this effort, and a review of its current reports indicated that this company had the organizational capacity and growth potential to establish such an activity and maintain it. Thus, the Government submitted a proposal to set up and organize a Pharmacology Institute in this industrial conglomerate with guidance and assistance from scientific experts from abroad. This proposal was supported by the recommendation of the present expert following his on-site review of the conditions both within Israel and the Industry as contained in his summary report on the preparatory mission submitted to UNIDO/UNDP on January 3rd, 1976.

As a result of the recommendation, the project was launched in July, 1976 by the movement of the scientific expert to the project site in Jerusalem for an initial 7-month mission which was extended subsequently to 11 months.

This final report summarizes the activities associated with the project during July 7th, 1976 to May 31st, 1977, the tenure of the expert. As will be detailed in the body of the report, accomplishments were identified in major duty areas as outlined in and mandated by the UNIDO job description document.

III. OBJECTIVES

The following major objectives for the pharmacology institute were identified:

1. Carry out medicinal chemical synthesis and natural product extraction for agents with potential therapeutic activities.
2. Pharmacologic, biochemical and toxicologic evaluation of synthetic and natural product compounds on isolated and intact animal systems.
3. Study of pharmacokinetic profiles of select agents in appropriate animal models.
4. Study of drug formulation, drug compatibility, and drug interactions.
5. Training of scientists in applied modern and classical pharmacological-toxicological and clinical research technique and philosophy.

The above objectives would be carried out in an integrated fashion within established departments of Medicinal Chemistry, Pharmacology- Biochemistry, Pharmaceutics, and Clinical Medicine with appropriate administrative, animal facility, analytical chemistry, data processing, and instrument laboratory services.

IV. FINDINGS

The mission objectives were concerned with the multi-faceted aspects of drug research and development, ranging from chemical synthesis, pharmacology-toxicology, pharmaceutics, and clinical pharmacology. These findings will restrict themselves to these aspects as they relate to their integration within a pharmacology institute.

A. Corporate Structure and Products

ASSIA-TEVA is a corporate conglomerate comprised of ASSIA-ZORI (a privately-held company), TEVA (a public corporation), ASSIA MABAROT (a veterinary arm of ASSIA in which 50% is held by ASSIA and 50% by Kibbutz Ma'abarot), and PAKA, (a newly-acquired yeast fermentation plant). The administrative head of the company is a Managing Director who is responsible to a Board of Directors headed by a President. Within the Pharmaceutical arm, TEVA, the Managing Director is in charge of the Divisions of Chemical Production, Pharmaceutical Production, and the newly-formed Research & Development. Each Division is headed by a

Director. In addition, there are Departments of Manpower, Marketing, Accounting, Export, Medical Advisement, and Drug Regulation.

The company manufactures over 500 medicinal drugs for human and veterinary use, biologicals (vaccines), and chemical products. Drugs and diagnostic agents account for over 90% of the corporate products with approximately 50% of these products marketed in Israel. The drugs are marketed either as "generics" formulated in accordance with international pharmacopeal standards or are products acquired under license from original manufacturers and subsequently reformulated or repackaged in Israel, often with only slight modification. Since TEVA does not have as yet a complete Research and Development capability, it has not had the capability to manufacture drugs that have been synthesized, studied in pre-clinical and clinical tests, approved, and marketed in Israel.

B. Divisional & Departmental Activities

1. Chemical Division. The Chemical Division is primarily responsible for production of bulk and fine chemicals and drugs. Chemical research which falls under the umbrella of R & D is divided into "process" or applied research (developing new chemical synthesis pathways for known compounds) consisting of six chemists, and basic research ("molecular modification" of known active drugs) consisting of three chemists. The Division has the responsibility for manufacturing, production, marketing, and promotion.

2. Pharmaceutical Division. This Division is the most highly developed consisting of such "line" departments as Technical, Operations, Production, Pharmaceutical Development, Quality Control, Medical Information, Medical Management, and Marketing. This Division has over 31 personnel with at least 9 technical position openings. The manufacturing capability of this Division includes the production of a variety of drug dosage forms (tablets, capsules, suppositories, solutions, suspensions, creams, ointments) and both sterile and non-sterile products. The Department of Pharmaceutical Development services both the Pharmaceutical and Chemical Division in a "trouble shooter" capacity, and carries out only very limited formulation and pharmacokinetic research on an ad hoc basis.

3. Research & Development Division. The R&D Division at TEVA has been established only recently. The management has indicated its readiness to expand its R&D activity by supporting the development and sustaining the activities of a Pharmacology Institute. The activities of the following departments in formation would be coordinated: Medicinal Chemistry, Pharmacology-Toxicology, Biochemistry-Clinical Chemistry, Pharmaceutics, Data Processing, and Clinical Pharmacology.

a. Medicinal Chemistry. TEVA has on-going medicinal chemistry synthesis research. An estimated 150 chemical compounds are synthesized annually comprising primarily of molecular modifications of known therapeutic agents. In addition, synthesis of known agents by new process research techniques yields compounds often requiring pharmacokinetic study. Basic chemical synthesis research is carried out in the country's many University and Research Institute Laboratories and departments.

b. Pharmacology-Toxicology. TEVA does not have either the personnel, equipment, or facility for carrying out the biological-toxicological evaluation of their synthesized compounds. A limited and rudimentary pharmacology screening activity is available at the departments of Pharmacology at the Hebrew University's Schools of Pharmacy and Medicine. TEVA sends compounds to these departments as well as to foreign commercial testing companies. While some toxicology evaluation is available at the Weizmann Institute and the Government Biological Research Institute, TEVA has preferred to send select compounds abroad for study. The Government supports this biologic evaluation program in the form of direct research grants covering as much as 80% of costs. No pharmaceutical company in Israel has any "in-house" pharmacologic-toxicologic testing capability.

c. Biochemistry-Clinical Chemistry. While some equipment is available for conducting biochemical and clinical chemical studies on candidate compounds, TEVA presently does not have the capability for such investigations "in-house". A degreed scientist on TEVA staff now is located in the department of Biochemistry at the Hebrew University where space is rented to TEVA on an annual basis. A similar arrangement was made for a TEVA medicinal chemist in the department of Chemistry.

d. Animal Facility. TEVA has no suitable facilities to house and maintain animals. Animal quarters would have to be constructed. Animal breeders in the country would be able to provide sufficient mice,

rats, guinea pigs, rabbits, cats, and dogs for experimental use. Non-human primates would have to be imported although limited colonies are available in the country.

e. Pharmaceutics. As noted, essentially no pharmaceutical pharmacokinetic studies are carried out at TEVA. The Pharmaceutical Department conducts product formulation work. In fact, Israel does not have a modern-trained pharmacokineticist within the Industry. A clinical pharmacologist at the University of the Negev in Beersheba is trained to carry out some pharmacokinetic study.

f. Data Processing. At present, TEVA does not utilize its computer banks for the processing and retrieval of scientific data. Such computer programs will be necessary in light of the institution of good laboratory practices codes by the regulatory agencies of Western countries.

g. Clinical Pharmacology. TEVA has carried out several clinical trials on known approved drugs and on at least one drug under development. The clinical trial protocol, formulated by TEVA and a clinician in a hospital where the trial is conducted, must be approved by the Ministry of Health Committee for Clinical Trials. Various sub-committees assigned to specific therapeutic areas help the Ministry review applications for clinical drug trials. Advisory committees also review applications for established drugs or drugs considered new molecular species or molecularly modified drugs. There appears to be no specific guidelines offered by the Ministry of Health for conducting clinical trials. It is known that, at times, new drug trials have been sponsored by pharmaceutical countries in the country's hospitals without approval of the Ministry and without the knowledge of the patients. The Ministry also may not be aware of these trials or does not have the personnel to enforce the regulations.

4. Medical Advisement

Medical advisement at TEVA is carried out by three physicians, two of whom are in semi-retirement. The physicians are on the staff of the Pharmaceutical Division, but they provide consultations to all divisions of the corporation. The medical advisors carry out the following: medical consultation to the various units of the corporation; preparation of drug marketing promotional material; training of detail personnel; the drafting of clinical trial protocols and the supervision

(monitoring) of such trials; presentation to the Ministry of Health Drug Regulatory Committee in support of drug licensing, registration, and re-registration. The medical advisors are permitted by TEVA to engage in some private clinical practice during the work week.

5. Medical Information & Regulatory Affairs

Medical and information and regulatory affairs are the responsibility of two pharmacists on staff of the Pharmaceutical Division. Their activities include the collection of data on drug products registered in Israel and abroad; preparation of product information for marketing; sales, detail personnel, and physicians; training of detail personnel, provide specific drug information requested by physicians; conduct of drug literature surveys; collection of information on adverse drug reactions (Phase IV clinical pharmacology); participate in the process of filing for drug registration and re-registration. It should be noted that the Regulatory Agency approves drugs for registration and re-registration (required every 5 years for all marketed drugs) on the basis of preclinical and clinical data submitted by the Drug Information Department. These data are obtained by TEVA from the foreign licensing company, and the application is prepared in accordance with the requirements set forth by the Regulatory Agency.

V. RECOMMENDATIONS

The following constitute recommendations for the proposed Pharmacology Institute, including the proposed design of the building, the Institute site, the respective Departments and Laboratories, the proposed research and organizational structure of research and development activities, and the required capital equipment. These recommendations are based on the premise that the Institute shall carry out activities directed toward the ultimate development of new therapeutic agents. These activities would require the coordinated efforts of an inter-disciplinary team of scientists.

Thus, IT IS RECOMMENDED that the following departments be established within the Research and Development (R&D) Division of TEVA

Pharmaceutical Industries, Ltd.:

1. MEDICINAL CHEMISTRY DEPARTMENT
2. LIFE SCIENCES AND THERAPEUTICS DEPARTMENT
3. MEDICAL DEPARTMENT
4. PHARMACEUTICS PRODUCT DEVELOPMENT DEPARTMENT
5. DATA PROCESSING & INFORMATION DEPARTMENT

In addition, IT IS RECOMMENDED that the following supporting services be established in or made available to the Institute:

1. ANIMAL FACILITY
2. ANALYTICAL CHEMISTRY
3. REPAIR SHOP
4. ADMINISTRATION

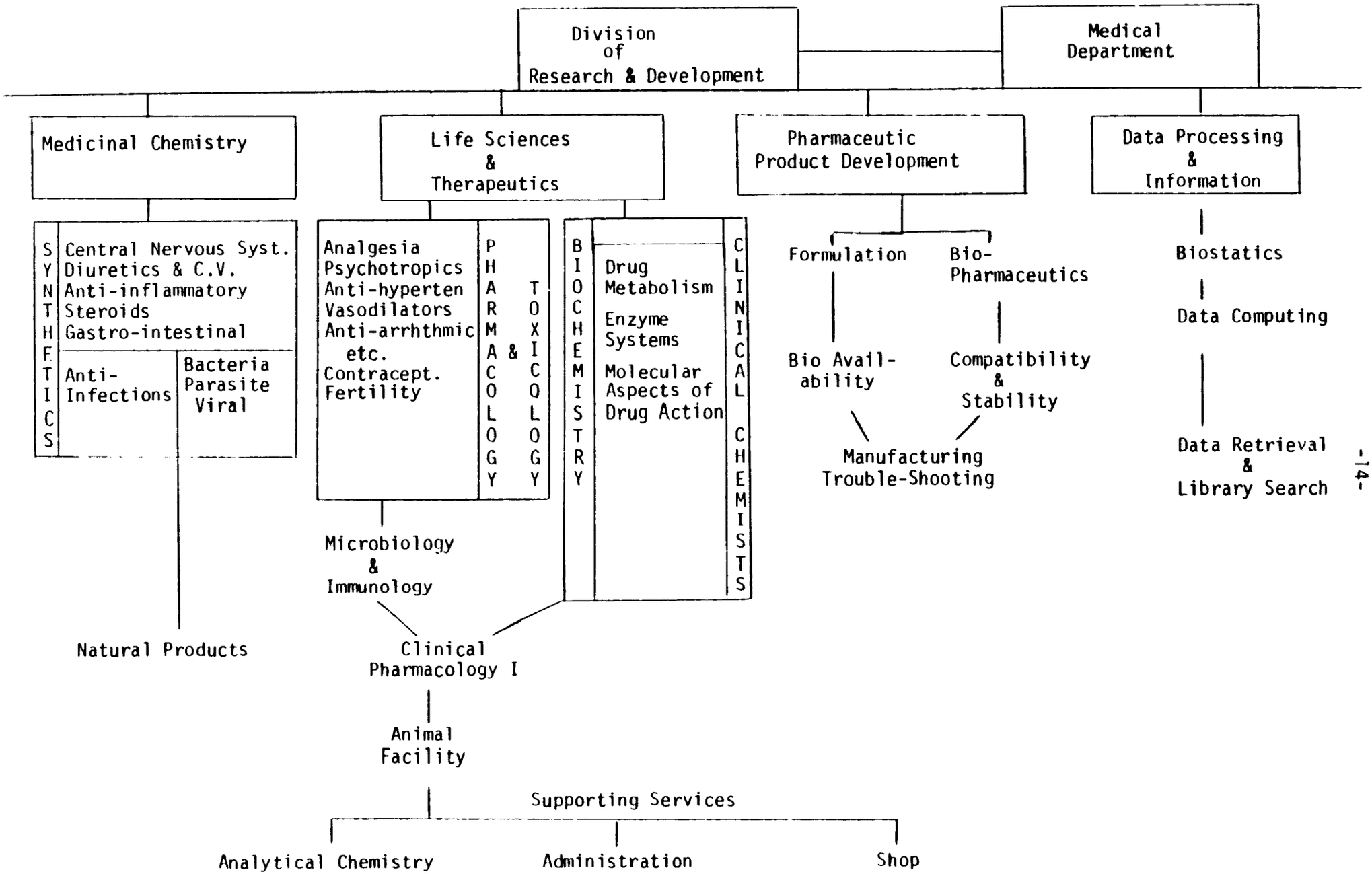
A. ORGANIZATIONAL STRUCTURE OF INSTITUTE DEPARTMENTS, SERVICES, AND ACTIVITIES.

