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UNITED NATIONS INDUSTRIAL DEVELOPMENT ORGANIZATION
Vienna International Centre, P.O. Box 300, 1400 Vienna, Austria
Tel: (+43-1) 26026-0 · www.unido.org · unido@unido.org

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ESTABLISHMENT OF A PHARMACOLOGICAL INSTITUTE IN ISRAEL *

DP/ISR/73/010

ISRAEL

Technical 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 Nadim Kassem,
senior pharmacologist

United Nations Industrial Development Organization
Vienna

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Explanatory notes

The following abbreviations have been used in this report:

BP	British Pharmacopea
CDC'S	Clinical Data Co-ordinators
FDA	Food and Drug Administration
HEW	Health Education and Welfare
IND	Investigational New Drug
MRA	Medical Research Associate
NCRD	National Council for Research and Development (government agency in Israel)
NDA	New Drug Application
PSR	Professional Services Representative (Detailman)
R&D	Research and Development Division
USP	United States Pharmacopea

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SUMMARY

Among the Divisions of TEVA Pharmaceuticals, the Chemistry Division is the only one that has a Research Department. The Pharmaceutical Division is well developed to service the present needs of the Corporation. However, no Pharmacology Division or Toxicology Department exists, and the Medical Department functions are "advisory" in nature and "service" at best, for the needs of the other departments, primarily those of Marketing. The Medical Department is only occasionally and minimally engaged in clinical research primarily because of the nature of the corporate setup, where either "generic" products, or products acquired under license from original manufacturers, are marketed. No original molecular structures have been synthetized, tested, approved and marketed by TEVA.

Being aware of this drawback of not having Original Research, the management of TEVA recognizes the necessity for establishing a division for Research and Development, and the fact that a Pharmacological Institute is the cornerstone in developing such a Division; the management of TEVA Pharmaceuticals is committed to develop the institute beyond the termination of UNDP support.

Bearing in mind that the ultimate objective of the Pharmaceutical Industry is the development of safe and effective drugs, and accepting the premise that a Pharmacological Institute is in the making, it is recommended that a Medical Department be established within the Research and Development Division of the Corporation. It is further recommended that the Medical Department be responsible for Medical Research, Medical Information, Computer and Information Sciences and Health Registration.

The recommended activities of each functional unit of the Medical Department are described in some detail in the body of this report.

INTRODUCTION

1. Project Background

Teva Pharmaceutical Industries, Ltd. is a conglomerate comprising ASSIA-ZORI (Private company in Petah-Tiqvah), TEVA (a public corporation in Jerusalem), ASSIA-MA'ABAROT (a veterinary subsidiary of ASSIA 50% of which is owned by Kibbutz MA'ABAROT), S.L.E. (a marketing company in Tel Aviv with offices in Haifa and Jerusalem) and PAKA - a yeast fermentation plant. In addition, a center for food additives and animal feeds in South Africa is owned by the Corporation.

Until 1970-71, the Corporation functioned as separate companies without a unified organization. It was in 1972 that a recommendation to reorganize towards centralization of functions took place, and in February of 1973 the first "centralized" Division, the Pharmaceutical Division was established. Upon the success of this division, the second "centralized" division of chemistry was established in 1974; and lastly, a division for Research and Development was started in October 1976, and is planned to be fully established by the end of 1977. Thus, 1977 is a turning point in the organization and development of the Corporation.

2. Pharmacology Institute

The management of the Corporation has long recognized the need for pharmacological research that would enable pharmacological screening for possible activity of new compounds within the pharmaceutical industry. However, since the industry was not developed sufficiently nor had the financial resources or the scientific personnel needed for such an expensive and sophisticated project. the National Council for Research and Development (NCRD) (a government agency in Israel) proposed in 1971-72 to reorganize the existing

Pharmacological Institute of Israel in such a way that the Pharmaceutical Industry participates in its administration, together with the NCRD and the Ministry of Commerce and industry. Nevertheless, and due to the limited resources of the industry then, and the costly investment needed, this proposal was not launched. However, the last few years proved that TEVA Pharmaceutical industries, known then as "ASSiA-TEVA", has the growth potential and the organizational capacity that prompted its management to be willing to make the commitment to establish the Pharmacologic institute within its Research and Development Program. Thus, the government of Israel recommended that the Pharmacological institute be set up and organized by TEVA Pharmaceutical Industries with guidance from scientific experts from abroad.

OBJECTIVE OF MISSION

In accordance with the job description DP/ISR/73/010/11-0/04 (32.1) provided by Dr. Nathan Back, the duties of the Senior Pharmacologist Consultant call for working under the direction of and in cooperation with the UN Scientific Advisor to advise on the coordination of all activities relating to clinical studies, medical affairs and drug information; to help design protocols for all phases of clinical pharmacology and clinical research; to help design and monitor pharmacokinetic studies in both normal volunteers and patient populations; to advise in establishing training program on current therapeutic agents for physicians and drug detail personnel; advise in preparing drug medical information for patent filing, package labels and inserts and for promotional purposes; advise in the preparation of New Drug Application for submission to the regulatory agencies, and advise in setting up consultative services to all divisions of the company.

ACTIVITIES

Upon my arrival in Israel, lengthy meetings were held by Dr. Back for briefing, orientation and review of the project. Other meetings were held with Mr. Ya'acov Saphir, Director of International Affairs, NCRD; Professor Andre DeVries, Director of R&D and key personnel of TEVA Pharmaceutical Industries, Ltd. Furthermore, meetings were held with Dr. Weissenberg of the Regulatory Agency, the Ministry of Health and with Professor Nir of the Hebrew University School of Pharmacy who serves as a scientific advisor to the Regulatory Agency.

FINDINGS

Scope of Activities

Since the objective of my mission is concerned primarily with the medical and the human clinical pharmacological aspects of the project, this report will address those findings pertinent to these aspects.

1. The Corporation manufactures over 500 products, comprised of medicinals, veterinary preparations and chemicals. Medicinals include drug preparations, vaccines for human use, and diagnostics and amount to about 95% of all corporate products and over 50% of the drug market in Israel.
2. The ethical products sold in Israel or exported for sale abroad are either duplicates of products produced abroad or based on materials imported and formulated or repackaged in Israel with minor variations.
3. Since the R&D Division is only now being organized, it is obvious that TEVA could not have produced any original molecular structures that were synthetized, tested, approved and marketed by TEVA Pharmaceuticals.
4. The marketed products are either "generics" formulated and produced in accordance with the BP* or the USP**, or products acquired under license from original manufacturers.

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*BP = British Pharmacopea

**USP = United States Pharmacopea

5. The Chemistry Division is the only division that has a Research Department where three chemists are engaged full-time in Chemical Research. The thrust of their research is in "molecular modifications" of known active molecules.
6. Pharmaceutical Production is well developed and the Corporation has the capability of producing sterile and non-sterile products, solutions, suspensions, capsules, tablets, suppositories, ointments, creams, etc.
7. The Pharmaceutical Development Department is engaged primarily in servicing the Pharmaceutical Production and Chemical Production Departments by ad hoc solutions of acute problems. Only minimal amount of formulation research is done.
8. TEVA has no Pharmacology Division: no animal pharmacology and no "screening" for pharmacological activity. Screening is done in part by the Pharmacology Departments of the Medical Schools and School of Pharmacy in Israel, but mostly abroad.
9. TEVA has no Toxicological Department.
   As a matter of fact there are no Pharmacological or Toxicological institutes in Israel capable of servicing the needs of the Pharmaceutical industry.
10. The "Medical Department" - There are two physicians acting as advisors to Corporate Management on "pharmaceuticals" on a part-time basis. Both have recently retired.

