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ESTABLISHMENT OF A PHARMACOLOGICAL INSTITUTE IN ISRAEL

DP/ISR/78/010

ISRAEL

Technical report:
DEPARTMENT OF PHARMACEUTICAL RESEARCH

AUG 1977

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

United Nations Industrial Development Organization

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Technical report: Department of Pharmaceutical Research

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 Joseph Adir,
pharmacologist biopharmaceutist

United Nations Industrial Development Organization
Vienna, 1977

Explanatory notes

A full stop (.) is used to indicate decimals.

A comma (,) is used to distinguish thousands and millions.

The monetary unit in Israel is the Israel pound (£I). During the period covered by the report, the value of the £I in relation to the United States dollar was $US 1 = £I 9.25.

The following abbreviation of an organization is used in this document:

FDA Food and Drug Administration (United States)

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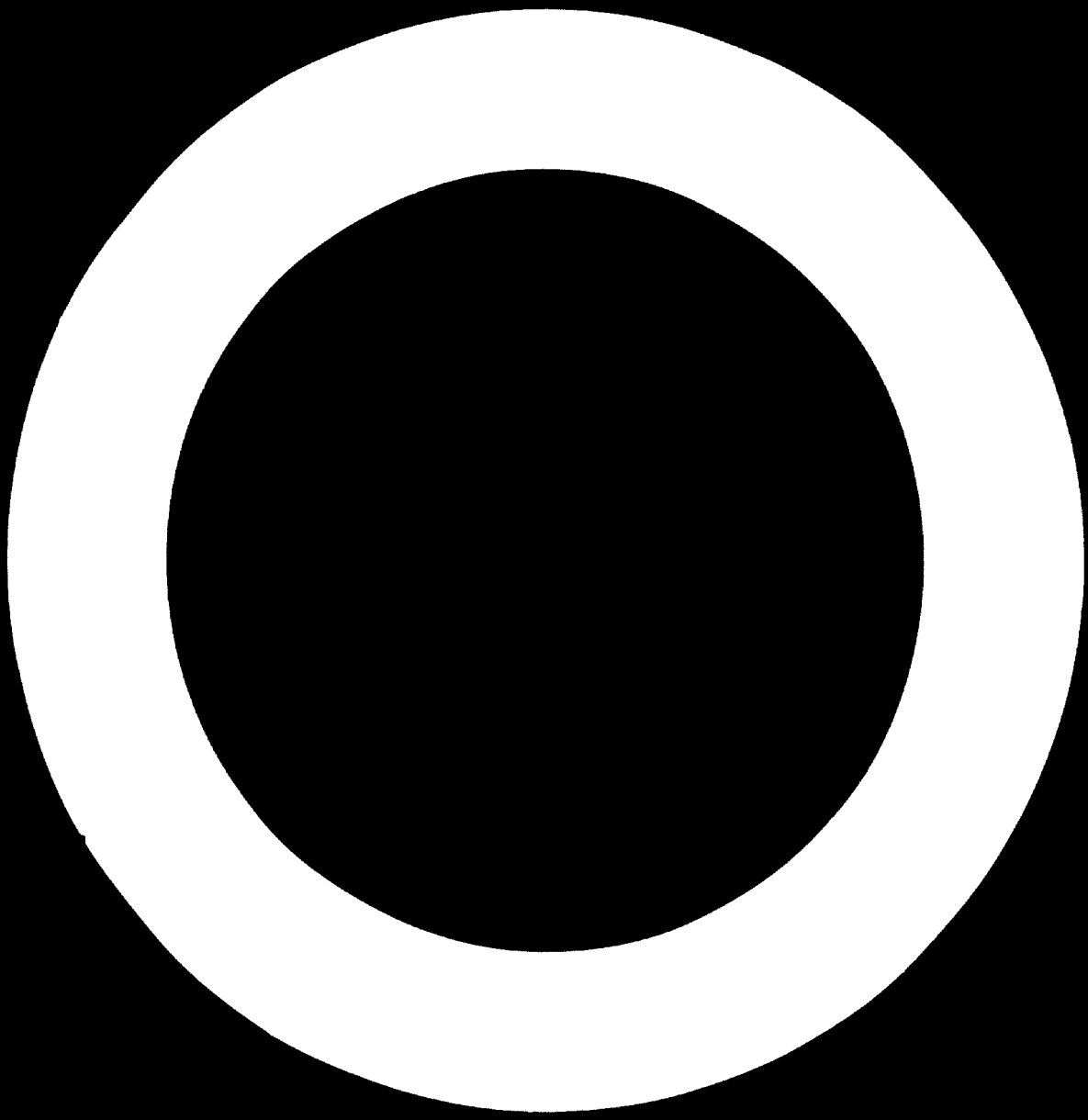
ABSTRACT