IT IS RECOMMENDED that the organizational structure of the various departments and services be established as indicated in Fig. I. The scheme allows for optimizing the dialogue and interaction amongst scientists of the respective departments. It is envisioned that compounds synthesized and/or extracted by Medicinal Chemistry would be submitted to Pharmacology-Toxicology and Biochemistry for testing and study. Select active compounds would be submitted to Pharmaceutic Product Development for formulation, bioavailability, biopharmaceutic, and stability study, and then ultimately for initial clinical study organized by Clinical Pharmacology. All data would be processed into the computer banks for statistical computation, storage, and retrieval. Such a scheme should provide for immediate feed-back of information to the respective scientific groups and enhance the possibilities for the development of new drugs as described in APPENDIX.

B. DESIGN OF THE PHARMACOLOGY INSTITUTE BUILDING

IT IS RECOMMENDED that the Pharmacology Institute building be based on a single one-floor, multi-laboratory concept comprising 400 sq. meter of gross space. The design was formulated to facilitate the exchange of information among the scientists in the various therapeutic disciplines and allow for the cross-utilization of both personnel and equipment.

FIGURE I. Suggested organization of departments within Pharmacology Institute



As presented in Figure II the preliminary design consists of two distinct areas comprising the following laboratories and rooms:

1. Research Area (Appx. 200 sq. meter)
   a. Administrative office
   b. Library and Conference room
   c. Central Nervous System Laboratory
   d. Anti-Inflammatory Laboratory
   e. Cardiovascular-Renal Laboratory
   f. Biochemistry Laboratory
   g. Pharmacokinetics Laboratory
   h. Instrument room
   i. Cold room
   j. Glass washing room
   k. General storage room
   l. Staff locker room

2. Animal Facility Area (Appx. 200 sq. meter)
   a. Six animal rooms for housing of rodents, rabbits, and dogs.
   b. Animal quarantine room
   c. Administrative office
   d. Cage and bottle washing room
   e. Clean cage storage room
   f. Food and bedding storage room
   g. General storage room

An incinerator and outside dog run area also is provided for. Since medicinal chemistry synthesis now is carried out in a separate chemistry building, it is recommended that this activity not be included within the Pharmacology Institute building at this phase. Under conditions of the present one-floor plan design, the activities of medicinal chemical synthesis would be incompatible with proper animal experiments and care. It is also recommended at this phase that the Medical Department activities be carried out in the main administration building where appropriate administrative and computer support is available (see below).

C. PHARMACOLOGY INSTITUTE SITE

IT IS RECOMMENDED that the Institute building be constructed on the TEVA company site in Jerusalem. This recommendation is based on a detailed analysis of all potential sites visited and an initital budget cost estimate of 1.2 million Israel pounds for a pre-fabricated building and 1.64 million pounds for a conventional building (Annex III), with an estimated construction time of 5 and 12 months respectively. A sketch and location of the proposed site is provided in Figure III. This industrial

Figure II. Preliminary layout

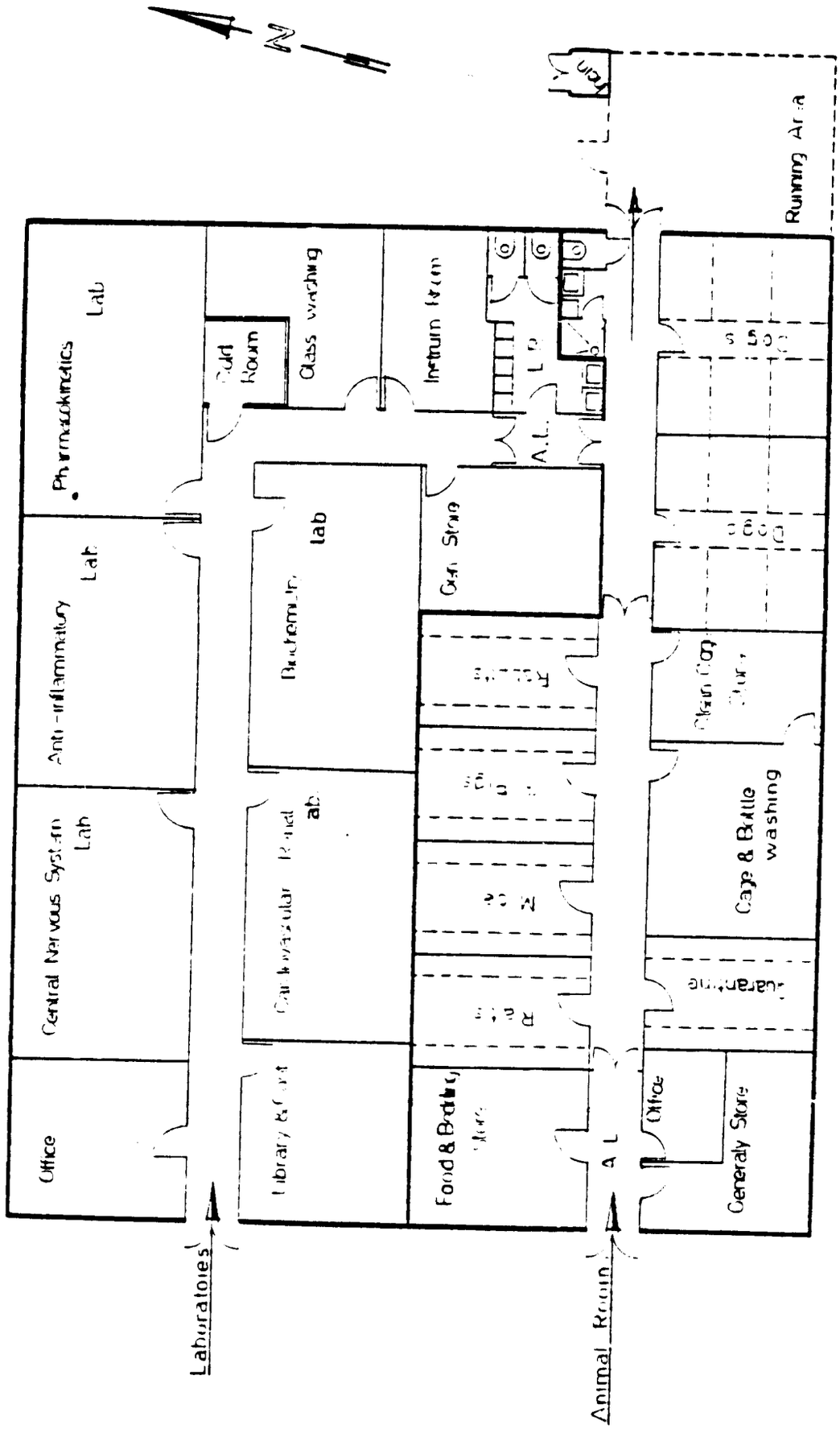
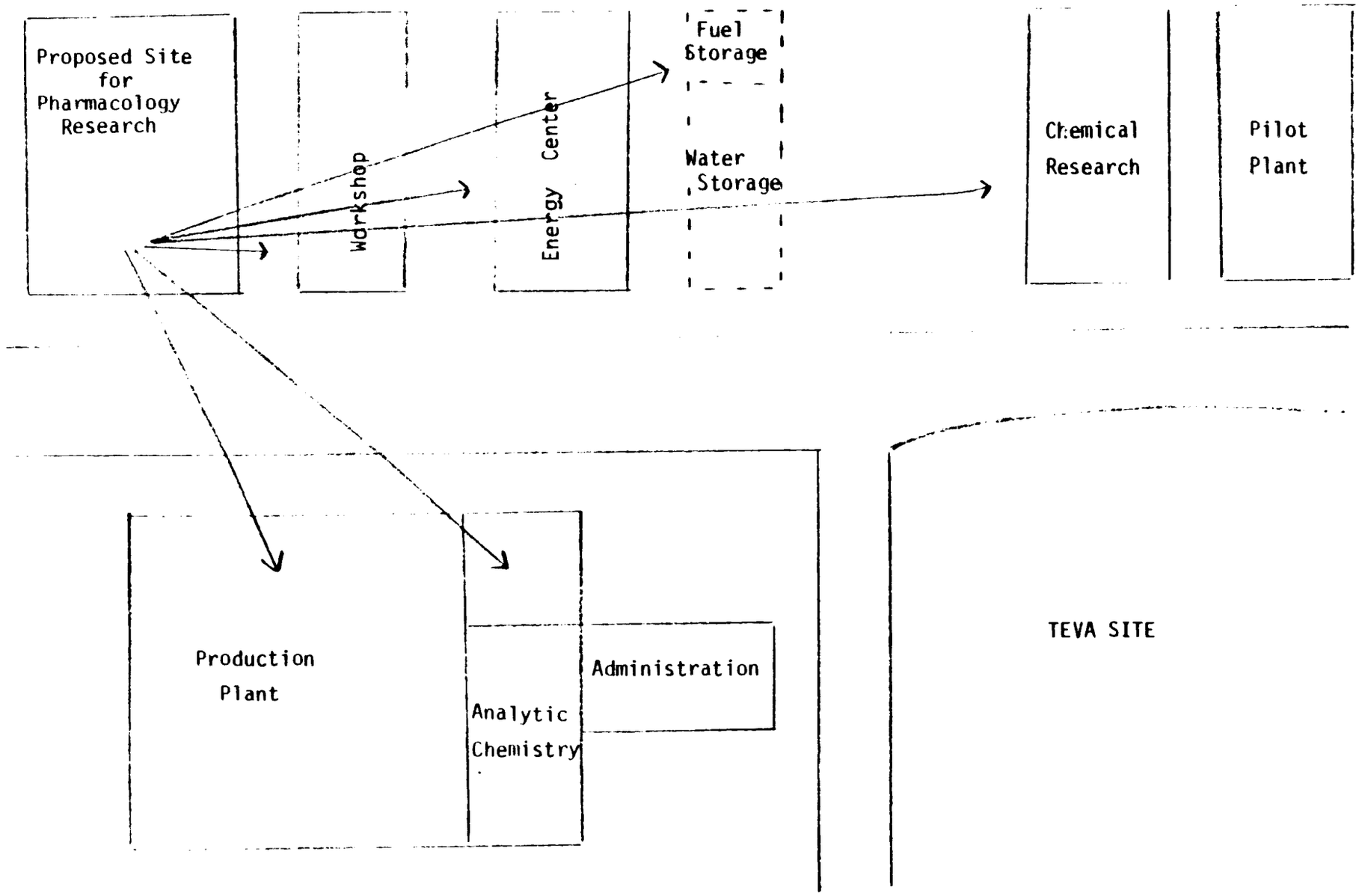


Figure III. Proposed site for pharmacology building



site:

1. provides for a closer integration of the chemical and biological research activities allowing for more immediate feedback of biological data to the chemist;
2. is located near the workshop, energy center, fuel-water storage and shipping areas;
3. is closely associated with the pharmaceutical production division;
4. is near the administrative offices of TEVA capable of providing a full range of support services as purchasing, accounting, computer, receiving, etc.

D. INSTITUTE DEPARTMENTS, STAFF, EQUIPMENT, AND ACTIVITIES

IT IS RECOMMENDED that the departments initially be staffed with the following personnel:

Central Nervous System Laboratory

1 Senior Pharmacologist
2 Research Assistants

Cardiovascular-Renal Laboratory

1 Senior Pharmacologist
2 Research Assistants

Anti-Inflammatory Laboratory

1 Senior Pharmacologist
2 Research Assistants
½ Pathologist

Pharmaceutical (Pharmacokinetics) Laboratory

1 Senior Pharmacokinetics Scientist
3 Research Assistants

Medical Department

1 Medical Director
1 Physician
2 Medical Information Personnel
1 Secretary

Biochemistry Laboratory

1 Senior Biochemist
2 Research Assistants

Animal Facility Rooms

1 Animal Caretaker
1 Laboratory Worker

Glass-Washing Room

1 Laboratory Worker

Library-Conference Room

1 Librarian

Scientific-Administrative Staff

1 Scientific Director
1 Deputy Director
1 Secretary
1 Typist

Thus, the total number of staff, excluding the medicinal chemistry department, analytical chemistry, and shop services, would comprise 29½ people; 9½ graduate-degreed scientists, 11 research assistants, and 9 technical assistants, secretaries, and library staff.

IT IS RECOMMENDED that the activities, floor area, and equipment for the respective laboratories and other facilities be as follows:

1. Central Nervous System Laboratory

Studies in this laboratory relate to screening of agents for general central nervous system activity, general behaviour, anti-anxiety (anxiolytic) activity, anti-psychotic activity, neuroleptic anti-depressant, and analgesic activities. Experimental animal model systems will allow for the evaluation of candidate compounds useful as analgesics, sedatives, anesthetics, anti-depressants, tranquilizers, hypnotics, and anti-psychotics.

Floor Area

Initially 25 sq. meter would be available. Within that area space would have to be provided for an isolation room in which to carry out specialized studies (initially one of the animal rooms may be used).