A third physician heads the Department;

a. He reports to the Director, Pharmaceutical Division.

b. His functions and responsibilities are:

1. Scientific negotiations with other Pharmaceutical companies.

2. Liaison with the Regulatory Agency.

3. Training of detail personnel.

4. Preparation of promotional materials.

5. Occasionally sets up clinical studies, as required by the Regulatory Agency.

II. Medical Information and Regulatory Affairs - These functions are carried out by another department in the Pharmaceutical Division which consists of a pharmacist and an associate.

A. Medical Information

With the cooperation of the Director of the Medical Department, the following functions are performed:

1. Basic training of detail personnel

2. Preparation of a brochure (prospectus) containing information about drugs for physicians

3. Responses to physicians requesting information about the various drugs, and

4. Literature search and follow-up on reports of side effects.

B. Regulatory Affairs and "Drug Registration"

1. Information on all new drugs submitted to the Regulatory Agency of the Ministry of Health for registration and approval for marketing in Israel. These drugs are acquired under license from foreign Pharmaceutical Companies, and have been approved for human use in the country of origin.

Registration is in essence the submission to the Regulatory Agency, of the pre-clinical and clinical data obtained from the Licensing Foreign Company after editing and re-organizing these data according to a specified format distributed by the Regulatory Agency.

2. Re-registration - All marketed drugs are required to be re-registered every five years. Specific guidelines are not available for re-registration.

12. The Regulatory Agency and Regulations for Drug Registration

Specific and detailed guidelines for carrying out clinical research in Israel do not exist. Instead, the requirements for registration of new drugs are, in my opinion, minimal and the Agency is usually satisfied with summaries of pre-clinical and clinical data the company secures from the Licensing manufacturer. No "raw data" are required. The new drug should be "safe and effective" and have some advantages over marketed products intended for use for the same indications.

These summaries are submitted to the Agency in a specific format and constitute a New Drug Application (NDA). The Agency distributes copies of this NDA to members of an Advisory Committee who review the material contained in it and then meet and submit their recommendations to the Agency.

There are several Advisory Committees to the Regulatory Agency: those who review new molecules and others who review "old" molecules. Moreover, there are different advisory committees for drugs intended for use in the different medical disciplines: gynecology, medicine, oncology, psychotropics, radiopharmaceuticals, etc.

13. Clinical Trials

Occasionally, the Agency will require that one or more clinical studies and/or clinical pharmacological studies be conducted in Israel. A physician investigator should submit an application to the Agency and secure its approval before he starts his study.

These studies are invariably undertaken in hospitalized patients although they are mainly of the "Phase III" type of clinical trials and in general need not be done in hospitalized patients.

In principle "Phase I" and "Phase II" clinical trials are permitted if the animal pharmacological and toxicological data are satisfactory. As a matter of fact, there is a "Committee for Clinical Trials" chaired by the Director General of the

Ministry of Health whose responsibility is to review and approve protocols for such trials. However, this committee is not active since no such trials have been undertaken.

One important item that is worth mentioning here is the patient's informed consent. On the one hand, the representatives of the medical department of the company say there is no such requirement for an informed consent; moreover, the investigator is the person who is responsible for the study and for the welfare of the patients since the approval to set up the study is given to the investigator not to the sponsoring company. On the other hand, the representatives of the Regulatory Agency say informed consent is required and that legally an "institutional Review Committee" should approve the study before the investigator starts it. The Agency seems to accept "the word" of the investigator and/or the Director of the Hospital in which the study will be done, that an "informed consent" will be obtained.

14. Research and Development Division (R&D)

The management of TEVA recognizes well the necessity for establishing a division for research and development; and indeed has committed itself to accomplishing this goal.

The management also recognizes the fact that the Pharmacological Institute is the cornerstone in developing the R&D Division and accordingly is committed to develop the Institute beyond the termination of UNDP support.

A detailed plan for developing this division is expected to be finalized by the end of 1977. This plan will, among others, address the problems of experimental pharmacology and toxicology and the establishment of a more active medical department.

I have confirmed this commitment to establish scientifically sound R&D programs during my meetings with the directors of the three divisions and the Director General of the Corporation.

RECOMMENDATIONS

Accepting the premise that,

a. A Pharmacology Progem is in the meking,

b. Toxicology will be cerried out, and that

c. Pharmaceutical formulations, dosage forms, stabllity, quallty control, etc. are developed,

and, bearing in mind that,

the ultimate objectlve of the Pharmaceutical Industry is the development end marketing of safe and efficecious drugs,

It is recommended that,

1. A MEDICAL DEPARTMENT BE ESTABLISHED WITHIN THE RESEARCH AND DEVELOPMENT DIVISION OF TEVA PHARMACEUTICAL INDUSTRIES, LTD., AND THAT

2. the primary responsibllitles of this department be carried out by the following major units:

I. MEDICAL RESEARCH

II. MEDICAL INFORMATION

III. COMPUTER AND INFORMATION SCIENCES

IV. HEALTH REGISTRATION

Rationale for and Specific Functions of the Units

1. MEDICAL RESEARCH

The development of a "new drug" starts in the Chemistry Lab and passes through several stages (animal pharmacology and toxicology) before its initial administration to man.

a. It is the responsibility of "Medical Research" to assess the adequacy of the pre-clinical information including laboratory animal studies (pharmacological and toxicological data), that will lead to the conclusion that the "new drug"* is reasonably safe to initiate clinical investigations in man. Pharmacologic actions in animals likewise elicit many effects that are predictive of similar effects in man.

Animal studies of drugs, however, cannot elicit some toxic effects that are observed in man. Moreover, the early stages of clinical investigation may not predict toxic manifestations that appear in expanded clinical trials. Such limitations necessitate the combined judgement of expert pharmacologists, toxicologists, and clinicians to ensure the orderly progression of animal studies in relation to both the initiation and the continuation of clinical investigation.

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*See Appendix I for definition of a "new drug".

b. It is the responsibility of "Medical Research" to carry out the investigational studies of the new drug in man in order to learn about its pharmacological action, its toxic effects and its general usefulness as an addition to the therapeutic armamentarium of the physician to combat disease and advance the general health and welfare of the public.

The Food and Drug Administration (FDA), (a branch of the Department of Health, Education and Welfare (HEW) of the government of the U.S.) has published general guidelines dealing with the kinds of pre-clinical toxicity studies that could be used to support the different phases of clinical investigation, as well as a new drug application (NDA).

As shown in the following table, FDA's recommendations concerning the length of animal toxicity studies are based, in large part, on the proposed duration of a new drug's use in man. These recommendations pertain to new drugs in general, but are not applicable to a new oral contraceptive or a new estrogen or progestogen, toxicity studies of which are required to be of much longer duration.

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.