The project entitled "Establishment of a Pharmacological Institute in Israel" (DP/ISR/73/010) arose from a request submitted to UNDP by the Government of Israel on 25 September 1975 and approved on 29 April 1976, with the United Nations Industrial Development Organization (UNIDO) designated as the executing agency and the Assia-Teva group of companies as government counterpart agency. The broad objectives of the mission, which took place from 4 to 29 March 1977, were to review overall plans for the establishment of a Department of Pharmaceutical Research within the Research and Development Division of the proposed Institute, and to provide assistance on various aspects of pharmacological research and development.

Noteworthy among the conclusions of the mission was the confirmation of the strong commitment of Assia-Teva, the corporate conglomerate recommended by the Government of Israel to establish the Pharmacological Institute, to continue and expand the Institute beyond the termination of UNDP support, and its firm intention to develop long-term scientifically-sound research and development programmes. Its main recommendation was that a Department of Pharmaceutical Research should be established within the Research and Development Division of the Assia-Teva conglomerate. The primary responsibilities of such a department could be allotted to the following major units: pre-formulation (dosage form research and development); pilot plant scale-up and manufacturing trouble-shooting; biopharmaceutic and pharmacokinetics research and services; and an analytical laboratory (biological fluids).



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INTRODUCTION

Academic institutions and the existing pharmaceutical industry in Israel have a large reserve of scientists skilled in chemical synthesis, chemical structural modifications, microbiology, pathology and medicine. However, they lack both pharmacological testing facilities and trained pharmacologists with industrial experience capable of organizing and conducting a drug screening programme vital for new drug development. The addition of such a pharmacological screening activity to industry would provide "in-house" programmes necessary to sustain and optimize the on-going chemical systhesis programme, and facilitate new drug development for the welfare of the world community and the country's economy.

The Government of Israel has decided that industry would provide the most favourable setting for a pharmacology institute. With the proper advice and support, industry is believed to be already capable of organizing, implementing and expanding such a project. The Assia-Teva complex of companies was identified as having the necessary organizational structure, the need and the long-range research and development commitment to initiate and develop the Institute. A request for UNDP assistance in the achievement of the above-mentioned goals was therefore made on 25 September 1975 and approved on 29 April 1976. This led to the project entitled "Establishment of a Pharmacological Institute in Israel", for which UNIDO was designated as executing agency and the Assia-Teva group of companies as the government counterpart agency. The initial project budget provided for a UNDP contribution of $US 72,000 and a Government contribution of £I 1,790,000.

The mission covered by this report took place from 4 to 29 March 1977. It had the following objectives:

(a) To review overall plans for the establishment of a Department of Pharmaceutical Development (Pharmaceutics) within the research and development division of the Institute;

(b) To assist in the drafting of specific experimental protocols for carrying out studies on drug formulation, drug bioavailability, compatibility and drug stability, drug bioequivalence, and pharmacokinetics;

(c) To assist in planning and designing specific pharmaceutics research laboratory facilities, drafting pharmaceutics equipment and instrument specifications, standardizing control pharmaceutics test systems, and training research personnel in a variety of assay techniques and model systems.

I. FINDINGS AND RECOMMENDATIONS

Assia-Teva is a corporate conglomerate comprising Assia-Zori (a private company), Teva (a public corporation), Assia-Ma'abarot (a veterinary arm of Assia in which 50% of the shares are held by Assia and 50% by Kibbutz Ma'abarot) and Paka (a yeast fermentation plant). The pharmaceutical and chemical production of the conglomerate is located chiefly in Teva-Jerusalem and partly in Assia-Petah Tikvah.

The newly-built plant at Teva-Jerusalem is a large modern facility which was constructed according to the United States Good Manufacturing Practices Regulations[1/] (1971) for pharmaceutical production, and is located on the Hebrew University Science-Based Industry Campus. The company manufactures over 300 products, 95% of which are drug preparations, vaccines for human use and diagnostics.