Equipment (Annex II)

(1) Hewlett Packard 8-channel Recorder
(4) Carrier Amplifiers
(1) Respirator Amplifier
(2) Pressure Transducers
(1) EEG Amplifier
(1) Oscilloscope
(1) Infusion Pump
(1) Respirator
(1) Electronic Stimulator
(1) Mettler Balance
(1) Refrigerator-Safety (11.8 cu. ft.)
(1) Freezer - Upright
(1) Analgesiometer
(4) Activity Cages
(2) Drug storage cabinets with locks
(2) Stimulator boxes
(2) Electroconvulsive Apparatus
Stereotactic equipment
Miscellaneous Psychopharmacology Equipment
Surgical Instruments

2. Cardiovascular-Renal Laboratory

This laboratory is designed to permit screening of compounds for anti-hypertensive, anti-arrhythmic, vasodilator, and diuretic activities. In vivo model systems will include the spontaneously hypertensive rat (SHR), and both surgically-induced and drug-induced hypertensive models. Diuretic activity will be studied in several animal species, and anti-arrhythmic screening carried out in isolated organ and in vivo systems.

Floor Area

An area of 25 sq. meters is assigned for this activity. No special space areas are required.

Equipment

(2) Hewlett Packard 4-channel Recorders
(10) Carrier Amplifiers
(2) ECG Amplifiers
(1) Respirator Amplifier
(6) Pressure Transducers
(1) Rate Computer
(1) Monitor Scope
(2) Pressure H-P units
(3) Bronwill Circulators
(1) Infusion Pump
(1) Respirator
(1) Syringe Pump
(2) Electric Counters
(2) Drop Selectors
(1) Electric Stimulator
(1) pH Meter
(1) Operating Table
(1) Mettler Balance
(24) Metabolism Cage units
(1) Refrigerator - Safety
(1) Freezer - Upright
(1) Power Supply
(1) Isolated organ perfusion equipment

3. Anti-Inflammatory Laboratory

Agents in this laboratory will be studied for anti-inflammatory/immunosuppressive activity. In vivo systems to be used will include the rat paw edema in normal and adrenalectomized animals, bradykinin antagonism in guinea pig lung overflow, adjuvant arthritis in the rat, ulcer formation in the rat and guinea pig, and experimental allergic encephalomyelitis. This laboratory will also carry out acute toxicity studies and histopathology and will have the capability of developing secondary screening models.

Floor Space

Twenty-five (25) sq. meter of floor space will provide ample area for this screening activity initially.

Equipment

(1) Hewlett Packard 4-channel Recorder
(4) Carrier Amplifiers
(1) Respirator Amplifier
(2) Pressure Transducers
(1) Cryostat Microtome
(1) Distillation Apparatus
(2) Kymographs, electrical
(1) Respirator (Harvard Rodent)
(1) Binocular Microscope
(1) Technicon Tissue Imbedder
(2) Microtomes
(1) Refrigerator - Safety (11.8 cu. ft.)
(1) Surgical Instrument Set

4. Pharmaceutical Research Laboratory

IT IS RECOMMENDED that a Pharmaceutical Research Unit be established to carry out Preformulation, Pilot Plant scale-up and Manufacturing trouble shooting, Biopharmaceutic and Pharmacokinetic, and Analytical studies. Preformulation studies will focus on the development of stable and effective drug delivery systems by optimizing the physical-chemical properties of the drug and their interactions with various excipients. Pilot plant scale-up studies will help establish reliable and precise manufacturing methods and uniform procedures for all pharmaceutical preparations. The factors influencing drug bioavailability and the kinetics of absorption, distribution, metabolism and excretion will be studied in the Pharmacokinetics laboratory, a special analytical laboratory suggested for assay of drugs in Biological fluids.

The above activities are envisioned as necessary within a Pharmaceutical Research Unit, and in the initial phase of development, some of these activities can be merged within one Pharmacokinetics laboratory with cross-utilization of space within the Instrument room, manufacturers plant, and Biochemistry laboratory. Ultimately all the above activities (apart from the pilot plant scale-up activity) should be concentrated in a Pharmaceutical Research Department with four units, each headed by a senior scientist as suggested previously.

Floor Space

An area of 25 sq. meter is recommended for this activity. While perhaps adequate in the very early stages of development, it is anticipated that additional space will have to be made available either within the existing Analytical Laboratory of TEVA (dealing presently with dosage-form oriented problems), and within the manufacturing plant where pilot plant scale-up studies can be expanded. The Biochemistry Laboratory also should be capable of accomodating some portion of the analytical drug assay studies.

Equipment

(1) Optical Microscope
(1) Coulter Counter
(2) Tissue Homogenizers
(1) Micronizer
(1) Electrical Blender
(1) Differential Thermal Analyzer
(1) Diffuison Reflectance Spectroscope
(1) Digital or Analog Computer (or hook-up)
(2) Infusion pumps
(1) Freezer - Upright
(1) Thin-layer Chromatograph
(1) Digital Flame Photometer
(1) Refrigerated Centrifuge (Beckman)
(1) pH Stat
(1) Mettler Balance
(1) Gas Chromatography System (Packard)
(1) Liqu d Scintillation Spectrometer (Tri-Carb)
(1) Fraction Collector (LKB)
(1) Solvent Evaporator
(2) Shakers

5. Biochemistry Laboratory

This laboratory is designed to carry out both applied research and supporting service activities of a biochemical nature toward a biochemical approach to the evaluation and prediction of drug action and toxicity essential to pharmacological evaluation. These approaches are diverse and sophisticated involving advanced biochemical and analytical chemical analysis techniques. As such, it will assist in the development of procedures for biochemical analysis of drugs and studies associated with bioavailability and pharmacokinetic problems. In addition, it will help establish enzyme technology processes for the preparation of specific drug products, develop in vitro methods for the study of drug action and interaction at the cellular and sub-cellular (molecular) levels, develop

methods for the fractionation, purification, and concentration of vaccines or pure antigens, help explore new product areas as diagnostic reagents and kits, and provide consultation to other scientists within R&D.

Floor Space

An area of 25 sq. meters is assigned for this activity. Some of the area may be occupied by the Pharmacokinetics Laboratory activity. A walk-in cold room is an imperative for this biochemistry activity.

Equipment

(1) Crushed-ice Machine
(4) Chromatography Cabinets & Jars
(1) Deep-Freeze Refrigerator (Upright)
(1) Refrigerator (Safety) 11.8 cu. ft.
(1) Mettler Balance - analytical
(1) Mettler Balance - top loading
(5) Magnetic Stirrers
(1) Calculator (Desk)
(2) Beam Balances
(2) Shaker Baths - Thermostatic
(4) Pipetors (Pipetman)
(3) Test-Tube Mixers (Vortex-Genie)
(1) Isolated Cell Culture Unit
(1) Lyophilizer (Freeze-Dryer Labcome)
(3) Hair-Type Dryers
(1) Fraction Collector & Accessories (LKB)
(1) Refrigerated High Speed Centrifuge
(1) Colorimeter (Beckman)
(1) Glass Blowing Apparatus
(1) U.V. Lamp
(1) Hydrolysis Oven
(1) Microhemotocrit Centrifuge
(1) Electrophoresis Apparatus

6. Animal Facility Rooms

The rooms in the animal facility area will provide for the housing and care of small (rodents, rabbits), and larger (cats, dogs, monkeys) animals for both acute and subacute studies, servicing all the departments within the R&D Division. Within this area shall be facilities for animal holding and quarantine, cage and bottle washing, surgery, storage of feed and cages, and special studies (isotopic) if needed. Animal room requirements are detailed in Appendix, and identify the heat given off per animal species (in BTU/hr/animal), air required (in CFM), recommended temperature, humidity, air changes, and air circulation for each animal species, as well as type of floor, wall,

drains and electrical specifications. The animal facility area will be separated from the scientific laboratory area by an appropriate air-lock system reducing the possibility for cross-contamination. Separate access to the facility from the outside will be possible.

Floor Space

An area of 165 sq. meter will constitute the animal facility space. This includes the office, washing and storage areas, quarantine, and animal holding rooms.

Equipment

(18) Dog Cage Units
(48) Rabbit Cage Units
(72) Rodent Cage Units
Food Container Units
Water Bottles
(2) Shadowgraph Animal Scales
(36) Cage Holders
(1) Bottle-Washer (VERNITRON)
(1) Autoclave (AMSCO)
(1) Cage Washer (Live steam)
(6) Animal Tables
(4) Animal Carts
(1) Incinerator
(4) Over-head Surgical Lamps
(2) Hair Clippers
(4) Food Bins
(1) Food Mixer
(2) Foot-Pedal Sink Units
(1) Dry-Ice Chest

7. Glass-Washing Room

This room will serve the laboratories, providing clean glassware for all activities. Utilities will be available for washing, drying, and sterilization of glassware, instruments, and other supplies as needed.

Floor Space

Six (6) sq. meter will be sufficient to accomodate this activity.

Equipment

(1) Pipette Washer
(1) Setrilizer
(1) Drying Oven (large)
(1) Distilled Water Still

8. Conference-Library Room

A vital factor in a reasearch institute, this library facility will be provided with a limited range of scientific journals, references, and texts to be used by the entire staff. The room also can be used for

periodic staff meetings, scientific seminars, and conferences, training courses, and contemplation. Abstracting and information retrieval services should be available.

Floor Space

An area of 16 sq. meter has been set aside for this facility.

Equipment

(1) Overhead Projector
(1) 35-mm Projector
(1) Screen
(1) Indexing Filing Unit
(1) Book Cart
(X) Filing Cabinets

9. Offices

A central Director-Secretarial office and reception area will be available near the entrance to the laboratory side of the Institute. This area also will be close to the library-conference room so that visitors may have access to the facility. Another office will be situated in the animal facility area to service that activity.

Floor Space

A total of approximately 15 sq. meter has been designed for this administrative activity.

Equipment

(2) IBM Electric Typewriters
(1) Photocopy Machine
(12) File CAbinets

All the scientific laboratories should be available with hot and cold water, distilled water, compressed air, natural gas, vacuum, and proper individual temperature-humidity control. The appropriate laboratories should be designed to conform as closely to the regulations outlined in the recently published Good Laboratory Practices (GLP) Code and Good Manufacturing Practices (GMP). The laboratories, thus, should have the appropriate laboratory benches, cabinets, sinks, emergency facilities, exhaust hoods and other requirements as indicated. All data, experimental and clinical, should be recorded and programmed so as to allow for easy, accurate and rapid retrieval in conformity with the required GLP monitoring procedures.

IT SHOULD BE EMPHASIZED THAT THE EXPERIMENTAL LABORATORIES ARE DESIGNED SO THAT THEY MAY BE USED FLEXIBLY AND INTERCHANGEABLY REGARDLESS OF SUGGESTED THERAPEUTIC AREA DESIGNATION.

E. THE MEDICAL DEPARTMENT

IT IS RECOMMENDED that a Medical Department be established within the R&D Division comprised of the following four major units:

1. MEDICAL RESEARCH
2. MEDICAL INFORMATION
3. COMPUTER INFORMATION SCIENCE
4. HEALTH REGISTRATION

The Medical Department will serve the R&D Division as well as provide consultative service to the Pharmaceutical Production Division and all other branches of the corporation as needed. The primary activities and responsibilities of each unit shall be as follows:

1. MEDICAL RESEARCH UNIT

The Medical Research unit has the responsibility to assess the adequacy of pre-clinical information (pharmacological-toxicological animal study data), and to design, organize, carry out, and monitor investigational clinical pharmacological studies of new drugs in the human so as to determine their efficacy, safety, tolerance limits, and pharmacodynamic effects. A physician trained in the art of Clinical Pharmacology would be required to carry out this responsibility.

In the design of the Phase I clinical pharmacology protocol, the physician should be guided by the FDA recommendations regarding proposed duration of a new drug's use in the human based on the length of animal toxicity studies, Table 1. Generally, these recommendations are applicable to most, but not all, new drugs (as for example, oral contraceptives). These clinical research studies are to be carried out in continuing phases as described in the consultants' report previously submitted. Clinical investigators conducting the study in hospitals should receive an "Investigator's Brochure", prepared by the Medical Research Unit, that summarizes all that is known about the new drug's safety and possible therapeutic usefulness. The brochure also should inform regarding any possible hazards, precautions, contraindications, or adverse reactions.

2. MEDICAL INFORMATION UNIT

The Medical Information unit engages in review of the national and international literature in drug research and therapy, provide summaries of current and pertinent literature dealing with recent drug and drug research-related discoveries, carry out on-going collection of

TABLE 1. ANIMAL TOXICITY STUDIES OF NEW DRUG IN RELATION TO PROPOSED DURATION OF HUMAN USE+

CATEGORY OF NEW DRUG	DURATION OF HUMAN USE	CLINICAL STUDY PHASE	SUBACUTE OR CHRONIC TOXICITY*
ORAL OR PARENTERAL	Several days	1, 2, 3, NDA	2 species, 2 weeks
	Up to 2 weeks	1	2 species, 2 weeks
		2	2 species, up to 4 weeks
		3, NDA	2 species, up to 3 months
	Up to 3 months	1, 2	2 species, 4 weeks
		3	2 species, 3 months
		NDA	2 species, up to 6 months
	6 months to Unlimited	1, 2	2 species, 3 months
		3	2 species, 6 months or longer
		NDA	Non-rodent, 12 months Rodent, 18 months
DERMAL	Single Application	1	1 species, single 24-hour exposure and 2-week observation
	Short-term use	2, 3	1 species, 20-day dermal toxicity (intact and abraded skin)
	Unlimited	3, NDA	As above, but intact skin study extended up to 6 months
OPHTHALMIC	Multiple Applications	1, 2, 3	1 species, daily applications as in clinical use, 3 weeks
		NDA	1 species, duration commensurate with clinical use
VAGINAL OR RECTAL	Multiple Applications	1, 2, 3, NDA	2 species, duration commensurate with clinical use
DRUG COMBINATIONS**		2, 3, NDA	LD_{50} by appropriate route, compared to components in 1 species 2 species, up to 3 months

+Adapted from Goldenthal, E.I.: Current Views on Safety Evaluation of Drugs. FDA papers, May, 1968.