Furthermore, certain requirements pertaining to the effect of the "new drug" on the Reproduction Systems of animals should be fulfilled and assessed by Medical Research prior to initiating studies in man. A general outline of the "Animal Reproduction Studies" can be found in Appendix II.

Thus, Medical Research has the scientific responsibility and the ethical duty not only to decide (on the basis of its assessment of the pre-clinical data) whether a new drug meets certain criteria that show it to be reasonably safe to initiate its administration to man, but also to decide (on the basis of the clinical data it secures) whether this drug is scientifically, ethically and legally a safe and effective drug.

To carry out these responsibilities the Medical Research Department should set up clinical research studies in stages or phases. In the United States, the submission to the FDA of a "Notice of Claimed Investigational Exemption for a New Drug "* is a prerequisite to clinical testing of an investigational new drug.

A general outline of the componant parts of an IND can be found in Appendix IV. This comprehesive document is appended as a guideline to shed some light on the FDA requirements, and the Medical Research Departments' responsibilities in the U.S.A.

It is obvious that the Medical Research Department recommended to be developed at TEVA should abide by the requirements and the guidelines of the Regulatory Agency in Israel, which might not necessarily be equivalent to those of the FDA.

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*Through common usage, this claimed exemption notice has come to be known as an "IND". See Appendix III.

THE INVESTIGATOR'S BROCHURE

Prior to the initial human studies of a drug, an "Investigator's Brochure" should be prepared and must be based, of course, on pharmacologic and toxicologic data from the preceding animal investigations. In this original version, the brochure should draw attention to possible side effects foreshadowed by the pre-clinical studies, and to known side effects and contraindications of related drugs.

Comprising a straightforward summary of what is known about a new drug's safety and possible therapeutic usefulness, the "Investigator's Brochure" is considered a form of labeling to be furnished to each investigator. Its content must be in harmony with the submitted data from pre-clinical studies and any earlier clinical studies or usage. The brochure should be informative particularly with respect to relevant hazards, contraindications, precautions, and adverse reactions suggested by prior investigations or knowledge. Further, it should not purport or imply that the safety or the effectiveness of the investigational new drug has been established.

As new information accumulates from the human studies, the Investigator's Brochure should be updated to include all such information. It is the sponsor's responsibility to ensure that new investigators are fully informed of the results of such studies.

The Investigator's Brochure ordinarily should present its information in substantially the following order:

- DESCRIPTION (Best Available Descriptive Name, Including Chemical Name and Structure; Dosage Form)
- HISTORY OF NEW DRUG
- PHARMACOLOGIC STUDIES
- TOXICOLOGIC STUDIES
- ACTIONS
- INDICATIONS FOR INVESTIGATIONAL USE
- CONTRAINDICATIONS
- PRECAUTIONS
- ADVERSE REACTIONS (Or Side Effects Suggested by Pre-Clinical Studies)
- DOSAGE AND ADMINISTRATION
- CLINICAL STUDIES
- BIBLIOGRAPHY

In the case of a new drug for which there is no information applicable to one of the headings outlined above, that heading should, of course, be omitted from the brochure.

PHASES OF CLINICAL INVESTIGATION

General Considerations

A. Clinical Pharmacology

This is divided into two phases:

Phase I starts when the new drug is first introduced into humans (usually, normal volunteers) to determine toxicity, absorption, metabolism, excretion, pharmacologic action, preferred route of administration and safe dosage range.

This phase of clinical investigation involves a comparatively small number of subjects. It is generally conducted under carefully controlled circumstances by physicians trained in clinical pharmacology. For phase I studies, the proposed investigational plan may allow considerable flexibility.

Early phase I investigation, including the initial introduction of the new drug into man, consists of single-dose and multiple-dose studies, usually in normal volunteers, to determine levels of toxicity. Subsequent phase I investigation may consist of dose-ranging studies in patients for safety and, in some instances, for intended pharmacologic effect. With some new drugs, the initial introduction into man is more properly done in selected patients with the disease to be treated.

The normal volunteers and the patients should be adults, but not females who are, or are at risk of becoming pregnant. Whenever feasible, all subjects and patients should have been off previous drugs for at least 2 and preferably 4 weeks. They should

be hospitalized or in other settings permitting close supervision. To screen out individuals with medically significant abnormalities, pre-treatment physical examinations should be performed, together with appropriate laboratory tests (CBC, including platelet estimate, BUN, or serum creatinine, FBS or 2-hour postprandial blood sugar, SGOT, alkaline phosphatase, serum billrubin direct and indirect, urinalysis, and ECG).

With single-dose studies, post-treatment physical examinations and appropriate laboratory tests should be performed to assure that there are no residual effects of the drug. Multiple-dose studies should be double-blind and placebo-controlled, physical examination should be done during and after the treatment period, and all laboratory tests should be repeated at intervals frequent enough to protect the experimental subjects. The duration of drug administration in the multiple-dose studies is dependent on the anticipated therapeutic use; if the latter is likely to be chronic, the duration of drug administration usually is at least 4 to 6 weeks.

Pharmacokinetic and metabolic studies of a new drug, in whatever stage of investigation these are performed, are considered to be phase 1 studies. Some, such as absorption studies, are carried out in early stages of the investigation, while others, such as efforts to identify metabolites, are ordinarily not done before phase 2 or 3. Early studies of blood levels, as a measure of drug absorption, are performed with single doses and with multiple doses, using available techniques. Methods for determining blood

levels of new drugs, using non-tagged compounds, commonly are not developed until phase 2 or 3 of clinical investigation is already underway.

As a general rule, outpatients should not be used as initial recipients of an investigational new drug. Exceptions, however, are exemplified by the following:

1. A drug that has been extensively studied abroad.
2. A combination of well-known drugs.
3. A drug that has been previously well-studied for other indications.
4. A drug like a corticosteroid or an estrogen having well-known pharmacologic activity.
5. A drug already marketed by another manufacturer.
6. A new formulation of a known drug.

Phase 2

This phase consists of initial, well-controlled trials in a limited number of closely monitored patients (seldom more than 100-200) to determine the drug's efficacy and relative safety. The general outline of these phases should (i) identify each investigator and the institution where the study will be performed, (ii) indicate the maximum number of study subjects, and (iii) estimate the duration of the specified phase of investigation. A detailed protocol of study, together with the case report form to be used, should accompany the general outline.

Phase 2 comprises controlled clinical trials designed to determine a new drug's effectiveness and safety. These controlled trials are conducted by investigators who are considered experts in the area of the particular disease for which the new drug is intended, or in the evaluation of drug effects on the disease process.

Women of child-bearing potential should be excluded from early phase 2 studies, unless they have been institutionalized long enough to assure a non-pregnant state. In late phase 2 studies, however, women of child-bearing potential may be included, provided that Segment II and the female part of Segment I of the animal reproduction studies recommended by FDA have been satisfactorily completed.

Patients selected for early phase 2 studies should be free of concomitant disease and should not be receiving concomitant medication, if either of these would interfere with an assessment of the investigational drug's effectiveness and safety. In later phase 2 studies, it may be appropriate to include some patients with concomitant disease who are on concomitant medication, since such patients are likely to be representative of parts of the population that would receive the investigational drug after approval of its marketing. Ordinarily, no more than 100-200 patients are treated with an investigational drug during phase 2, a similar number receiving a placebo or a control medication.