In addition to identifying the specific needs of the conglomerate in the areas of pharmaceutical research and development, the mission confirmed the company's strong commitment to continue and expand the Institute beyond the termination of UNDP support and its keen desire to develop long-term, scientifically-sound research and development programmes within the conglomerate.

It is recommended that a Department of Pharmaceutical Research should be established within the Research and Development Division of the Teva-Assia-Zori conglomerate. The primary responsibilities of this Department may be allotted to four major units: preformulation (dosage-form research and development); pilot plant scale-up and trouble shooting; biopharmaceutic and pharmacokinetics research and services; and analytical laboratory (biological fluids). The Department would be headed by a Director, while each unit would be directed by a senior scientist-group leader and include scientists and technicians. The Director would appoint special task-force or project committees to handle the research activities of each drug product. Each unit would be located in facilities equipped with special instrumentation according to its objectives and scope of operation as suggested in this report and illustrated by prototypes of experimental approaches.

1/ Federal Register, 36, 133 (1971).

II. RATIONALE AND SPECIFIC FUNCTIONS OF THE PROPOSED UNITS

A. Preformulation

Preformulation is the process of development of a stable, safe and effective drug delivery system through optimization of the physical and chemical properties of the drug substance and possible interactions with the various excipients intended for use in the final product. It is an effort that encompasses the study of such parameters as solubility, polymorphic form, crystal size and shape, pH profile of stability and drug-excipient interactions, which may have a profound effect on a drug's physiological availability and physical and chemical stability. The data obtained from these studies are integrated with those obtained from preliminary pharmacological and biochemical studies, providing the pharmacist with information that permits the selection of the best drug form and the most desirable excipients for use in its development. The need for a preformulation unit in Teva has become clear from previous case histories in the company, and its establishment is anticipated in the near future.

Within this unit, preformulation work can be initiated on the following products: new compounds which showed sufficiently impressive results in biological screening tests; standard drug substances (United States Pharmacopoeia, British Pharmacopoeia etc.) which the company has decided to market locally in Israel; compendial drug substances which the company has decided to or was asked to supply to foreign markets; previously-marketed drug products which require a change in manufacturing process as a result of production problems; previously-marketed drug products which require a change of formulation as a result of suspected poor bioavailability or at the request of the regulatory agency (see below the section dealing with the rationale and function of the biopharmaceutic and pharmacokinetic unit); and previously-marketed drug products for which new dosage forms must be developed because of strength, therapeutic or patient (such as the development of a pediatric suspension of a preparation previously intended for adults) considerations.

B. Pilot plant scale-up and trouble-shooting

Despite extensive efforts in research and development, the success or failure of a new drug or dosage form is often determined by the adequacy of

the manufacturer's production techniques, which should meet standards that guarantee the physical and chemical integrity of the drug. Such procedures also must be economically feasible and capable of meeting today's mass market requirements. It is during the pilot scale-up phase that a precise and reliable method of manufacture must be developed to effect an orderly transition from laboratory procedures and formulations to routine production operations.

To date, many of the problems dealt with in the research laboratory of the Pharmaceutical Division of Teva-Assia-Zori conglomerate are of a trouble-shooting nature. In addition, although batch protocols for most of the conglomerate's products exist, these have been in many cases incomplete, and, at best, lack a master formula which provides detailed and uniform guidelines for all pharmaceutical preparations. Such a formula for a batch protocol is needed to provide trouble-free, standardized manufacturing procedures which, in the long term, not only will increase the effectiveness of the production but also reduce its cost.

C. Biopharmaceutics and pharmacokinetics

Biopharmaceutics is defined as the study of the factors influencing the bioavailability of a drug in man and animals and the use of this information to optimize pharmacologic or therapeutic activity of drug products in clinical applications.[2/] The term bioavailability means the rate and extent to which the active drug ingredient or therapeutic moiety is absorbed from a drug product and becomes available at the site of drug action.[3/] Pharmacokinetics is the study of the kinetics of the absorption, distribution, metabolism and excretion of drugs in animals and man.[2/]

2/ "Definition of terms", Journal of Biopharmaceutics and Pharmacokinetics, Vol I, No. 1 (1973). The same or similar definitions have been accepted by the American Pharmaceutical Association, British Pharmaceutical Association, and the World Health Organization.