*Acute toxicity should be determined in 3 species.

**Where toxicity data are available on each component.

TABLE 2. CLINICAL DOCUMENT FLOW THROUGH CENTRAL FILES

I. Documents Received and Stamped	II. Documents Indexed and Logged	III. DOcuments Copied	IV. Documents Microfilmed	V. Documents Filled
Time Span: Same Day	Time Span: 1-2 Days	Time Span: 1-3 Days	Time Span: 1-4 Days	Time Span: 1-4 Days

IIIa. A copy of indexing goes to keypunch and the master file for the automated retrieval system is updated.

Time Span: 1-3 Days

On the time span estimates, the shortest time listed pertains to rush projects, the longest time to normal documents in process.

critical references on research projects both current and projected, collect and store data and documentation on clinical trials, and maintain an up-to-date library service in clinical therapeutics. These activities would be centralized within an appropriate library facility designed to provide informational feed-back service on a continuing and request basis. In this fashion a monitoring of what others are doing in the field would be provided as well as a search and information retrieval system established to support the R&D program. This unit also disseminates approved information outside the company through brochures, detailman, etc.

It is recommended that this Information Unit be divided into the following sub-units:

a. Library to contain all appropriate textbooks, current journals, periodicals and other references.

b. Clinical documentation whose responsibility will be to store all clinical data and documents. Retrieval systems provide direct answers to questions, special computer readouts, document copies, and summary information. Microfilming of all data insures maximum security of the data base and reduces stored original documents to more convenient space. The clinical document flow through central file is represented in Table 2.

c. Professional Services and Medical Education activities directed toward providing professional training and/or continuing education to such audiences as pharmacists (community and hospital), sales and marketing representatives, and practicing physicians.

3. COMPUTER INFORMATION SCIENCES UNIT

The responsibilities of this unit center on the processing, analysis, storage, and retrieval of all clinical data generated by the clinical research activity. Included in this unit is a biostatistical service designed to evaluate and establish the necessary clinical protocol that would satisfy statistical criteria of studies (of a clinical or pharmaceutics nature) and provide for the statistical evaluation of all data. This unit prepares the proper case report forms and case report statistical analyses, and helps determine the clinical protocol to ensure proper conduct of the study. The data would be banked in the computer to allow for immediate retrieval for analysis, review, and preparation of all reports to investigator, management, and regulatory agencies.

4. HEALTH REGISTRATION UNIT

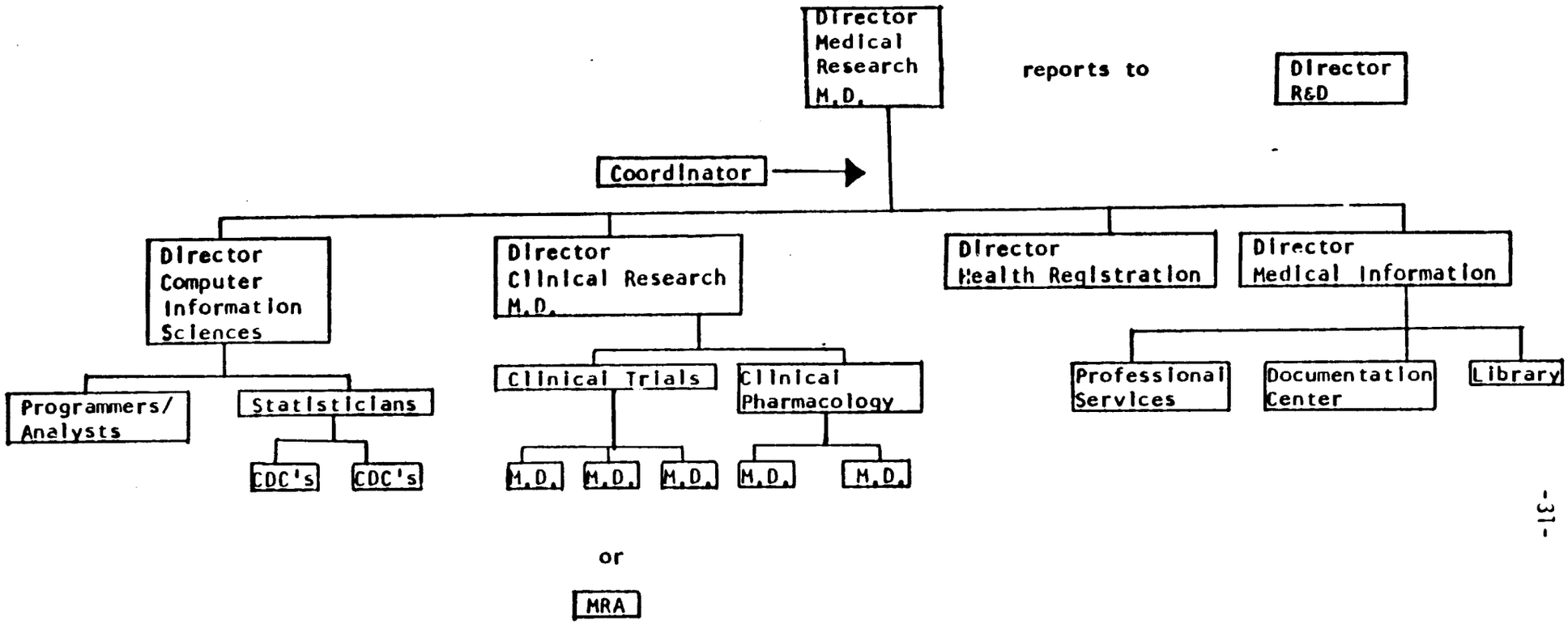
Activities in this unit are concerned primarily with helping to fulfill requirements for the drug regulatory agencies. As such, this unit is conversant with and aware of all guidelines and regulations dealing with drug manufacturing, testing, registration, re-registration and marketing. Major problems of toxicology and clinical studies are understood and solved in compliance with regulations. This unit acts as a liaison between the industry and the drug regulatory agencies (Ministry of Health, FDA, etc.). Thus, this unit prepares the required regulatory applications for the marketing, registration and re=registration of drugs, and makes any necessary presentations or defense of these applications before the appropriate regulatory agency. In addition, this unit helps safeguard against any abuses of regulations that may occur unintentionally on the part of investigators, and also provides interpretation of the regulations to management and R&D. The director of this unit should be an M.D. or a Ph.D. with medical science background.

The optimal organizational structure for the various units of the Medical Department is represented in Figure IV.The number of physicians and Medical Research Associates (MRA) for this Department depends on the number of active research projects operative. Since the present clinical research activities at TEVA is very limited, IT IS RECOMMENDED that the Department have a Director who would assume responsibility for the Clinical Research and Health Registration Units; two staff members for the Medical Information Unit; and one staff person for the Library and Documentation Center Units.

F. RESEARCH DIRECTION

At present, TEVA's research programme is in six major therapeutic areas. The majority of these areas are represented in the laboratories recommended. There is need for the scientific management to define more precisely and carefully the overall objectives of its chemical-biological research activity, both "in-house" and "extra-mural", and to reduce its scope of activity to fewer therapeutic areas. It has been recommended that TEVA's R&D programme concentrate on one major therapeutic area (as cardiovascular), and to develop "in-depth" a screening capability in that area. This would necessitate the development of both primary and

FIGURE IV. **ORGANIZATIONAL STRUCTURE OF THE MEDICAL RESEARCH DEPARTMENT**



secondary screening techniques, and the adoption of the philosophy to carry the development up to and into the clinic. The scientific capability to do this is available, and the limited scientific resources would support this approach.

Thus, relative to the direction of research efforts, IT IS RECOMMENDED that TEVA:

1. adopt a single therapeutic area and develop the research capability to study candidate compounds at the primary and secondary screening level, and into Phase I and Phase II clinical pharmacology.

2. develop an overall general screen for all newly synthesized compounds so as to identify any type of biological activity (autonomic, CNS, anti-inflammation, anti-microbial, anti-parasitic).

3. select an area of more basic research in tandem with one of the applied areas for development (enzymology, molecular biology, hormone, aging, biologically-active peptides).

4. develop a relationship with an international testing facility to study the biologic activity of presently available compounds. Pharmacologic information on these compounds would help in the selection of the most promising therapeutic area to develop, coupled with the world-market surveys and analysis. This relationship also would provide an on-going consultative and collaborative association.

5. establish a secure and meaningful bridge between TEVA and the University. TEVA is located on the Science-Based Industries campus of the Hebrew University, and thus should seek to strengthen Industry-University ties so as to fulfill objectives set by such an industrial park relationship. This should include continuing collaborative research programmes, training of both students and faculty in applied research, and intensifying cross-utilization of ideas, facilities, and personnel, inter alia.

Since it is envisioned that the various research areas in the Institute would develop during several time phases, the above recommendations would allow for such sequential developments, and also would provide the time required for study and evaluation of those areas on which to embark. Research direction also will depend upon the availability of senior personnel expert in those respective areas.

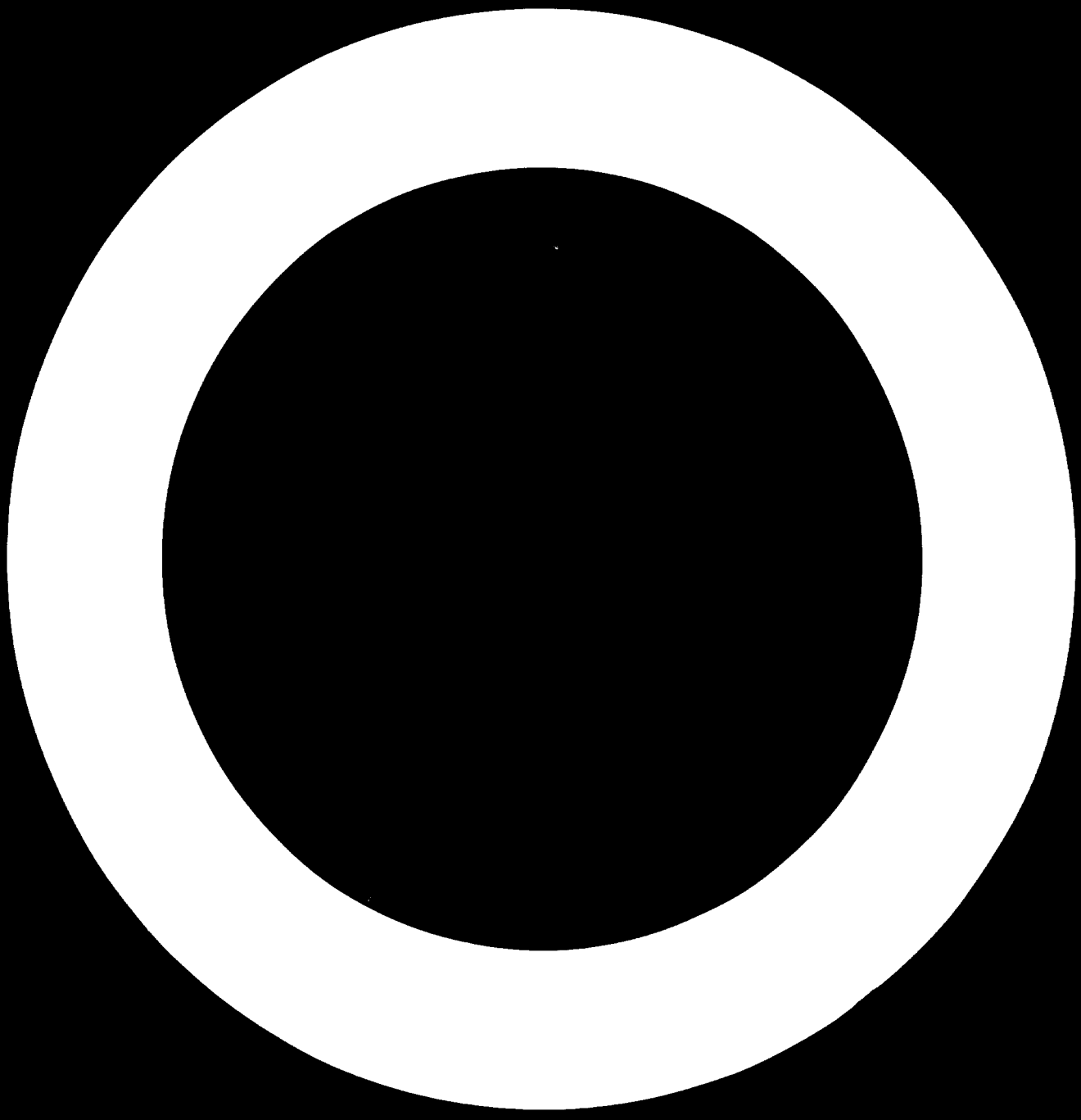
G. EXPERIMENTAL PROTOCOLS

Since experimental protocols for carrying out specific screening programmes often are based on the personal bias and experience of the Director of Pharmacology and the investigators, no attempt was made to develop a comprehensive set of protocols for each of the areas recommended. Rather, a set of protocol types has been provided from the international testing facilities visited. These protocols have been made available to TEVA. Such protocols are in the public domain, and often are based on previously published procedures.