The duration of the clinical trials varies depending on the nature and the safety of the investigational drug, but should be compatible with the duration of the prior animal toxicity studies. The nature and the safety of the drug also govern how often patients should be seen and laboratory tests performed in phase 2 trials. Generally, patients should be seen by the investigator at least weekly for the first 2 to 4 weeks (the length of time depending on the number and the results of phase 1 studies). Routine "safety" laboratory tests should be performed at frequent intervals (platelet estimates being included in CBC's). Ordinarily, patient visits should then be bi-weekly for another 6 to 8 weeks. After 3 months, patients may be seen at monthly intervals for 2 or 3 months, and at bi-monthly intervals thereafter.

When an investigational drug or a control drug is altered significantly in manufacture or use of excipients, in order to accommodate a single-blind or double-blind trial, blood level studies (or urinary excretion studies, if blood level studies are not feasible) should be done to ensure that the alteration has not materially affected the drug's absorption or excretion. The mere placing of a tablet in a gelatin capsules as a means of blinding would not necessitate such bioavailability studies.

For a systemically active drug that is administered chronically, complete ophthalmologic examinations (pre-drug and post-drug) should be done in a representative number of patients who are followed on the drug for 6 or more months. For systemic drugs that are given for shorter periods, the possibility of delayed effects on the eye should be considered.

B. Clinical Trials

Phase 3

When the data obtained in phase 2 studies offer reasonable assurance of a new drug's safety and effectiveness, a proposal for the phase 3 program of expanded clinical trials is in order.

Phase 3 clinical trials are intended to gather further evidence of a new drug's effectiveness and safety, and to define its adverse effects. As such, these expanded trials should consist mainly of controlled trials. If uncontrolled, even extensive clinical trials ordinarily carry little weight in the assessment of a new drug. Patients should be seen and laboratory tests performed at intervals dictated by the type and the safety of the new drug.

In addition to accomplished clinical investigators, practicing physicians less experienced in the evaluation of new drugs may serve as investigators in phase 3. A large number of patients may be treated by different physicians in this phase, so that a broad background of experience with an investigational drug is thus acquired.

As in late phase 2 studies, some patients with concomitant disease and on concomitant therapy may be included in phase 3 trials, since such patients are probably representatives of certain portions of the population that would be treated with the new drug following its

approved marketing. Women of child-bearing potential also may be included in phase 3 trials, provided all three segments of the animal reproduction studies have been satisfactorily completed. Fetal follow-up should be carried out in women who become pregnant while receiving an investigational drug.

Details concerning protocols for clinical investigation of new drugs, the responsibilities of the sponsor for filing an IND, and the responsibilities of the clinical investigators monitoring clinical investigations are appended to this report in Appendix V.

EVALUATION OF INVESTIGATIONAL DRUGS IN CHILDREN

The determination of a safe dose of a drug for infants and children cannot be made by mere extrapolation from the adult dose. Moreover, there are, as yet, no established methods of toxicologic study in animals that will reliably forecast the potential toxicity of a new drug for the human infant, although some information is obtainable from pre-clinical studies comparing a drug's effects in newborn and in adult animals.

New drugs with a potential for use in infants and children should be evaluated in these age groups, but such investigations must be approached with considerable caution. Once a drug has been shown to be safe for the human adult, and no evidence of toxicity has been found in suitable pre-clinical studies, the cautious evaluation of the drug for the intended indication (that is, phase 2 investigation) may appropriately be initiated in older children. Evaluation of the drug in young children and in infants should be delayed until evidence of safety has accrued in the studies involving older children. The use of investigational drugs in <u>normal</u> infants and children (that is, phase 1) is clearly not defensible.

Adequate and well-controlled studies in children are likely to be difficult and sometimes actually impossible due to the lack of adequate methodology, the problems of patient consent in such studies, the paucity of pediatric investigators able and willing to evaluate new drugs, and the lack, in some instances, of adequate patient populations. When studies of a new drug are performed in pediatric patients, it may take a good deal longer to gather the evidence of the drug's safety and effectiveness than it did when the evaluation was carried out in adults.

THE NEW DRUG APPLICATION (NDA)

A New Drug Application (NDA), for approval to market a drug intended for human use, may properly be submitted to the Regulatory Agency after clinical investigation of the drug has progressed through phase 3, and the sponsor is convinced that the drug is safe and effective under specified conditions of use. The usual NDA consists of a completed NDA form, the proposed labeling, and literally thousands of pages of supportive data. The supportive data in the NDA include, among other items, full accounts of all pre-clinical and clinical investigations of the drugs, and full descriptions of the manufacturing methods, facilities, and controls.

Component parts of an NDA are appended to this report in Appendix VI.

Phase 4

Sometimes a new drug is released for marketing, with the provision that additional clinical studies must be carried out with the approved drug following its marketing. The term "phase 4" is used to designate such post-marketing clinical trials.

The phase 4 clinical studies that FDA may require are of these types:

1. Additional studies to elucidate the incidence of adverse reactions, to explore a specific pharmacologic effect, or to obtain more information of a circumscribed nature.

2. Large-scale, long-term studies to determine the effect of a drug on morbidity and mortality.

3. Additional clinical trials, similar to those of phase 3, to supplement pre-marketing data when it has been deemed in the public interest to release a drug for more widespread use prior to acquisition of all data that would ordinarily be obtained before marketing.

Phase 4 clinical trials of a drug do not include studies of a new indication or of a dosage differing from that in the approved labeling.

II. MEDICAL INFORMATION

The functions of this unit of the Medical Department are implied in its name. This unit should be responsible for:

1. gathering any and all medical information needed by the various departments in the company to keep the personnel of these departments abreast of any new developments in the various fields of pharmaceutical knowledge, e.g., new drugs in the market, new compounds or leads in this investigative field, etc.,

2. disseminating information within the Company,

3. disseminating approved information outside the Company through brochures, detailmen, etc.,

4. collecting and storing data and documentation on clinical trials,

5. collecting and documenting adverse reactions to the company's drugs as reported by physicians using these drugs, and,

6. responding to inquiries regarding information on marketed drugs*.

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*Inquiries concerning information on investigative drugs should be handled by the physician monitoring the development of such a drug.

The Medical Information Unit could be divided into subunits as follows:

A. Library

The existence of a good library as well as the ability to obtain a copy of any reference in the literature whether domestic or foreign go without discussion.

One or more qualified librarian(s) will be a must in such a setup.

The library should contain textbooks, journals, periodicals and other references in all the disciplines of medicine and the allied basic sciences.

B. Clinical Documentation

The responsibilities of Clinical Documentation are as follows:

B.1. Storage of all clinical data and documents in the capacity of a central repository for all research areas.

The following types of documents should be sent to Clinical Documentation within five days of company receipt or generation.

a. Clinical case reports and all related documents containing patient data, which include hospital records, lab data, photos, slides, investigator summaries (including prepublication manuscripts), adverse reaction forms and all letters and memos containing patient data or information of the clinical study.

b. General clinical documents which include IND documents (original Statements of Investigators, curriculum vitae, final signed protocol, sample blank case report form, randomization schedules, statistical summaries, Clinical Study Reports, Formulated Materials Packaging/Shipping Requests and Request for Disposition of Clinical Materials).