3/ United States Food and Drug Administration (FDA) Bioavailability/ Bioequivalence Requirement, The Gold Sheet, 10, No. 12 (1976).

The science of biopharmaceutics and pharmacokinetics has been developed in the last decade and is recognized today as the cornerstone of drug production and therapy. No single drug entity is recognized as such unless evidence for its absorption, distribution and elimination, which are important determinants of its activity have been documented. Dr. Gerhard Levy, Distinguished Professor of Biopharmaceutics at the State University of New York at Buffalo (United States) and one of the fathers of this science, states that "... Free enterprise in the area of health care requires a particularly high level of individual and corporate responsibility or the privileges of freedom that we value so highly will soon be eroded. The public expects, and rightfully so, that we in the health sciences and health professions adhere to standards of performance and ethics which are higher than average."[4/] It is imperative, therefore, that a leading pharmaceutical conglomerate in Israel such as Teva-Assia-Zori, should take advantage of the most recent scientific endeavors and discoveries to improve its contributions to the health profession in the country.

As a part of the Department of Pharmaceutics, this unit will have the following tasks; to determine the pharmacokinetic parameters of newly-developed drug substances in animals; to devise the dosage regimen, i.e., dose and frequency of administration of new drugs; to assess the in vivo bioavailability in animals of the drug from the proposed dosage form; to study the in vivo animal bioequivalence (bioequivalent drug products means those pharmaceutical equivalents or pharmaceutical alternatives whose rate and extent of absorption do not show a significant difference when administered at the same molar dose of the therapeutic moiety under similar experimental conditions, either single dose or multiple dose[3/]) of the company's generic products for local or foreign markets, about 20% of these products falling within the category of drugs for which bioavailability and bioequivalence data are required by the FDA (see footnote 2); to conceive, draft and supervise the implementation of bioavailability, bioequivalence and pharmacokinetic protocols in humans to be subcontracted to and carried out by qualified clinical settings; to analyse the data of the above-mentioned studies; to correlate the in vivo data with the in vitro findings

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4/ G. Levy, "Bioavailability, clinical effectiveness and the public interest", Pharmacology, Vol VIII, No. 33 (1972).

carried out by the Preformulation Unit; to review biopharmaceutic and pharmacokinetic information obtained by the company's Drug Registration Department from abroad for submission to the Israeli regulatory agency; to provide input to the process of product labelling and physician or patient package inserts; to participate in the education of detail men in the areas of biopharmaceutics and pharmacokinetics; and to answer inquiries from physicians, medical centers and hospitals concerning the biopharmaceutics and pharmacokinetics of the company's drug products.

D. Analytical laboratory (biological fluids)

The existing analytical laboratory (pharmaceutics) at Teva-Assia-Zori is dosage-form-oriented, i.e., is capable of the chemical analysis of active ingredients which usually have the following characteristics: present intact (not metabolized); obtainable in relatively large concentrations since the active ingredient can be extracted from more than one unit dosage (tablet, capsule, ampule etc.) and, accordingly, no particularly sensitive quantitative methodology is needed; easily extractable due to the absence of uncontrollable or unknown substances which may interfere with the assay; forming known compounds to the extent that the specificity and reproducibility requirements for chemical analysis are easily attainable and demonstrable. Furthermore, it performs microbiologic assays which are known for their sensitivity to contamination.

On the other hand, assay of the same drug in biological fluids is often very complex. It is usually present at a very low concentration (because of dilution in large volumes); by and large it co-exists with several and sometimes many of its metabolites; the biological fluids contain many interfering substances, and the extraction and clean-up of the active ingredient is therefore a long and tedious process; it requires more sensitive and specific instrumentation; and, finally, a great deal of manipulation, research and development to ensure its reproducibility. Consequently, a special analytical laboratory for assay of drugs in biological specimens is deemed necessary.

III. EXPERIMENTAL APPROACHES OF THE PROPOSED UNITS

The following experimental approaches are purposely presented in a general outline because a specific and detailed methodology depends on the objectives of the research project and on the drug or preparation to be investigated. They are intended as prototypes of the research endeavors to be undertaken by each unit, and thus provide a rationale for the facilities, equipment and personnel requirements.