Protocols were provided for the following experimental pharmacological-toxicological screening techniques:

1. Neuropharmacological profile
2. Analgesia, anesthesia
3. Anti-depression, anti-psychotic
4. Antihypertension, cardiovascular
5. Anti-inflammation
6. Anti-anaphylaxis
7. Acute and long-term diuresis
8. Anti-microbial, anti-fungal, anti-viral
9. Anti-parasitic, anti-protozoal
10. Anti-cancer
11. Acute toxicity

IT IS RECOMMENDED that the Director of the R&D Division undertake the development of an "in-house training programme for staff involved in pharmacological screening studies. The skills and experience of pharmacologists at respective departments within the countrys' Universitites should be mobilized for this training. In addition, select personnel should be sent for training to pharmaceutical companies and testing agencies abroad. In this fashion, screening procedures will remain current and relevant.



Annex I

JOB DESCRIPTION

The following job description for the pharmacologist expert was drafted by UNIDO, and the post title identified as the Pharmacology Institute Advisor. The duration of the assignment was for 7 months, duty station Jerusalem, Israel, and the duties listed as follows in cooperation with ASSIA-TEVA, The National Council for Research & Development, and UNIDO. The duration of the assignment was extended subsequently to 11 months.

1. Study the chemical and pharmaceutical agents produced by ASSIA-TEVA and evaluate present "in-house" drug research programmes and activities.
2. Review and evaluate all "extra-mural" biological screening, metabolic, toxicologic, and clinical testing programmes supported by ASSIA-TEVA.
3. Develop an overall prospectus for the Research & Development activites as well as the directions and goals for the coordinated departmental research.
4. Review and discuss with the Ministry of Health current scientific and legal requirements regulating pre-clinical and clinical new drug development, and review with the Ministry of Commerce and Industry overall aims and goals relative to new drug development.
5. Develop an appropriate recruitment programme for staffing the scientific departments and supporting services within the R&D Division, and provide an overall organizational plan for administering and executing the proposed programmes of the Institute.
6. Evaluate existing facilities, equipment, and services in those departments currently carrying out drug research and development, and plan and design or renovate laboratory and animal facilities for the R&D Divisional programmes.
7. Inventory existing equipment, and prepare a detailed list of required capital equipment with specifications, suppliers, and cost estimates.
8. Determine needs for experimental animals, survey the quantity and quality of animals available in the country, and draft recommendations to provide a continuing supply of animals.
9. Contact, or visit if necessary, select major pharmaceutical companies, drug regulatory agencies, and testing companies in Europe and the United States to gain information on changing pharmacological-toxicological requirements and protocols, and to establish possible future relationships.

Annnex II

CAPITAL EQUIPMENT

1. First priority equipment

		$
(4)	Hewlett Packard 4-channel Recorders @$8,000 ..	32,000
(2)	Hewlett Packard 8-channel Recording System @$10,000 -	20,000
(20)	Carrier Amplifiers @ $700 (H-P)	14,000
(8)	ECG Amplifiers @ $800 (H-P)	6,400
(2)	Respirator Amplifiers @ $1,300 (H-P)	2,600
(12)	Pressure Transducers @ $600 (H-P)	7,200
(1)	Numerical display (options 01,011,014,015)	2,200
(1)	Rate computer	900
(1)	4-channel portable instrumentation recorder ..	6,000
(1)	Monitor scope (2-channel)	1,000
(1)	Oscilloscope (4-channel)	2,000
(2)	Pressure (presson) units @ $600 (H-P)	1,200
(1)	Cryostal microtome	3,500
(1)	Distillation apparatus	1,500
(6)	Kymograph electrical@ $150	900
(1)	Spectrofluoremeter (Turner)	5,000
(1)	Digital Flame photometer	9,000
(1)	Serum protein meter (B&L)	300
(4)	Circulators, Bronwill @ $300	1,200
(1)	Conductivity meter CDM3	1,000
(2)	Infusion pump (Harvard #975 @ $1000	2,000
(1)	Syringe pump (Harvard) I.V. #2684	500
(2)	Lambda pump (Harvard #1302) @ $500	1,000
(2)	Respirator (Harvard Rodent #618) @ $600	1,200
(2)	Respirator (Harvard Dog #613) @ $1000	2,000
(2)	Electric counter (Harvard #390) @ $400	800
(1)	Colorimeter	600
(2)	Drop selector (Harvard #364) @ $250	500
(6)	Animal tanks @ $275	1,650
(5)	Animal carts @ $200	1,000
(3)	Electronic stimulator @ $250	750
(1)	Gel column electrophoresis & accessories	3,000
(1)	Recording densitometer	4,000
(1)	Microhematocrit Centrifuge (#IEC-MB)	300
(1)	Freeze Drying Apparatus (Labcome)	1,500
(2)	Refrigerated centrifuge (Beckman) @ $8000	16,000

		$
(3)	Drying ovens (SP) @ $150	450
(1)	Oven (precision)	1,000
(1)	Incubator	1,350
(1)	pH meter	500
(1)	pH stat (Touminem)	6,500
(2)	Binocular microscope (AG) @ $1600	3,200
(1)	Blood gas analyzer	4,000
(2)	Operating table @ $700	1,400
(1)	Tissue homogenizer (Ultrasonic-Biosonic III)	1,000
(3)	Mettler Balance (H20T) @ $1000	3,000
(24)	Metabolism units (Econo) @ $50	1,200
(2)	Top-loading Animal Balance (Mettler) @ $600	1,200
(1)	Torsion Balance (PL-2)	500
(1)	Gas chromatography system (Packard #8077)	10,000
(1)	Analytical Package Flame Ionization Detector	1,500
(1)	Electron capture Detector (#714-04)	2,000
(1)	Single Pen Recorder	1,200
(1)	Gas Proportional counter	4,500
(4)	Gas Regulators @ $100	400
	Gas Line Filters	156
	Glass columns	310
(1)	Minigrator with printer	3,500
(2)	Thermostat shaker baths @ $250	500
(1)	Glass blowing apparatus	300
(1)	Spectrophotometer (Varian)	12,000
(1)	Liquid Scintillation Spectrometer(Tri-Carb)	20,000
(1)	Automatic Channel Selector #3090	700
	Animal cages & racks	6,000
(1)	Electronic Desk Calculator	5,000
(1)	Desk computer (WANG)	7,500
(1)	Fraction Collector (LKB 7000)	10,000
(1)	Flat bed recorder (2 channel LKB)	2,500
(1)	Absorptiometer (Uricord)	3,500
(2)	Shaker Bath Incubators @ $800	1,600
(2)	Refrigerators-Safety (6.3 cu.ft.) @ $500	1,000
(2)	Refrigerators-Safety (11.8 cu. ft.) @ $600	1,200
(2)	Freezer (Upright) @ $1,000	2,000
(1)	Power supply (1000V, 100mA)	400
(2)	Thermostats (circulating) @ $500	1,000

		$
(1)	Analgesiometer	2,500
(4)	Activity cages @ $1,000	4,000
(1)	Pipette cleaner Siphon (Harvey)	1,500
(1)	Jiggle Platform (BRS/LVE)	1,000
(2)	Autoclave (Fisher)	1,200
(1)	Drug storage cabinet	250
	Chromatography cabinets & jars	1,400
(2)	Evaporators (1-Evapomix; 1-Rotary)	1,150
(50	Magnetic stirrers @ $150	750
(2)	Beam balances @ $150	300
(3)	Vortex test-tube mixers @ $100	300
(4)	Hair Dryers @ $100	400
(1)	U.V. Lamp	100
(2)	Stimulator boxes @ $1200	2,400
	Miscellaneous psychopharmacology equipment	8,000
(1)	Electroconvulsive apparatus..	500
	Subtotal	301,841.
	Cages, bottles (if needed)	10,000
	Cage Racks (if needed)	5,000
	Cage Washing Apparatus (if needed)	20,000
	Grand Total	336,841.

2. Minimum Equipment Required for Pharmacology Laboratory Facility

The following constitutes the minimum equipment required for the on-site pharmacology laboratory facility. Prices estimated may change depending on the unit purchased and what is available in the country.

		$
(1)	Hewlett-Packard 4-channel Recorder	8,500
(1)	Hewlett-Packard 8-channel Recorder	10,500
(10)	Carrier Amplifiers (Hewlett-Packard)	9,000
(4)	ECG Amplifiers (Hewlett-Packard)	4,000
(2)	Respirator Amplifiers (Hewlett-Packard)	2,600
(5)	Pressure transducers (Hewlett-Packard)	3,000
(1)	Oscilloscope (4-channel)	2,000
(1)	Cryostat microtome	3,500
(3)	Kymographs, electrical	400
(1)	Serum protein meter (B & L)	300
(3)	Circulators, Bronwill	900
(1)	Infusion pump (Harvard)	1,000
(1)	Syringe pump, I.V. (Harvard)	500
(1)	Lambda pump (Harvard)	500
(1)	Respirator,Rodent (Harvard)	600
(1)	Respirator, Dog (Harvard)	1,000
(1)	Colorimeter	600
(1)	Drop selector (Harvard)	250
(2)	Animal tables	600
(1)	Electronic stimulator	250
(1)	Microhematocrit centrifuge (IEC-MB)	300
(1)	Freeze drying apparatus (Labcomo)	1,500

		$
(1)	Refrigerated centrifuge (Beckman)	8,000
(2)	Drying ovens (SP)	300
(1)	Oven (precision)	1,000
(1)	Incubator	1,000
(1)	pH meter	500
(1)	Binocular microscope (A-0)	1,600
(1)	Tissue homogenizer (VHrasonic-Biosonic)	1,000
(2)	Mettler Balances (H Z 0 T)	2,000
(12)	Metabolism units	600
(2)	Top-loading Animal balances (Mettler)	1,200
(1)	Torsion balance (PL-Z)	500
	Animal cages and racks	10,000
(2)	Refrigerators	1,000
(1)	Freezer (upright)	1,000
(1)	Analgesiometer	1,500
(2)	Activity cages	2,000
(1)	Jiggle platform	750
(1)	Drug storage cabinet	250
(2)	Beam balances	300
(1)	Stimulator boxes	600
(1)	Electroconvulsive apparatus	500
(1)	Cage washing unit	20,000
	Drinking bottles	600
	Miscellaneous equipment and instruments (surgical instruments, stimulators, etc.)	3,000
	TOTAL	$ 103,400

The above list does not include equipment or instruments for the Biochemistry or Pharmacokinetics laboratories.

The list of equipment can be contracted in accordance with the types of laboratories established, the range of studies decided upon, and the number of annual screening studies projected.

Annex III

ESTIMATED CAPITAL INVESTMENTS

The projected capital investment for the proposed Pharmacology Institute is based on costs as of June, 1977. Estimates would have to be adjusted for increases in costs due to cost-of-living increases, inflation, and currency devaluation. Because of these rapidly changing fiscal situations, no attempt was made to project costs for scientific, technical, and administrative staff.

Institue Building (400 sq. meter, conventional)		$200,000
Capital Equipment, complete list		336,850
	Total	$536,850

Capital investment costs would be reduced if only the minimum capital equipment were purchased initially:

Building cost		$200,000
Equipment, minimum list		103,400
	Total	$303,400

The first years' costs for expendable items would include:

Consumable supplies		$20,000
Animals and maintenance		15,000
	Total	$35,000

Annex IV

PRELIMINARY SPECIFICATIONS FOR ANIMAL ROOMS

1. Animal Room Requirements

a. Heat given off and air required

Animal	Wt (gms)	Heat given off (BTU/hr/aminal)	Air Required (CFM)
MOUSE	21 - 22	0.6	0.10
RAT	200	3.6	0.75
RAT	250	4.3	0.90
GUINEA PIG	350	5.6	1.5
GUINEA PIG	410	5.7	1.5

(Figures are average for active and quiet periods)

b. Recommended temperature

Mice	$74^{o}F \pm 4^{o}$
Rats	$72^{o}F \pm 4^{o}$
Guinea Pigs	$70^{o}F \pm 4^{o}$

c. Recommended Humidity

50% ± 5%

d. Air Changes

14 - 18 per hour

e. Circulation

Bring air in wall near ceiling;
Exhaust air in wall at floor.

f. Animal rooms preferably should have pitched floor, central floor drains, coved based, and properly surfaced floors and walls.

2. Electrical specifications

a. Fixtures

Fluorescent fixtures in labs and offices. Vaportight fluorescent fixtures in all animal rooms.

b. Emergency power

An appropriate auxiliary generator to take over critical loads in case of power failure, including automatic transfer switch.

c. Convenience Outlets

Vaporproof convenience outlets provided in all animal rooms.