B.2. Retrieval

As the central information center for all clinical information, Clinical Documentation provides reference service to all management, staff, and line functions within Research by providing direct answers to inquiries, special computer listings, document copies, and/or summary information as required.

B.3. Microfilming

To insure the maximum security of the data base, all incoming documents are microfilmed for security purposes. In addition to security microfilming, all original documents purged from files for storage in a secondary warehouse facility could be reduced to microfiche for on-site storage.

The following procedures are followed within Clinical Documentation upon receipt of ciinical documents.

1. All documents are date stamped on day of receipt.

2. The documents are then indexed for an automated retrieval system and the individual case report pages logged in on a computer file for that study.

3. Copies are made and distributed of the documents as requested by the sendor. At this time, a copy of the indexing will be sent to be keypunched.

4. The documents are microfilmed for security.

5. The documents are then filed. All case reports and summary data needed for submission will be filed by study number.

CLINICAL DOCUMENT FLOW THROUGH CENTRAL FILES

I. Documents Received and Stamped

Time Span: Same Day

II. Documents Indexed and Logged

Time Span: 1-2 Days

III. Documents Copied

Time Span: 1-3 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

IV. Documents Microfilmed

Time Span: 1-4 Days

V. Documents Filed

Time Span: 1-4 Days

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

C. Professional Services

The activities of the Professional Services Department should include the following:

C.1. Audience Development

This activity is essential and addresses two main groups of Audience:

C.1. a. Established Practitioners and students and trainees on their way to become practitioners, and

C.1. b. Pharmacists

Audience development could be directed to specific group(s) of professionals and experts in a specific field(s) of medical practice for which the company has developed a drug(s) or is engaged in developing such.

C.1.a. The objectives of a certain Audience Development in a certain field (Dermatology, for instance), would be to establish the company as the one most knowledgeable about and most interested in dermatology in order to:

1. maintain and increase sales levels of present products,
2. facilitate development of new products,
3. facilitate acceptance of new products, and
4. facilitate areas for sales representatives.

Meetings with the officers and executives of the "Dermatology Society" in the country for instance could explore the "needs of Dermatology", and a possible role for TEVA in helping to meet those needs. After defining the greatest educational need of the Society, a program(s) should be developed and financed at least in part by TEVA, (a slide-sound format; a booklet format, etc.) and copies distributed to training centers and practicing physicians.

A series of slide-sound programs for use by dermatologists in teaching dermatology to medical students would be another program. This might also be useful for nurses and perhaps for general practitioners.

Educational support program to provide unrestricted educational funds for departments of dermatology in the medical schools or hospitals is yet another program aimed at Audience Development.

Providing financial support to Dermatological Organizations and attending their meetings will be useful in giving the home office personnel and/or the field personnel a better insight and feeling for the speciality as well as providing the company with increased visibility.

C.1.b. Hospital Pharmacy

The objectives of Audience Development here would be:

to build the Company's image in the field of pharmacy, by showing an interest in the profession and providing a service that will benefit its members,

to facilitate getting the company's products on hospital formularies,

to build rapport with influential educators, officials of the pharmaceutical association and pharmacy leaders in both civilian and government hospitals and,

to facilitate the company's representative calls on hospitals.

Hospital Pharmacy Seminars could be arranged and sponsored by TEVA while conducted by various pharmacy schools around the country. All logistics are arranged for and handled by Professional Services.

Such a program over a number of years will realize the desired results in building the company's image.

C.2 . Medical Education

The objectives of this activity of the Professional Services Department are:

C.2.1. To provide for the Medical/Scientific Education of the Field Force - including:

a. Education of New Representatives and

b. Continuing Education for Senior Representatives

In the Form of:

a. Lectures

b. Written Materials (Backgrounders, etc.)

Concerning:

a. Established TEVA Products

b. New TEVA Products

c. Competitive Products

C.2.2. To supply the Marketing Team with requested Medical/Scientific information of all types.

C.2.1.a New Representative Training Class Lectures

The department should offer several lectures in the New Representative Training Classes. Lectures include the pharmacology of a TEVA production as well as the anatomy, physiology, pertinent biochemistry and pathology, pertaining to a given therapy area. Each therapy area generally is covered in a one day period, with the greater part of the day alloted to medical lectures.

A typical lecture outline in Muscle Joint Therapy for instance would be as follows:

1. Connective Tissue Structure and Function
2. Inflammation
3. Overview of the Rheumatic Disorder
4. The Normal Joint (Knee)
5. Rheumatoid Arthritis
6. Non Articular Rheumatism
7. The Adrenal Cortex
8. The Steroid and Corticosteroids
9. Osteoarthritis
10. Feedback and Control Mechanisms in Corticosteroidal Synthesis and Release
11. The Mineralocorticosteroid
12. The Glucocorticosteroid
    a. biochemical and physiologic effects
    b. pharmacologic effects
    c. comparison of the available glucocorticosteroids
13. TEVA'S "Corticosteroid"
14. The Competitive Products

Synopses or Summaries of all lectures presented in the New Representative Training Classes should be prepared as study aids for the students. The synopses should include all information considered pertinent for a thorough understanding of the lecture material.

C.2.1.b Senior Seminar Lectures

The department should offer several lectures to senior representatives in the Senior Seminars. Since it is impossible to lecture completely on a given therapy area, specialized topics should be chosen. Usually, most of the lecture period should be taken up by questions asked by members of the class. These question/answer sessions may be just as valuable as formal lectures.

A typical lecture schedule is attached in Appendix VII.

Backgrounders

Backgrounders are used to provide basic medical/scientific and clinical information to the members of the Field Force. Backgrounders also contain competitive product information to familiarize the members of the Field Force with other products available. They are generally in the range of 70-100 pages.

A typical backgrounder outline is as follows:

1. Introduction to the therapy area or class of drugs.
2. Basic anatomy, physiology, and biochemistry of the organ systems involved.
3. Basic pathology of the organ systems.
4. General treatment of the diseases in the therapy area.
5. Pharmacology of the drug.
6. Pertinent Clinical Data Summary
7. Expanded and annotated package insert.
8. Competitive product information.
9. Glossary
10. Index

All backgrounders are reviewed by several departments including the Sales, Marketing (Product Managers), Medical and Law Departments. All criticisms and comments are taken under consideration and incorporated into the final copy as appropriate.

Minibackgrounders

Minibackgrounders are 10-20 page packets of information designed for Field Force use in specialized areas.

1. Competitive product information. In this case, the minibackgrounds contain information on a competitive product. Generally the minibackgrounder includes information on the general pharmacology of the product and also compares it to the company's product involved.

2. New Product information for low priority or line extension products.

3. Specific information relating to use of company's established products. In this case the Field Force is given expanded information concerning one aspect of the medical/scientific information of an established product.