A. Preformulation

A good practice in planning preformulation work is to outline the work in the form of a flow diagram. The data are summarized in a work sheet which serves as an effective means of transfer of information. The major direction of the investigation is determined by the type of compound under investigation, and the intended dosage forms to be developed. The preformulation process begins by collecting information or carrying out studies on the chemical characteriestics of the compound in question. These could very well be or have been carried out by the analytical laboratory (pharmaceutics) which is not part of the Research and Development Division. Examples of the required data are the following:

(a) Purity of compound, i.e., loss on drying, water content, residue on ignition, inorganic elements, heavy metals, organic impurities etc.;

(b) Macroscopic properties, e.g., appearance, taste and odor, color in solution, pH of solution or suspension, melting point, refractive index etc.

The next step entails the delineation of the pharmaceutical properties of the compound and should probably be carried out in the unit. This will involve consideration of the factors listed below:

(a) Particle size. Drug dissolution rate, absorption rate, content uniformity, taste, texture and stability are dependent, to varying degrees, on particle size and size distribution. This parameter could be determined by sieving, microscopy, sedimentation, stream scanning, light scattering, acoustical counters, laser holography or scanning image analysis;

(b) Partition coefficient and pK. The oil/water (e.g., octanol-water, chloroform-water etc.) partition coefficient is a measure of the molecule's lipophilic character. This depends also on the degree of ionization. Therefore the partition coefficient and dissociation constant (pK) in preformulation are important because they may be an indication of a drug substance's absorption, distribution and elimination characteristics;

(c) Equilibrium solubility and pH-solubility profile. These studies must be carried out in buffers at pH 1, 3, 5, 7, 9 and 11, in 0.9% sodium chloride solution and distilled water;

(d) Dissolution rate data. This parameter provides some insight into the potential in vivo absorption characteristics of a new drug entity and depends on its chemical form (acid, base, different salt forms etc.), crystal form, particle size, surface properties etc. Therefore the dissolution rate of the drug as a fraction of these parameters must be determined. It is recommended that the methods outlined in official compendia and other experimental methods of determining the dissolution rate should be used;

(e) Stability. The effect of temperature, light and humidity on the drug solid state must be determined. In addition, stability of the drug's solution (the effect of solvent, pH, light, oxygen etc.) must be determined. The temperatures to be used are 25°, 50°, 60° and 70°C, and the pH values are 1, 3, 5, 7, 9 and 11;

(f) Physico-mechanical properties. The bulk and tap density and compressibility of the substance should be determined;

(g) Compatibility. The compatibility (interaction) with important excipients must be determined. The excipients chosen will depend on the dosage form. Examples of excipients to be tested are alginic acid, ascorbic acid, Aviecel, calcium acetate, phosphate or sulfate, corn starch, lactose, magnesium stearate, PEG 4000, PVP, sodium bicarbonate lactose etc. These studies must be carried out with various ratios of excipient drug.

The next step in preformulation is to analyse the data obtained from the above-mentioned studies (a-g) and to develop various formulations. These formulations will be tested for dissolution and stability as outlined above.

B. Pilot plant scale-up and trouble-shooting

The basic components of the pilot study are formula and equipment evaluation, stability and uniformity of product, evaluation of raw materials, evaluation of process, and optimization of physical layouts.

To operate at maximum efficiency, this unit must represent a transition between research and production, and therefore accommodate the needs of both. Because production involves many departments, it would be impractical to provide specific recommendations. Rather, the statement at the beginning of this paragraph should be the basic policy and modus operandi of the unit.

C. Biopharmaceutics and pharmacokinetics

Some drugs and drug products may require investigations using only physical model; others may require both physical and animal models, and often all three models, physical, animal and human, may be needed. Requirements for physical models such as disintegration and dissolution will be met by the studies performed in the Preformulation Unit described above. The correlation between these studies and the in vivo findings will be carried out by the Biopharmaceutics and Pharmacokinetics Unit. Therefore the research activities of the Biopharmaceutics and Pharmacokinetics Unit may be classified in two major categories, namely animal studies and human studies. An outline of the methodologies in each category will be presented below. However, it should be emphasized that facilities and equipment will be needed only for the first category of research, whereas the activities carried out under the human studies category will be limited to protocol drafting, study assignment, monitoring and evaluation.