Annex V

CANDIDATES INTERVIEWED* FOR POSSIBLE
POSITIONS IN R&D DIVISION

NAME	DEGREE	LOCATION	RESPONSE/ACTION
		BIOCHEMISTRY	
Aboud, M.	Ph.D.	Bat Yam, Israel	Interested
Baran, A.	Ph.D.	Tufts Med. Sch. Boston, Mass.	Not suitable
Barzilay, I.	Ph.D.	MIT, Brookline, Mass.	Awaiting Action
Batzri, S.	Ph.D.	NIH, Rockville, Maryland	No response
Bogin, E.	Ph.D.	Kimron Vet. Sch., Israel	Awaiting action
Daskal, J.	Ph.D.	Baylor Texas Med. Center,Houston	No response
Eldan, M.	M.Sc.	Durham, North Carolina	Interested
Erlich, B.	B.Sc.	Israel	Not suitable
Fleischer, Y.	M.Sc.	Israel	Not Suitable
Gafni, Y.	M.Sc.	Israel	Not suitable
Heldman, E.	Ph.D.	Woods Hole, Mass.	Interested
Horn, H.	Ph.D.	Hebrew Univ. Jerusalem, Israel	Not suitable
Ish-Shalom, D.	M.Sc.	Israel	Not suitable
Jonas, Z.	Ph.D.	Univ. of Copenhagen	No action
Kidroni, G.	Ph.D.	Harvard, Boston, Mass.	HIRED
Ladany, S.	Ph.D.	Columbia Univ., New York	No action
Melamud, E.	Ph.D.	Fox Chase Cancer Inst. Penn.	Interested
Mizraci, L.	-	Israel	Not suitable
Nachum, S.	M.Sc.	Bar-Ilan Univ. Tel Aviv, Israel	Interested
Nowacki, A.	B.Sc.	Cote St. Lue, Canada	Awaiting action
Pour-El, A.	Ph.D.	ADM Co., Decatur, Illinois	Not suitable
Sacher, R.	Ph.D.	Monsanto Co. St. Louis, Mo.	Not interested
Sevilia, N.	M.Sc.	Hebrew Univ. Jerusalem, Israel	Suitable
Sharoni, Y.	Ph.D.	Hebrew Univ. Jerusalem, Israel	Not presently interest
Rumney, G.	Ph.D.	Rambam Hosp., Haifa, Israel	Not suitable
Weinberg, R.	M.Sc.	Hebrew Univ., Jerusalem, Israel	Not suitable
Zeiger, A.	Ph.D.	Jefferson Med. College, Penn.	Not suitable
Zinder, O.	Ph.D.	NIH, Rockville, Maryland	Awaiting action
		BIOLOGY	
Altstock, N.	Ph.D.	Univ. New Mexico, Albequerke	No response
Balshin, M.	Ph.D.	Research Inst. Toronto, Canada	Awaiting Action
Baran, A.	Ph.D.	Univ. of Haifa, Haifa, Israel	Interested in future
Baran, Zvi	Ph.D.	Univ. of Haifa, Haifa, Israel	Not suitable
Belinski, R.	B.Sc.	Micro. Biol. Assoc. Rockville, MD.	Awaiting action
Eltan, Z.	B.Sc.	Israel	Not suitable
Feldman, M.	Ph.D.	Hebrew Univ. Jerusalem, Israel	Not suitable
Glazer, E.	B.Sc.	USA	Interested
Kidron, M.	Ph.D.	Hebrew Univ. Jerusalem, Israel	Not interested
Kook, A.	Ph.D.	Weizmann Inst. Rechovoth, Israel	Not suitable
Lerman, M.	B.Sc.	Venice Family Planning, Calif.	Awaiting action
Paster, Z.	Ph.D.	Tel Aviv, Israel	Not suitable
Ron, R.	M.Sc.	Jerusalem, Israel	Interested
Yanai, J.	Ph.D.	Purdue Univ., Lafayette, Ind.	Interested

CLINICAL MEDICINE

Mannor, S.	Ph.D/M.D.	Temple Univ. Penn.	Awaiting action
Morag, A.	M.D.	SUNY/Buffalo, N.Y.	Awaiting action
Zehavi, U.	Ph.D.	Weizmann Inst. Jerusalem, Israel	No action

ENGINEERING

Averbach, T.	Ph.D.	Cambridge, Mass.	Awaiting action
Binembaum, Z.	Ph.D.	Hoffman LaRoche, Nutley, N.J.	No response
Borik, S.	Ph.D.	Baylor Coll. Med. Houston, Texas	Awaiting action
Damenstein, A.	M.Sc.	Western Univ. Evanston, Ill.	Awaiting action
Geller, E.	Ph.D.	Wyeth, Inc., Phila. Penn.	Awaiting reply
Levit, S.	Ph.D.	Med. Coll. Chap.Hill, So. Car.	Not suitable
May, D.	Ph.D.	Univ. Wisconsin, Madison, Wisc.	Not suitable
Perlmutter, A.	M.Sc.	Chicago, Illinois	Awaiting action

MICROBIOLOGY

Asculai, S.	Ph.D.	Monsanto Co. St. Louis, Mo.	Interested
Barak, Z.	Ph.D.	Princeton Univ. Princeton, N.J.	Not suitable
Belinski, R.	B.Sc.	Microb. Assc. Washington, D.C.	No response
Blackman, U.	Ph.D.	Univ. Calif. Duram, Calif.	No response
Boros, D.	Ph.D.	Case Western Res. Durham, So.Car.	Not suitable
Chevicn, M.	Ph.D.	Jerusalem, Israel	Interested
Dafni, Z.	Ph.D.	NIH, Bethesda, Md.	Interested
Epstein, I.	Ph.D.	Haifa Technion, Haifa, Israel	Interested
Kaplan, R.	Ph.D.	Hebrew Univ. Jerusalem, Israel	Not suitable
Kolodny, A.	Ph.D.	Jerusalem, Israel	Interested
Lupo, M.	Ph.D.	Lafayette, Indiana	No response
Moreno, V.	Ph.D.	R. Guardia, Montreal, Canada	Interested
Ofek, I.	Ph.D.	Univ. of Tenn., Memphis, Tenn.	No response
Ossowski, L.	Ph.D.	Rockefeller Univ., N.Y., N.Y.	Awaiting action
Shavit, F.	Ph.D.	Hebrew Univ. Jerusalem, Israel	Interested

ORGANIC/PHARMACEUTICAL/CHEMISTRY

Almog, J.	Ph.D.	Harvard, Cambridge, Mass.	No response
Babad, E.	Ph.D.	Schering Corp. Bloomfield, N.J.	Not interested
Belkind, B.	Ph.D.	PolyTech. Inst. Brooklyn, N.Y.	Interested
Bendery, A.	Ph.D.	Univ. of Alberta, Canada	Not interested
Boger, E.	Ph.D.	BioResearch Inst. Cambridge, Mass.	Awaiting action
Braunstein, I.	M.Sc.	Hebrew Univ. Jerusalem, Israel	Not suitable
Cohen, N.	Ph.D.	Boulogne, France	Awaiting action
Dubleman, S.	Ph.D.	N.Y. Univ., N.Y., N.Y.	Interested
Gendel, M.	Ph.D.	Searle Corp. No. Chicago, Ill.	Awaiting reply
Gold, E.	Ph.D.	Schering Corp. Bloomfield, N.J.	Not interested
Goldberg, I.	Ph.D.	UCLA, Los Angeles, Calif.	Awaiting action
Grushka, E.	Ph.D.	SUNY/Buffalo, N.Y.	Not interested
Hooky, S.	Ph.D.	SK&F Co., Phila. Penn.	Interested/future
Houminger, Y.	Ph.D.	Hebrew Univ. Jerusalem, Israel	Not interested/present
Kampf, A.	Ph.D.	Univ. of Kansas, Lawrence, Kansas	No response

Katz, R.	Ph.D.	Biomedical Sci., Baltimore, Md.	Interested
Levy, D.	Ph.D.	Boston Univ., Brookline, Mass.	Awaiting action
Neiman, Z.	Ph.D.	Hebrew Univ. Jerusalem, Israel	Awaiting action
Reichman, U.	Ph.D.	Sloan Kettering, New Rochelle, N.Y.	Interested
Ronel, S.	B.Sc.	Hydro Med. Sci. Princeton, N.J.	Not suitable
Rotman, A.	Ph.D.	NIH, Bethesda, Maryland	Interested
Rozen, S.	Ph.D.	Boston, Mass.	No action taken
Scheinfeld, I.	B.Sc.	Brooklyn Polymer Res., N.Y.	Not suitable
Schwarzberg, M.	Ph.D.	Sylva, Inc. Palo Alto, Calif.	Interested
Shasha, B.	Ph.D.	Periovia, Ill.	No response
Sterling, J.	Ph.D.	Hebrew Univ., Jerusalem, Israel	HIRED
Tamir, M.	B.Sc.	Searle Corp. Buffalo Grove, Ill.	No response
Tishbee, A.	Ph.D.	Univ. Houston, Texas	No response
Weiner, B-Z.	Ph.D.	Schering Corp. Bloomfield, N.J.	HIRED
Weismann, B.	Ph.D.	NIMH, Bethesda, Maryland	No response
Zehavi, U.	Ph.D.	Weizmann Inst. Israel	

PARASITOLOGY

Hamburger, J.	Ph.D.	Ohio State Univ. Columbus, Ohio	No response

PATHOLOGY

Friedman, I.	Ph.D.	Jerusalem, Israel	HIRED

PHARMACEUTICS

Adir, J.	Ph.D.	Univ. Maryland, Baltimore, Md.	Interested
Hami, D.	Ph.D.	Jefferson Med. Coll. Phila. Pa.	Awaiting action
Mayron, D.	M.Sc.	Wyeth, Inc. Phila. Penn.	Not interested
Sax, P.	Ph.D.	Hebrew Univ. Jerusalem, Israel	Hold for Future
Varsano, J.	Ph.D.	Morristown, N.J.	Not available
Yakobi, A.	Ph.D.	Chicago, Ill.	Not interested

PHARMACOLOGY

Corne, J.	Ph.D.	Appro. Nicholas, Ltd. England	Not interested
Friedman, E.	Ph.D.	N.Y. Med. College	Not interested
Hamburger, A.	Ph.D.	Oss, Holland	No action taken
Kaiser, N.	Ph.D.	Univ. Calif., San Francisco	Not interested
Kassem, N.	M.D.	Schering Corp., Bloomfield, N.J.	Negotiations in prog.
Kisin, I.	M.D.	Natanya, Israel	Interested
Leon, S.	Ph.D.	Albert Einstein Med. Sch. N.Y.	Interested
Levy, A.	Ph.D.	SUNY Med. Center, Syracuse, N.Y.	Interested
Levy, L.	M.D./Ph.D.	USPHS, San Francisco, Calif.	No action taken
Maslian, J.	M.Sc.	Jerusalem, Israel	No action
Posner, J.	M.D./Ph.D.	Northwick Park Hosp. London	Not interested
Rosenberg, P.	Ph.D.	Univ. of Conn.,	Interested
Salem, H.	Ph.D.	Philadelphia, Pa.	Not interested
Schorr, Y.	Ph.D.	Jerusalem, Israel	Interested/future
Shek, E.	Ph.D.	Syntex Corp. Palo Alto, Calif.	Not interested
Szpicberg, R.	M.Sc.	Torande Co., Paris, France	Awaiting action
Tamir, M.		Israel	Not suitable
Yellin, T.	Ph.D.	ICI, Inc. Wilmington, Del.	Not interested
Zeidin, A.	M.Sc.	Hebrew Univ. Jerusalem, Israel	Interested

		PHYSIOLOGY	
Ashkenazi, R.	Ph.D.	Hebrew Univ. Jerusalem, Israel	Interested/training
Dafny, N.	Ph.D.	Univ. of Texas, Houston, Texas	Not interested
Eldan, M.	Ph.D.	Durham, North Carolina	No response
Greenbaum, B.	Ph.D.	Hebrew Univ. Jerusalem, Israel	Not suitable
Katz, Y.	Ph.D.	Hebrew Univ. Jerusalem, Israel	Not suitable
		PRODUCTION	
Kishony, G.	B.Sc.	New York, New York	Awaiting action
		STATISTICS	
Meyer, J.	Ph.D.	Squibb Labs, New Jersey	Interested
		VETERINARY MEDICINE	
Bornstein, R.	DVM	Tulane, Calif.	Awaiting Action
		VIROLOGY	
Margalith, M.	Ph.D.	St. Louis Med. Sch. Missouri	Awaiting action
Morgag, B.		SUNY/Buffalo, N.Y.	Awaiting action

* The candidates were interviewed in person, by correspondence or by phone.

Annex VI

INTRODUCTION OF A NEW DRUG

The genesis of a new drug most often is in the organic chemistry laboratory. This beginning initiates a time-consuming and costly series of steps before a potential drug finally enters into the market and clinical practice. The following is a brief outline of these steps required.

A. Chemistry

The chemical synthesis activity involves the organic synthesis of entirely new structures and analogues of parent compounds. This de novo synthesis program may be able to generate large numbers of compounds designed for either specific therapeutic areas or for general broad pharmacologic activity testing. New compounds also are often prepared from known agents, and chemical modification of these known compounds may constitute a major part of the synthesis program. Compounds for study also derive from extraction of chemicals from various biological sources as plants, bacteria, animal tissues, or marine life. All compounds emerging from this program are studied for their structure and physical-chemical properties as molecular weight, water, elemental and charge composition, melting point. These studies involve advanced analytical technique and often computerized analysis programs.

After the chemical formula is established with certainty, a sufficient quantity of the compound is prepared to enable biological testing of the compound. The amount to be prepared depends on the test or series of tests to which the compound is to be subjected, and also depends on the nature of the compound.

B. Biological/Pharmacology Screening

The extent of biological screening of a drug is dependent on the nature of the drug synthesized. If the drug is a novel compound, it may be screened for a wide variety of activities. Perhaps the most useful and initial primary screen in animals, conducted almost always in rodent's (mice), is the neuropharmacological profile which serves to provide an early indication of pharmacological activity of all new compounds, synthetic or natural, helps to categorize the activity of the compounds, and also distinguishes the active compounds from the inactive ones. Thus, the NPP test, properly conducted, should be able to categorize agents in the following activity areas: CNS depressants, psychotherapeutics, muscle relaxants, psychostimulants, anticonvulsants, and diuretics. Indirectly the NPP test can be indicative for anticholinergics, cathartics, vasodilators, local anesthetics, antihistamines, anticoagulants, anorexogenics, and antinauseants. The test will not predict or detect antacids, antibiotics, anti-diabetics, anti-hypertensives, anti-neoplastics, anti-inflammatories, endocrines, antiseptics, antitussives, adrenergic blocking or cholinergic stimulating agents, myocardial stimulants, ganglionic blocking agents, or coronary dilators. Thus, a program designed for any of the above activities must have a primary screen developed to uncover that activity (i.e. anti-inflammatory, etc.).