C.2.2 MEDICAL/SCIENTIFIC INFORMATION

a. Bulletins

Medical/Scientific Informational Bulletins are (1 to 3 page) bulletins concerning specific information on one of the company's products or the introduction of a competitive product. Informational Bulletins may contain a table comparing a TEVA product with competitive products or a list of questions and answers commonly asked by members of the Field Force. In general, these may be used when important, but limited amounts of information must be sent to the Field Force.

b. Journal Article Perusal

Medical/Scientific Journals should be continually perused throughout the year. Members of the department should scan the most important medical/scientific journals all of which should be circulated through the department. As each journal is scanned for interesting/important articles, notes should be taken on file cards. Important papers, which may be useful for Professional Services/Medical Education purposes are copied. Papers read and/or copied may be used for the following purposes:

1. To upgrade knowledge and to continually keep members of the department informed as to new medical/scientific developments.
2. To aid the Professional Services Department in answering Physicians, para-medical and PSR requests for information.
3. To find papers concerning the company's products or therapy areas which may be used by the Field Force.

C.3 GRANTS PROGRAM

Objectives:

(1) To foster a healthy and well-informed medical community.

(2) To help maintain good relations with the medical and and related groups.

(3) To help maintain a good business climate.

(4) To faciiitate the access of the company's people to hospitais, doctors, pharmacists, and others important to the company's business.

TEVA should be interested in fostering a healthy and well-informed medical community and to this end it should have a program of educational support for medical and related groups and organizations. This program should be maintained because the quaiity and growth of TEVA's business is directly proportional to the quality of health care available.

C.4 SAMPLE LITERATURE SECTiON:

Objectives:

To provide service to the medicai and para-medical profession by administering requests for samples and literature received from them by the company.

C.5 PROFESSIONAL CORRESPONDENCE

Objectives:

To fulfill TEVA's obligation to supply promptly the best current information available on the company's products and their proper use to the individuals using or prescribing their use.

To provide for the information needs of marketing personnel on request as necessary.

A. Letters

Written inquiries are usually received from PSR's, M.D.'s, hospital and retail pharmacists, nurses, poison control centers, laboratory workers, medical and pharmacy students, and lay people. After review, if the subject is one involving medical and/or legal questions previously approved by appropriate authorities, the letter is then typed in final form. If the subject is new or if there is any doubt regarding medical accuracy, legal implication, company policy or appropriateness, the draft is submitted to the Director of Professional Services for approval. On his judgement the draft may be approved, edited, rewritten or submitted to a member of the Medical or Law Departments for review prior to mailing. All letters in final form should be read by the Manager to insure accuracy before mailing.

B. Telephone Inquiries

Phone calls regarding marketed products should be received in Professional Services. These come from the same groups as those who write in. (See A). This is a very demanding service, requiring thorough knowledge of the company's drugs, regulatory requirements, company policy, the literature, TEVA's publications, where information may be obtained or from whom. Tact and ingenuity are essential in all calls.

Emergency calls, such as an overdosage, severe adverse reaction, or a problem a physician is having with a specific patient and wants advice on how to handle the situation are transferred to the doctor most familiar with that drug.

C.6 MISCELLANEOUS

In addition to the previously mentioned programs the Professional Services Department should get involved in the following:

- o Reproduction of Rx Pads (with TEVA products) and instruction sheets for physicians requesting them.
- o Providing materials for the Professional Services Portion of exhibits.
- o Corresponding with medical, para-medical and lay groups regarding their requests.
- o Handling logistics of other audience development programs and seminars, symposia, and Doctor to Doctor meetings.

Objectives:

(a) Doctor-to-Doctor Symposia

(b) New Products

(c) Trouble-Shooting Teams

(a) Doctor-to-Doctor Symposia

These are round-table discussions held with 4-6 M.D.'s who are specialists in the field. The subjects are selected specifically to stimulate discussion about the use of a certain product in the particular area. The program is held to generate a brochure which can be used as third party documentation in areas where clinical papers are scarce. The material is intended for Field Force use.

(b) New Products

Professional Services has three functions involved in new product introduction. These are (1) providing the scientific material needed by the representatives to detail the product, (2) preparing to answer the questions that will come from physicians, pharmacists, nurses, and others after the introduction of the product, and (3) providing marketing support for the introduction in terms of Doctor-to-Doctor meetings, symposia, brochures, and other such activities.

All of these functions require considerable lead time and planning making necessary close cooperation between Professional Services and Marketing Planning. For many of the market support programs to be successful, Professional Services should have information and, if necessary, input into the clinical research phases.

(c) Trouble-Shooting Teams

The trouble shooting (epidemiology) program is conducted by the Sales Department. The Professional Services Department is called upon when needed as scientific advisors. This may involve, in some instances, sending someone to a hospital(s) which is having a problem with say, an antibiotic resistant organism. This person will then attempt to determine the cause of the resistance, the source (reservoir), and the mode of spread and will advise on how to either eliminate the organism or prevent its continued spread. This involves working with the Infection Control Team, the Infectious Disease Department, the microbiology lab, and the nurse epidemiologist in the hospital.

III. COMPUTER INFORMATION SCIENCES UNIT

The structure of the Computer Information Sciences Department, which supports both the Medical and Laboratory functions within the corporation, should be composed primarily of three types of people.

1. A group of Statisticians, having training in both Mathematical statistics and experimental design. The levels of these people would vary between Masters and Ph.D. degrees. The objective of these people is to work with both medical and laboratory personnel in the design and analysis of both clinical and laboratory trials as well as to assist in the utilization of pharmacokinetic modelling of drug absorption excretion patterns in both animals and human models.

2. A second group of people in the department would be Programmer/Analysts. These people support both the clinical and laboratory programs in the area of statistical and mathematical programming, data base development and the general programming support required to carry out large scale clinical and laboratory experiments. The Programmers/Analysts will have a Bachelors or Masters degree in mathematics or physical science and several years relevant experience, working in either a pharmaceutical or health care type environment. The individuals must be quite flexible in the types of programming languages they utilize (FORTRAN, PL1, APL, some COBOL and where appropriate, ASSEMBLER language coding). The function of a programmer does not necessarily have to be separated from that of an analyst. It is essential that the function be joint and that an individual be capable of taking a project from its initiation to its completion; that is, both the definition of the program as well as the implementation of the programming code to the documentation and implementation stage.

3. The third group of people associated with the department should be a group called Clinical Data Coordinators (CDC's). These people support the work under the direction of the Statisticians. Their primary function would be to assist in the development of a protocol as well as develop the appropriate case report form (self-encoding where possible) and to follow this with review of the documents both in a computer sense and a manual sense when they are received. The second function of the CDC is to create the data base associated with the clinical trial and to edit this file such that the quality of the data reaches an acceptable level to be processed. As a general overview, some type of computer resource is essential to the functioning of this type of group.

As a final comment, competent people in this area are extremely limited and it is therefore quite essential to attempt to keep the various personnel challenged at all times.

IV. HEALTH REGISTRATION UNIT

The main function of the Health Registration Unit is liaison between the Company and the Regulatory Agency.

All correspondence addressed to or received from the Agency should be handled by the Health Registration Unit.