Animal studies

The purpose of these studies is to provide important information on the drug itself and on the drug preparation. The first type of information, which is basic, pertains to the fate of the drug in the body, such as its effect on protein binding, its absorption from the site of administration to the general circulation, the physiological distribution of the drug and its concentration in various tissues and organs, the pathways and mechanisms of its metabolism and excretion, the quantitative aspects of the processes of absorption, distribution and elimination (i.e., pharmacokinetics), and the effect of diseases and environmental and chemical substances on the pharmacokinetic parameters. Studies on the drug preparation will provide information primarily on the absorption parameters of the drug from the specific dosage form. The choice of the experimental animal will depend on its similarity to man in handling the drug. After the experimental animal is determined, the methodologies to be employed will depend on the drug, the animal and the aims of the study. Therefore, it is not possible to outline a specific methodology for such a study. The decision must be made on a case-by-case basis.

Studies designed to provide information on the absorption characteristics of the drug alone or in a specific dosage form from the point of view of its administration may be performed using one or more of the following techniques described in the available literature:

Everted gut preparation. This technique was used by many workers to study the active and passive transport processes of substances, to elucidate the effect of excipients of pharmaceutical preparations on the permeation of the drug, to investigate the effects of complexing agents, surfactants, electrolytes, glucose and other substances on drug absorption etc.;

In situ preparation. This technique involves either the perfusion of part of the intestine of the animal or a closed loop, and is useful in determining the effect of many physiological parameters such as pH, gut metabolism, blood flow, and other factors relating to the absorption of drugs.

Isolated tissues and organs. These preparations are used for the study of the absorption of specific drugs or dosage forms such as ointments (skin), aerosol (lung), eye drops (eye) etc.

Intact animals. Large animals (dogs, cats, small pigs and monkeys) may be used to assess the bioequivalence or the bioavailability of intact dosage forms, whereas smaller animals (mice, rats and guinea pigs) can be used to study the relationships between the physico-chemical variables of the parent drug (salt form, particles size etc.), dissolution rates, and pharmacologic effects. For example, excellent correlations between dissolution rates of various formulations and LD_{50} values have been shown for amphetamine, etryptamine, benzphetamine and acetaminopen.

Human studies

Pharmacokinetic studies in humans must be carried out if the drug is a newly developed substance. However, these studies must be carried out under extremely carefully controlled conditions and after every measure for the safety and welfare of the participants has been taken. With respect to *in vivo* bioavailability/bioequivalence, the basic principle is that no unnecessary human research should be done if an appropriate animal model exists and correlation of results in animals and humans has been demonstrated. In some situations, an *in vivo* bioavailability/bioequivalence study in humans may preferably and more properly be done in suitable patients. Critically ill patients should not be included.

Criteria for bioavailability/bioequivalence studies

Subject selection. Normal healthy adults ranging in age from 20 to 40 years who are within 10% of their ideal body weight should be used. Individuals with a history of gastrointestinal, liver, or kidney diseases or any other significant organ abnormality or disease should be excluded. The subjects should be given a thorough physical examination and appropriate pathology laboratory tests, including hemoglobin, hematocrit, WBC, platelet estimate, differential count, BUN, serum alkaline phosphatase, serum total bilirubin, SGPT, SGOT, fasting blood sugar, serum creatinine, urine specific gravity, pH, albumin, sugar, bile, RBC, WBC, and granular casts.

Protocol of studies. This depends on the drug to be tested. In general, however, blood samples should be collected over a period of three to four half-lives of the drug or until its levels are no longer detectable. Urine must be collected over a period of at least seven drug half-lives. Other biological specimens such as faeces and bile should be collected, if possible.

Drug dosage. Single or multiple doses of the drug may be used.

Statistical design. The study should be carried out in a cross-over fashion provided a period of at least 10 half-lives is allowed between drug administrations.

Data analysis. The areas under the blood, plasma, or serum concentration-time curves (AUC) may be compared. Alternatively, urinary excretion data may be used in certain cases. In addition, the maximum blood, plasma, or serum drug concentrations (or urinary excretion rates) and the time of achieving these concentrations should be compared.

It should be cautioned that there are many additional requirements and pitfalls in bioavailability/bioequivalence studies which may invalidate these studies. These must be taken into account in the design and implementation of these studies.