Pharmacological tests may progress from the primary to the secondary screening stage if initial activity warrants it. Generally, a highly developed pharmacology screening program will include the following tests: acute toxicity, central nervous system (analgesia, anticonvulsion, tranquilizer, hypnotic, etc), antiemetic, anti-inflammatory, anti-microbial, anti-parasitic, anti-viral, cardiovascular (anti-hypertensive, anti-arrhythmic, vasodilator, myocardial contractility), diuretic, endocrinologic, metabolic (blood sugar, fats, cholesterol), anti-obesity. Of great importance is the selection of the proper experimental animal or in vitro model to explore and test these activities which can be extended into secondary, more developed tests. Experimental models can range from the intact animal to isolated tissues or perfused organs. At times, no good animal model exists (as for mental disorders) and model systems based on activities known to be effective in the human are used.

These initial screens should provide information on the acute toxicity, effectivity, onset and duration of action and other pharmacodynamic parameters in the animal species studied. This information should be fed back to the chemist at the earliest possible time to allow for evaluation and change, if necessary, of the chemical synthesis program based on chemical structure - biological activity considerations.

Initial biochemical studies on the action of the drug on enzyme or endogenous chemical systems may be carried out concommitantly with pharmacological studies. Decision regarding these studies depends on the nature of the compounds under study, and may give clues as to possible mechanism(s) of action for which the drug may have been synthesized initially. Such biochemical studies may also provide vital information which will help determine whether to proceed with the drug toward studies directed clinically.

C. Pharmaceutical Studies

If the initial toxicology, chemical synthesis, pharmacology, and biochemical studies data are demonstrated to be sufficiently promising, then a decision may be made to forward the candidate compound further toward eventual clinical trial. The decision to consider clinical trial will depend on such further activities as manufacturing, quality control and formulation, biopharmaceutics, more extensive toxicology, drug metabolism studies.

1. Manufacturing

It is necessary to scale up the synthesis of the compound to provide sufficient drug for such studies as formulation, toxicity, metabolism, and possible clinical trials. Such scale up programs should be carried out in a pilot plant facility which should contain all the relevant control procedures necessary to assure purity, sterility (if indicated), and all other controls according to the GMP. Quality-control chemists must devise methods for identifying and quantitating the candidate compound and all potential impurities. These standardized tests must be applied to all production batches that are labeled and identified properly. The quality-control chemist also must provide information on the stability of the compound based on shelf-life studies involving changes in temperature and humidity conditions.

2. Biopharmaceutics

As described in the Summary Report on Biopharmaceutics Activity (Appendix K), studies will have to be undertaken to study the relationships between the physical-chemical properties of the candidate compound and the formulation in which the compound ultimately will be administered clinicably and its bioavailability and fate in the body. Thus, such studies ultimately will involve investigations in the appropriate animal species into the compound's absorption, distribution, metabolism, and elimination profiles. Parameters that require measurement so as to determine the factors influencing the ability of the compound to reach the site of action include the dissolution rate, dissociation constant, aqueous solubility as a function of pH, membrane permeability characteristics. These studies, carried out in vitro and extended to in situ and in vivo models, should provide vital information for assisting the making of a decision to move forward with the drug. It is not uncommon that a candidate compound may falter at this experimental stage. Information also will be available to provide for the best formulation to be used in eventual clinical trials. Since formulation can affect the absorption and bioavailability of a compound, and thus its pharmacological activity, it is most important to develop the final formulation early in a reproducibly and uniform fashion to assure a proper form for the clinical trial.

3. Drug Metabolism Studies

Drug metabolism studies should be carried out to help determine the active molecular species of the drug, its absorption form, its metabolites to determine whether any of them are active, its principal metabolic pathway(s), and its excretion form(s) and pathway(s). The degree of tissue uptake, tissue(s) of major concentration and release, storage characteristics, compartmental features -- all of these characteristics will aid in clarifying and determining both the pharmacological, therapeutic, and toxicological natures of the drug. Thus, it will be necessary to develop assay procedures with a high level of sensitivity and specificity to enable the measurement of minute quantities of the drug and metabolites in all types of tissue and body fluids. Predictions of the onset and duration of action can be made, and allow for formulation manipulation to arrive at the optimum form desired. Such studies may have to be continued well into the clinical trial. But as full a pharmacokinetic profile should be developed prior to clinical trial so that dosage regimens and clinical protocols can be developed.

D. Animal Toxicity Studies

Animal toxicity studies of varying durations are a vital part of the pre-clinical studies. The range of such studies in preparation for clinical study and eventual marketing depends greatly on the duration of clinical tests, the frequency of drug administration, and the ultimate clinical utilization of the new drug. Regulatory agencies in different countries have established different requirements regarding duration of toxicology studies for animals based on duration of human administration, as seen in Table I. Additional information regarding FDA guidelines and effectiveness of chronic toxicity studies in predicting human toxicity is available.

Acute, subacute, and chronic toxicity studies must be carried out in several different animal species by different routes of drug administration employing at least one route and dosage form that will be used clinically. Acute toxicity will identify frank toxicity and enable the comparison of relative toxicitics amongst several candidate compounds. Subacute and chronic toxicity protocols will depend on the information gathered on the drug up to this stage. Rats, dogs, and sometimes monkeys are most often used for chronic studies involving at least three dose levels over 6-24 month test periods. Evaluation of the toxicity data must take into account many factors including information obtained from control animals receiving the drug vehicle. Generally accepted procedures are noted in Table 2. Some chronic studies, including special studies as carcinogenicity, mutagenicity, teratogenicity, reproduction, may not have to be initiated until the clinical studies have started. Decision is based on the nature of the drug and the requirements of the respective drug regulatory agency. Important sources of toxicology information gathered from a number of other sources are summarized in Table 3. Animal toxicity studies are very involved and costly. Therefore, the decision to move forward with clinical studies on a candidate compound must be made with as much initial data to support the decision.

E. Clinial Studies

Clinical studies must be organized on the basis of properly-designed clinical protocols and carried out by experienced clinical pharmacologists. Clinial study of a new drug is divided into four phases. Phase I represents the first time a new drug is given to a healthy human and helps establish the range of tolerance, pharmacokinetic profile, pharmacodynamics, and dose-ranging for the drug. Phase II, where the drug is given to patients with the disease for which the drug was designed, helps establish the degree of safety and therapeutic efficacy. Generally, these first two phases are relatively safe for the subjects since they are under very close clinical observation. If the clinical data justify, a broad clinical Phase III study in a large patient population is carried out by practicing physicians who ultimately will use the drug. This phase determines whether the drug is safe and effective for marketing in the particular therapeutic area indicated. Phase IV, a relatively new phase, involves a constant monitoring of the drug's clinical performance after it has been marketed and during its widespread clinical use.

F. Summary

A description of the development of a new drug has been presented, a development involving pre-clinical and clinical studies utilizing a variety of chemical, bio-medical, and pharmaceutical disciplines. In the USA the estimated time for development of a marketed new drug is 10 years at an approximate cost in excess of 10 million dollars. At various times during this development, critical decisions must be made whether to proceed to the next step, as seen in the drug development flow pattern . (p.57) The proper decision at the proper time is predicated on the coordinated activity of the scientists and administrators in each department.

TABLE 1 * *

SYNOPSIS OF DURATION OF TOXICOLOGY STUDIES FOR ANIMALS IN DIFFERENT COUNTRIES
(from Hebold 1972)

Duration of human administration	USA	Gr. Brit.	FRG	Sweden	Switz.
single dose		21 days	2-4 weeks	2-4 weeks	not less than 14 days
several days up to 1 week	2 weeks	39 days		3 months	
up to 2 weeks	2 weeks-3 months				not more than 3 months required
up to 1 month		90 days			
over 1 month		180 days	3-6 months		
up to 3 months	4 weeks-6 months				
6 months to unlimited	3 months-12 months dogs 18 months rats				

	USSR	EEC	WHO	ESSDT*
single dose		2-4 weeks	less than 3 months	1-3 weeks
several days up to 1 week	10 days			1 month
up to 2 weeks	30 days			3 months
up to 1 month	2-6 months		3-6 months	
over 1 month		3-6 months		
up to 3 months				
6 months to unlimited				

* European Society for the Study of Drug Toxicity

** Zbinden, G., Progress in Toxicology. Springer Verlag, N.Y. 1973, pg. g.

TABLE 2 **

Prolonged Toxicity Studies

Subject	Generally Accepted Procedure	Major Alternatives Still Under Discussion
Animal Species	1 rodent (rat), 1 nonrodent (dog), third species if significant toxicity occurs.	Always third species. Monkey, pig, mouse, rabbit, cat or which? Species which metabolize drug or which respond pharmacologically like man. Inbred or random-bred, conventional or specified pathogen free animals. Litter mates equally divided among groups. One or more defined strains.
Feeding	ad libitum	Paired feeding of treated and controls.
Number of Test Groups	At least 3 and 1 control.	or more.
Magnitude of Doses	Highest: must cause significant toxicity; lowest: small multiple of therapeutic dose in mg/kg. Others in between.	Adjustment of dose depending on age, general tolerance, etc. Determination of dose depending on blood or tissue levels. Special procedures for poorly absorbed, pharmacologically highly active, cytotoxic (irritant) or extremely non-toxic drugs.
Number of Animals per Group	Rodents: at least 10 of each sex; nonrodent: at least 5 of each sex.	Larger groups. Groups large enough to permit meaningful statistical treatment.
Duration of Treatment	2 weeks to several years depending on projected human use (see Table 2).	---
Routes and Frequency of Administration	Same routes as projected for use in man. Oral: admixture to diet or 6x intubation per week. Parenteral: 6x weekly.	Routes which assure maximal blood or tissue level, frequency of administration which assures continuous levels or levels similar to those obtained in clinical use in man. Interrupted administration to minimize adaptation. Daily treatment. Treatment schedule as in clinical use.
Age of Animals	Rats: start with immature animals. Dogs: 1 year.	Studies on newborn and very old animals.
Reversibility	Not part of routine procedure.	Special groups treated and taken off drugs after various time periods and for various lengths of time.
Measurements and Observations	Weight, appearance, eye examination.	Food and water consumption, food efficiency, reflexes, behavioral tests, ECG, EEG, neuromuscular and psychomotor function, sexual behavior, memory, etc.

Table 2 (continued)

Hematology	Before test, after 1,2,3,6, 9,12,etc. months in part of test animals. RBC, hematocrit, Hb, WBC, diff. count, platelet count, reticulocyte count, prothrombin time.	Examine all animals. ESR, red cell fragility, metHb, other coagulation tests, bone marrow examination, spleen and lymph node cytology, phagocytic activity, etc.
Blood Chemistry	In nonrodent: SGPT, alk. phosphatase, BUN, serum creatinine, fasting blood sugar, plasma proteins, bilirubin.	Selected or all animals including rodents. Additional enzyme and organ function tests, electrolytes, clearance studies, cholesterol, total lipids, triglycerides.
Urinalysis	Nonrodent: spec. gravity, sugar, protein, bile, ketone, pH, sediment.	Selected or all animals including rodents. Total volume, electrolytes, enzymes.
Autopsy	Complete, in part of rodents and all nonrodents. Weight of liver, kidney, testicle, ovary.	Complete, in all animals. Weight of additional organs, e.g., thyroid, adrenals, uterus, epididymis, heart, etc.
Histopathology	15-20 major organs, routine staining.	More organs and tissues, special staining methods, histochemistry, electron microscopy.
Known Standard Drug	Not part of routine procedure.	Treatment of one or more groups with known standard drug (positive control).
Special Studies		
Reproduction-Teratology	Fertility and reproduction study in rats. Teratological study in rabbits and mice or rats. Perinatal and postnatal study in rats.	Use of various strains, e.g., with propensity to develop certain type of malformation. Use of primates.
Mutagenicity	Not part of routine procedure (yet).	In selected cases or with all drugs? In vitro cytogenetics with human, animal, or plant cells. In vivo cytogenetics. Host mediated assays with different indicator organisms. Dominant lethal test. Specific locus test. High dose, therapeutic dose, acute, subacute or chronic treatment?
Carcinogenicity	Not part of routine procedure (yet).	In selected cases or with all drugs? Long term studies in rodents. One or more species, one or more strains? Use of dogs, non-human primates. Short term screening tests.
Drug Interactions	Combined LD_{50} with drugs likely to be used in combination with new drug.	Combined subacute and chronic tests. Potentiation or inhibition of specific pharmacological and toxicological effects.