This unit will collate and organize the componants of the IND and NDA prepared by the Medical Research Unit and/or the Biology or Toxicology Departments for submission to the Regulatory Agency. Furthermore, the Director of the Unit or his representative should be responsible for setting up necessary meetings and review conferences with the Agency and its Advisory Committees for discussed any part(s) of the IND and/or NDA that the Agency may require. Accordingly, the Director should be an M.D. or a Ph.D. with medical sciences background, who must have full knowledge of and familiarity with the Rules and Regulations of the Ministry of Health that govern research involving human subjects.

ORGANIZATIONAL STRUCTURE AND MANPOWER

The following organization structure chart shows the various units of the Medical Research Department and is self-explanatory.

It is suggested that a physician (M.D.) heads this Department and reports to the Director, Research and Development.

Each of the four units of the Medical Department will have its own director reporting to the Medical Director.

Each of the three subunits of the Medical Information Unit will be headed by a manager reporting to the Director of the Unit.

Secretaries and clerks are not shown in the chart.

The number of Physicians (M.D.'s) and Medical Research Associates (MRA'S) needed in the Clinical Research Unit will depend on the number of active research projects the Unit is engaged in.

A Coordinator reporting to the Director of the Medical Department will help the Director in organizing the different functions of the various units and coordinate their functions with those of the basic sciences units.

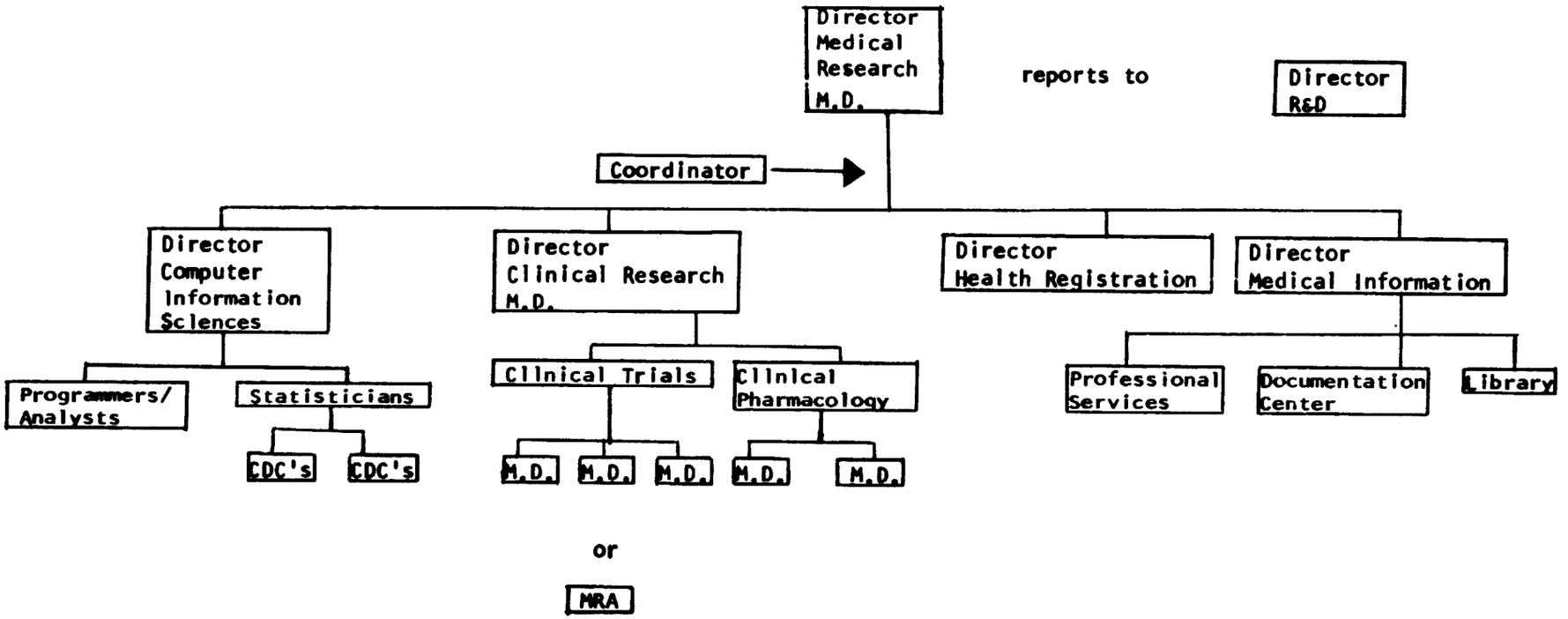
Present Manpower Needs

In the present circumstances, where the clinical research activities are rather very limited at TEVA, it is recommended that the Director of the Medical Department assumes the responsibilities of directing the Clinical Research and Health Registration Units. There seems to be no need for a Coordinator at the present time.

Medical Information should remain a separate unit with at least 2 people in Professional Services; one person will be able for the time being to manage both the Library and the Documentation Center subunits. The Medical Information Unit should be part and parcel of the Medical Department with excellent ties with Marketing.

As projects are undertaken by the Medical Department, the need will rise for more personnel in the various units.

ORGANIZATIONAL STRUCTURE OF THE MEDICAL RESEARCH DEPARTMENT



Appendix I

WHAT IS A "NEW DRUG"?

Unless a drug is generally recognized by qualified experts as being safe and affective for its proposed use, it is regarded as a "new drug". Conversely, and "old drug" is one that is generally recognized as safe and effective (GRASE). A drug may be "new" without necessarily being a new substance. For example, new combinations of old drugs are considered new drugs. The newness of a drug may arise, moreover, by reason of a new indication, dosage, or method of administration.

Appendix II

ANIMAL REPRODUCTION STUDIES

Animal studies concerning the effect of a new drug on reproductive processes are an important aspect of the drug's toxicologic characterization. FDA recommends that animal reproduction studies be divided into three segments, each related to the effect of the test-drug on a specific area of the mammalian reproductive process:

Segment I — Study of fertility and general reproductive performance in both male and female animals (usually rats)

Segment II — Teratologic study in at least two species (the most frequently used species are the mouse, rat, and rabbit)

Segment III — Perinatal and post-natal study (usually in the rat)

If Segment II and the female part of Segment I have been satisfactorily completed, women of child-bearing potential may be included in late phase 2 clinical trials of a new drug. Before phase 3 clinical trials are initiated satisfactory completion of Segments I, II, and III is required. Generally, women of child-bearing potential should be excluded from phase I and early phase 2 clinical study; and exception are women who are institutionalized and whose non-pregnant state is assured.

Animal reproduction studies need not be performed on a drug combination, if it has been shown that the individual components do not adversely affect reproduction, and that toxicologic interaction does not characterize the drug combination. If either component, however, has been shown to have an adverse effect on the reproductive process, animal reproduction studies on the drug combination are required.

Appendix III

"IND": PRE-REQUISITE TO CLINICAL TESTING OF AN INVESTIGATIONAL NEW DRUG

Federal law provides that, without FDA approval, a new drug may not be shipped or delivered interstate for use in man. To gain permission for interstate shipment or delivery of a new drug for testing in humans, an exemption from the foregoing law is necessary. Thus, the "sponsor" (Usually a pharmaceutical firm) must first submit to FDA a completed and signed "Notice of Claimed Investigational Exemption for a New Drug" (Form FD-1571). Through common usage, this claimed exemption notice has come to be known as an "IND".