D. Analytical laboratory (biological fluids)

The techniques to be employed are so diversified and complex that a review of even the most basic ones cannot be covered in this report. Assay methodologies for each drug could be found in the existing literature or developed in the laboratory. The laboratory must meet the new Good Laboratory Practice regulations which were issued recently by the FDA.[2/]

2/ Federal Register, 41, 51206 (1976).

IV. ORGANIZATION AND PERSONNEL

The purpose of this section is to develop a working model for the smooth operation of the Department of Pharmaceutics within the Research and Development Division and in relation to other divisions of Teva-Assia-Zori. The working model is by no means complete as far as the personnel requirements of each unit are concerned, since it is not accompanied by a specific timetable and is probably subject to budgetary considerations.

The Department is to be directed by a research-oriented, scientifically-qualified and administratively-competent person who will initiate, monitor and implement its specific goals and appoint the key personnel in each unit. This person should possess a Ph.D. in pharmaceutical sciences and have extensive experience in industrial pharmacy, an established record in research, initiative and direction, and a demonstrated aptitude for administration. The Director will report to the Head of the Research and Development Division, but will be a senior member of the policy-making council within the Division, and also of the policy-making, operations, production and marketing councils of the company, as deemed necessary.

Each unit will have a senior scientist-group leader who will ensure its smooth operation and be responsible to the Director of the Department. The Director will appoint task force or project committees which will co-ordinate all activities relating to a specific drug product and ensure the smooth handling and transfer of the various tasks of the project between the units and among the other divisions. The qualifications of each group leader will depend on the scope and objectives of each unit as described above. For example, the Preformulation Unit would be headed by an individual possessing a Ph.D. in physical pharmacy with additional training in industrial pharmacy. The Pilot Plant Scale-up Unit would be better directed by a high-ranking mechanical engineer with training or interest in the biomedical sciences. The group leader of the Biopharmaceutics and Pharmacokinetics Unit would be a person who has a Ph.D. and demonstrated experience in these areas, while the Analytical Laboratory (biological fluids) is to be directed by a Ph.D. graduate in analytical chemistry.

It is anticipated that each unit will consist of one or more scientists who will report directly to the senior scientist-group leader, but may serve

as member of the various project task forces as deemed necessary. Scientists with special qualifications should be included in these units. For example, the Preformulation Unit should be predominately composed of pharmacists, the Pilot Plant Scale-up Unit of engineers, the Biopharmaceutics and Pharmacokinetics Unit of pharmacists or pharmacologists in addition to a statistician and computer programmer, and the Analytical Laboratory (biological fluids) of chemists. In addition, each unit will include a number of technicians and assistants.

V. FACILITIES AND EQUIPMENT

All facilities should be equipped with laboratory benches and their air, gas, electricity, vacuum, pressure, distilled water and other requirements met in accordance with the Good Manufacturing Practices Regulations[6/]. Laboratory and office allocations are difficult to predict and obviously depend on availability. However, each unit (except the Pilot Plant Scale-Up Unit) should consist initially of a 150-200 m^2 laboratory and a 12-15 m^2 office. A special facility for housing animals should be provided.

In addition to the usual equipment present in most laboratories (balance, pH meters, glassware, centrifuges, waterbaths etc.), the following special equipment would be required in the units:

Preformulation. Optical microscope, Coulter counter or Hiac counter, homogenizer, micromizer, blender, differential thermal analyser, diffusion reflectance spectroscope, differential scanning calorimeter, thermogravimetry analyser; research models for tablets, capsules, suppositories, ampules, drying, pan coating, liquids, ointment machines, dissolution apparatus etc.

Pilot Plant Scale-Up. Most of the research efforts of this unit should [illegible] at the production facilities and only few minor pieces of [illegible].

Biopharmaceutics and Pharmacokinetics. Animal surgery tables and instruments, digital and/or analog computer instruments or hook-ups, equipment for drug administration (infusion pumps, cannulae etc.) equipment for biological specimen collection and preservation etc.

Analytical Laboratory (biological fluids). Thin-layer, gas, liquid, nitrogen and high-performance chromatrographs; spectrophotometer, spectrophotofluormeter, liquid scintillation counter, equipment for extraction, clean-up, and solvent evaporation; shakers, refrigerated centrifuge etc. In the long term, a mass spectrometer may be acquired.