** Zbinden, G., Progress in Toxicology. Springer Verlag, N.Y. 1973, pg. 6-7

Table 3 **

A: Essential for all drugs, to be known before first clinical trial

B: Essential for certain types of drugs, to be known before first clinical trials

C: Very desirable, to be known before or during early clinical trials

D: To be investigated during clinical trials

E: To be investigated in selected cases during clinical trials or after commercial introduction; particularly if suspected from clinical observations or theoretical considerations

Selected, Important Sources of Toxicological Information

Chemical and Physical

Chemical Structure	A	p K	A
Chemically related drugs	A	Organic solvent-water partition coefficient	A
Stability at various pH	A		
Chemistry of decomposition prod.	D	Solubility in water and urine at various pH	A
Chelating properties	D		
Photochemical properties and stability	E	Water solubility of major metabolites	D
		Oxidizing properties	C
Surface activity	D	Binding with DNA, RNA, lipids and other macromolecules	E
Binding with serum proteins	C		

Pharmaceutical Formulation

Chemical composition	D	Rate of release of active drug	D

Absorption, Distribution, Metabolism, Excretion

Absorption for all routes of clinically anticipated administration	A	Modification of absorption by pharmaceutical manipulations and nutritional factors	D
Chemical alterations of drug by intestinal flora	E	Penetration through biological membranes (blood-brain, placenta, aqueous humor, etc.)	D
Penetration through normal and inflamed skin	B	Tissue distribution incl. fetus	C
Distribution in body water	D	Excretion in milk	D
Binding and storage in specific tissues, cells or cell components	E	Blood and tissue levels after single and repeated administration	C
Sites of metabolism	C	Chemical identity of major metabolites	D
Half-life of active drug and major metabolites in blood and major target organs	C	Modification of metabolism due to various diseases	E
		Renal clearance of drug and metabolites	D
Major pathways of excretion	A		
Effect on urinary pH	C	Change of excretion by damaged organs	D
Ability to induce or inhibit drug metabolizing microsomal enzymes	A	Effect on conjugation mechanisms	D
		Ease of removal by peritoneal dialysis	E
Metabolism in newborn animals	D		

Table 3 (continued)

Drug Interactions

Modifications of pharmacological effects of drugs likely to be used in combination	D	Potentiation of ethanol, barbiturates and inhalation anesthetics	D
Effect on ethanol metabolism	E	Potential toxicity in combination with enzyme inhibitors	E
Effect on metabolism and anticoagulant action of coumarin anticoagulants	D	Ability to displace bilirubin and selected drugs from albumin binding sites	D
Competition with other drugs for microsomal metabolizing enzymes	E	Interactions with other modes of therapy	E

In Vitro Investigations

Effect on selected enzymes (carboanhydrase, monoaminoxidase, Krebs-cycle, etc.)	E	Mitochondrial respiration	D
		Cytotoxicity in mammalian cells	D
		Chemotactic motility of leukocytes	E
Phagocytic activity of leukocytes	E	Platelet adhesion and aggregation	E
Osmotic and mechanic red cell fragility	C	Effect on 6-GPD deficient red cells	E
		Isolated organs (heart, atrium, uterus, etc.)	E

Pharmacological Investigations

Central and peripheral neurotoxicity	C	EEG	C
		Convulsant action	C
Interactions with known convulsants	E	Behavioral toxicity	D
Learning and memory	E	Sexual behavior	E
Physical and psychological dependence	D	Withdrawal effects	D
		Effects on sensory organs	D
Neuromuscular function	D	Extrapyramidal reactions	E
Eating and drinking behavior	D	Blood pressure and regulating mechanisms	A
ECG	A		
Cardiac function	C	Intraocular pressure	D
Pulmonary pressure	D	Various respiratory parameters	D
Regional blood flow	E	Cholinergic and anticholinergic effects	C
Adrenergic and adrenolytic effects	C		
Gastric secretion	D	Gastrointestinal ulcers	D
Gastrointestinal motility	D	Emetic effects	E
Liver function	A	Interference with absorption of nutrients	E
Bile flow	D		
Intrabiliary pressure	E	Kidney function	A
Diuretic effects	C	Body temperature	A

Intermediary Metabolism

Basal metabolic rate	C	Fasting blood sugar and glucose load	C
Insulin release	E	Insulin sensitivity	E
Free fatty acid mobilization	D	Blood and liver lipids	D
Cholesterol synthesis	E	Liver triglyceride secretion	E
Protein synthesis	D	Serum proteins	C
Aminoaciduria	D	Bilirubin and bile acid metabolism	D
Oxalate metabolism	D	Synthesis, storage and release of biogenetic amines	D
Uric acid formation and excretion	E		
Water and electrolyte balance	C	Vitamin metabolism	E
Porphyrin metabolism	E	Iron metabolism	E

Table 3 (continued)

Endocrine Investigations

Pituitary function	E	Pituitary-adrenal axis	D
Estrus cycle	D	Stimulation and inhibition of sex hormone dependent organs	D
Thyroid function	D		
Parathyroid function	E	Anabolic and anti-anabolic effects	D
Antidiuretic effect	D		

Experimental Pathology

Effect on injured organs	E	Mitosis, growth, differentiation, regeneration	E
Effect on experimental diabetes	E		
Inflammatory responses	D	Bacterial, virus and fungus infections	D
Immune reaction, antibody synthesis	D	Complement action	E
Function of reticuloendothelial system	E	Blood coagulation and hemostasis	D
		Fibrinolysis	D
Interaction with stress	E	Red cell and platelet survival	E
Methemoglobin formation	A	Effects on spontaneous diseases including tumors	E
Phototoxicity, photosensitivity	E		
Interference with diagnostic tests	E	Contact sensitization	B
Experiments with animals having genetic enzyme abnormality	E	Effects of unbalanced diets	E

Toxicity Studies

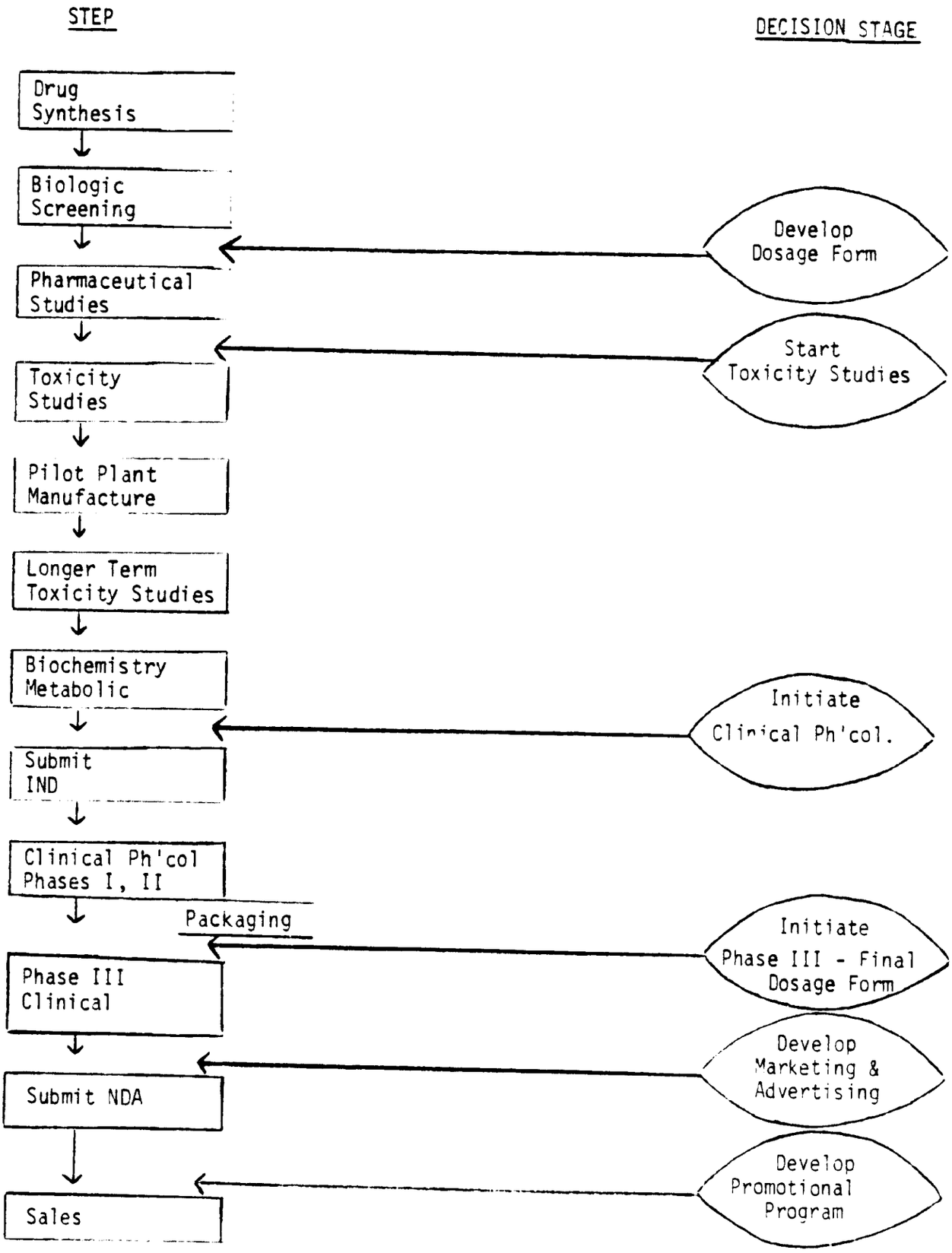
Acute toxicity	A	Subacute and chronic toxicity	A-D
Reproduction	C	Teratogenic effects	A-D
Neonatal development	D	Carcinogenic effects	E
Mutagenic effects	A-E	Sensitizing properties (parenteral)	A-E
Local toxicity (skin, eye, vagina, intrathecal, etc)	B		

The check-list is not a complete collection of all sources of toxicological information. And not all its points are essential or even applicable for all types of drugs, but it contains several bits which I have neglected to collect repeatedly and which then had to be gathered in a hurry. It is hoped that it will help others to avoid such embarrassment.

A similar but more voluminous check-list should be used for the clinical evaluation of the side-effect liability of new drugs. It is not wise to wait for the first patient to fall down the staircase before making the necessary effort to look for orthostatic hypotension with appropriate procedures. Thus, clinical trials should not merely register side-effects as they happen but should be designed to assess frequency and dose-dependency of adverse effects. Apart from providing important clinical information, such studies will be most valuable for the toxicologist who depends on clinical feedback for the evaluation of the toxicological assay procedures.

** Zbinden, G., Progress in Toxicology. Springer-Verlag, N.Y. 1973, pg. 20-22

STEPS IN THE DEVELOPMENT OF A NEW DRUG



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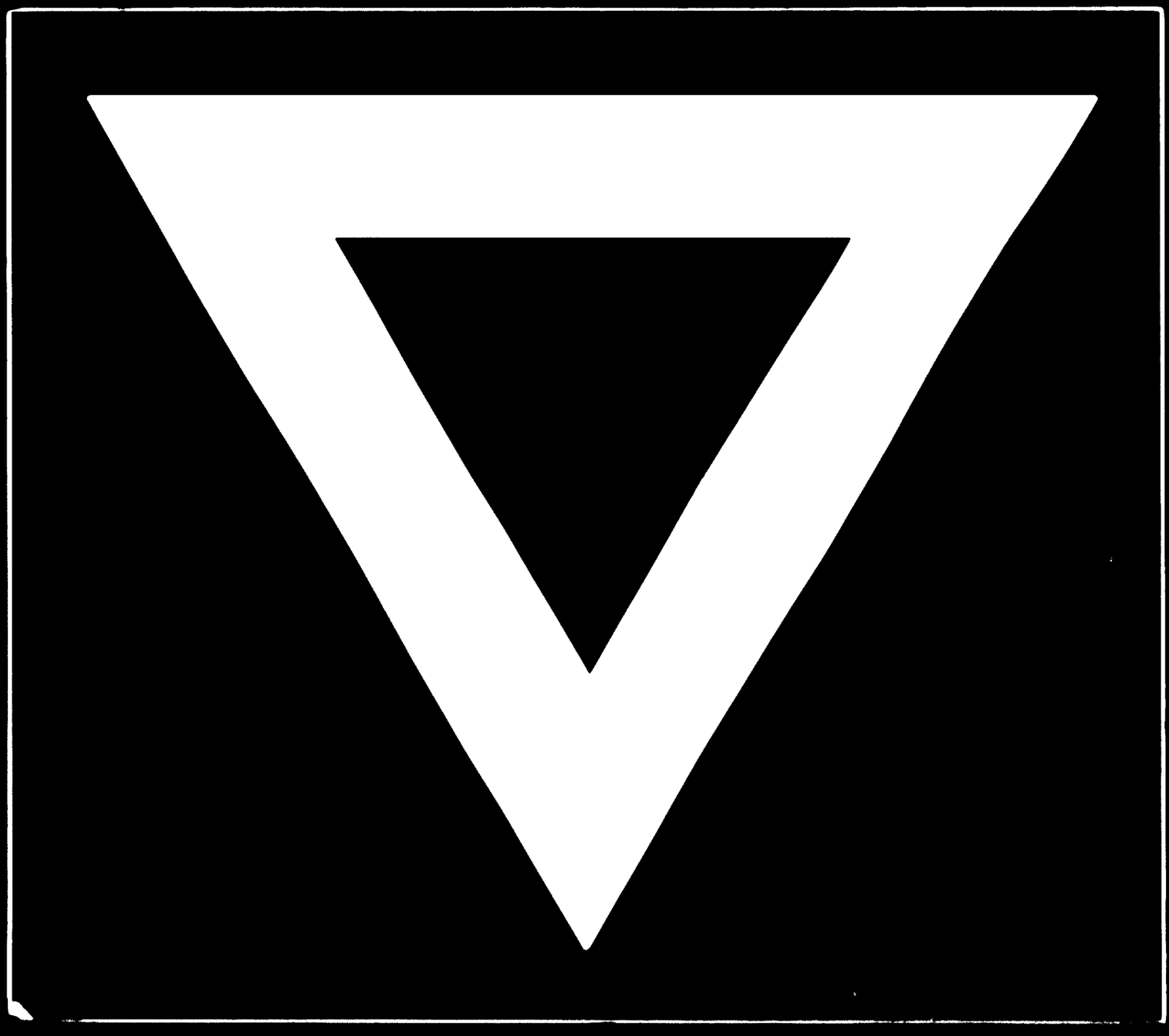

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