6/ See footnote 1.

REFERENCES

1. Federal Register, 36, 133 (1971).

2. FDA's Bioavailability/Bioequivalence Requirement, The Gold Sheet, 10, No. 12 (1976).

3. G. Levy,"Bioavailability, Clinical Effectiveness, and the Public Interest", Pharmacology 8, 33 (1972).

4. Federal Register, 41, 51206 (1976).

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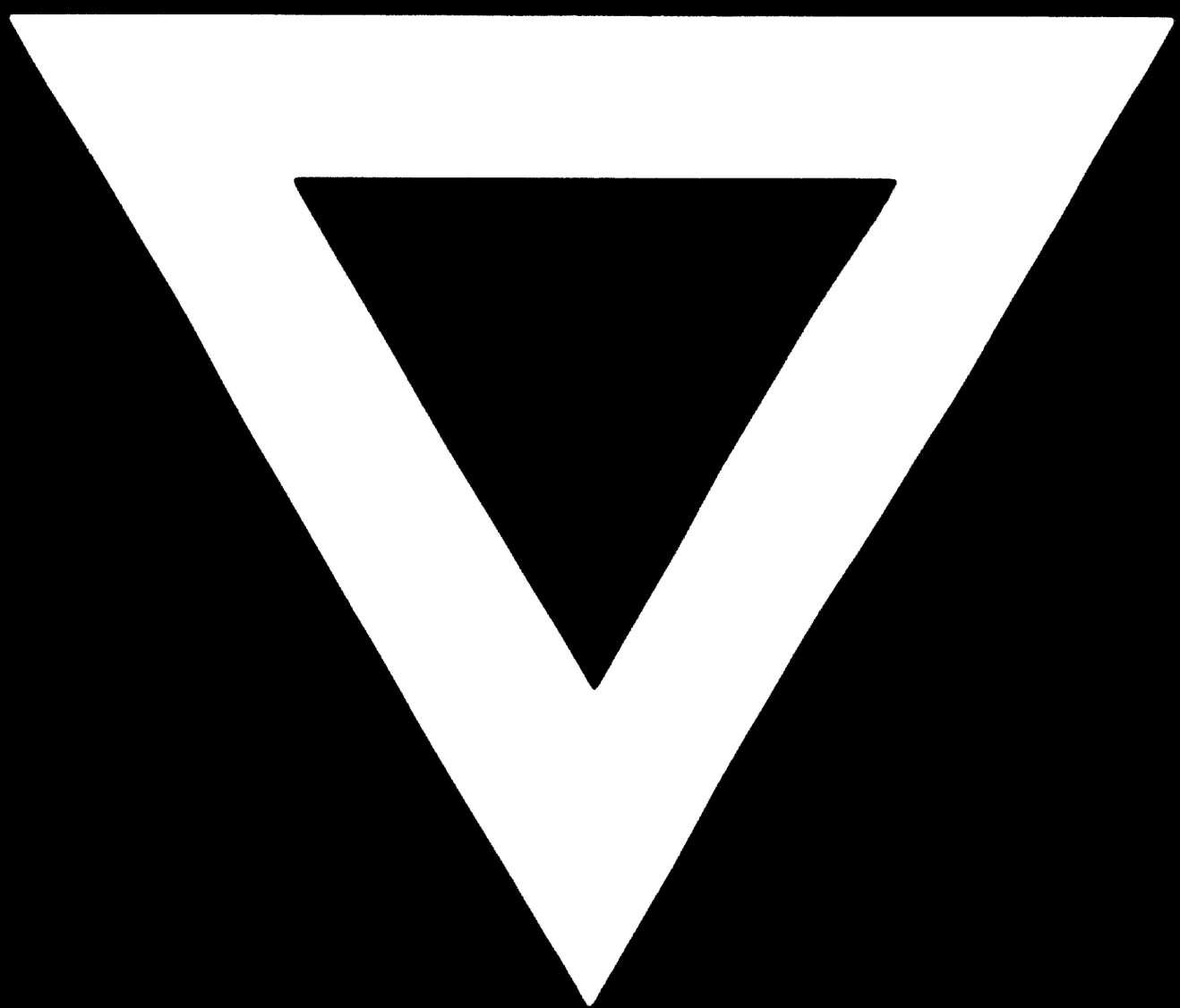

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