An IND is required to include all available information that has led the sponsor to conclude that it is reasonably safe to initiate clinical studies of an investigational new drug. The regulations provide that, before initiating such clinical studies, the sponsor must wait 30 days from the date of FDA's receipt of the IND. If requested by FDA before expiration of that 30-day period, the sponsor must continue to withhold or to restrict the clinical studies. When such a request is made, FDA must inform the sponsor about the specific respects in which the IND is considered deficient, and must agree to a conference if the sponsor wishes one.

Amendments to IND

After an IND has been filed with FDA, it usually becomes necessary, from time to time, to file amendments to the IND. Some of the reasons for filing an amendment are:

- o Addition of new clinical investigators
- o Change of the person originally charged with monitoring the investigation
- o Revision of the protocol of clinical study
- o Modification of the new-drug formulation
- o Change in manufacturing methods, facilities, or controls

Appendix IV

COMPONENT PARTS OF AN IND (Form FD 1571)

The IND is currently a 15-part document. The informational requirements of the sequential parts are summarized here, with more attention to those parts that bear directly or indirectly on clinical investigation:

Parts 1-5: identification of the investigational new drug including chemical name and structure, and route of administration; its complete composition and source, and manufacturing information adequate to show that appropriate standards exist to ensure safety.

Part 6: All information available to the sponsor from pre-clinical studies and any clinical studies and experience with the new drug:

a. Adequate information about the pre-clinical investigations, including laboratory animal studies, on the basis of which the sponsor has concluded that it is reasonably safe to initiate clinical investigation of the new drug. Such information also should furnish (i) the identification of the person who conducted each pre-clinical study, (ii) the identification and qualifications of the persons

who evaluated the results and judged it reasonably safe to initiate clinical investigation, (iii) a statement of where the pre-clinical studies were conducted and where the records are available for inspection, and (iv) sufficient details about the pre-clinical studies to permit scientific review.

b. Data from foreign marketing or foreign investigations of the new drug, and a complete bibliography of any publications about the drug.

c. If the new drug is a combination of previously investigated or marketed drugs, a summary of information from pre-clinical and clinical investigations and experience with the individual components, including reports of side effects, contraindications, and ineffectiveness, a bibliography of pertinent publications, reference to any relevant information previously submitted to FDA by the sponsor, and a statement of the expected pharmacologic effects of the combination.

d. If the new drug is a radioactive substance, enough information from animal studies or prior human studies to permit reasonable calculation of the radiation absorption dose on administration to man.

Part 7: All informational material, including label and labeling to be furnished to each investigator.

"Label" refers to the descriptive matter on the immediate container or the package of the new drug as it is supplied to the investigator. The label must contain full disclosure (to comply with regulations governing interstate shipment of drugs), but can be designed to prevent the investigator from distinguishing the new drug from any control medication. Additionally, the label must carry the statement "CAUTION: New Drug for Investigational Use."

"Labeling" refers to what is usually termed the Investigator's brochure. This is an orderly compilation of all existing information about the new drug, pertinent to safety and possible usefulness under the conditions of the proposed clinical investigation. The investigator's brochure must describe relevant hazards, contraindications, side effects, and precautions suggested by prior investigations and experience, and must not represent that the safety or the usefulness of the new drug has been established for the purposes to be investigated.

Part 8: A statement of the training and experience that the sponsor considers appropriate to qualify the investigators as suitable experts to evaluate the new drug.

Part 9: The curriculum vitae of each investigator, and of the person charged with monitoring the investigation and with evaluating evidence of the drug's safety and effectiveness as it is received from the investigators; additionally, assurance that a completed and signed "Statement of Investigator" form has been obtained from each investigator, and that the investigator is qualified by training and experience to undertake the phase of investigation described in Part 10 of the IND.

Part 10: An outline of the phase or phases of the planned clinical investigation, and a description of the Institutional Review Committee.

Institutional Review Committee: If clinical investigation of the new drug is to be conducted on institutionalized subjects (including outpatients of an institution), the sponsor must give assurance that an Institutional Review Committee exists and is responsible for initial and continuing review and approval of the proposed clinical study.

The Institutional Review Committee must be composed of persons of various backgrounds (lawyers, clergymen, laymen, as well as scientists). It must approve all aspects of the study, including the patient consent form to be used prior to initiation of the study. When the study is underway, the Committee must carry out reviews at intervals appropriate to the degree of risk but not exceeding one year. Written records of its meetings must be maintained.

Part 11: A statement that the sponsor will notify FDA if the investigation is discontinued, and give the reason why.

Part 12: A statement that the sponsor will notify each investigator if an NDA for the drug is approved or if the investigation is discontinued.

Part 13: A statement that the new drug will not be sold during the proposed clinical investigation.

Part 14: Assurance that the sponsor will wait 30 days from FDA's receipt of the IND, before beginning the proposed investigation, and will continue to withhold or restrict the investigation if requested by FDA to do so prior to expiration of the 30 days.

Part 15: An environmental impact analysis report, when such is requested by FDA.

Appendix V

PROTOCOLS FOR CLINICAL INVESTIGATION OF NEW DRUGS

WRITING THE STUDY PROTOCOL

NEED FOR CORROBORATIVE CLINICAL INVESTIGATION

CASE RECORD FORMS

RESPONSIBILITIES OF SPONSOR AFTER FILING AN IND

RESPONSIBILITIES OF CLINICAL INVESTIGATORS

MONITORING CLINICAL INVESTIGATIONS

PROTOCOLS FOR CLINICAL INVESTIGATION OF NEW DRUGS

The Medical Research Physician (MRP), charged with monitoring the clinical investigation of a new drug, is responsible for drafting the clinical study protocol. This is accomplished in close collaboration with the prospective investigators, who must expressly approve the final version of the protocol.

In order to ensure the validity of inferences drawn from the clinical study of a new drug, it is just as important to utilize available statistical expertise in the development of the study plan as in the analysis of the eventual study data. The purpose of the clinical study is to draw inferences about the new drug's safety and effectiveness in the target population for which the drug is intended. Therefore, the study protocol should indicate how patients or subjects are to be selected so that the population studied will be comparable to the target population, and should describe the method of randomization to be used, the specific conditions under which the trial will be conducted, and the clinically important parameters that will be assessed.

Writing the Study Protocol

The following outline furnishes guidance for putting together study protocols that are consistent with principles generally recognized as basic to "adequate and well-controlled clinical investigations":

1. Study Objectives

   As specifically and clearly as possible, state why the study is to be conducted. Avoid statements like "to show that -- ", which imply that the results are already known. If more than one question is to be answered by the study, list these in the order of priority.

2. Summary of Study Plan

Briefly describe the type of study (e.g., double-blind, parallel-group), the treatments to be compared, the study population (i.e., number and kind of subjects), the method of randomization, the duration of treatment, and the type and frequency of clinical observations and laboratory tests to be performed.

3. Selection of Subjects

a. Eligibility Requirements - Define all requirements for admissibility to the study, including:

(i) Age range - If the age range includes patients under the age of 18, parent or guardian consent forms must be obtained.

(ii) Sex - Male, female, or both

(iii) Kind of subjects - Inpatients, outpatients, or normal volunteers

(iv) Primary diagnosis

(v) Diagnostic criteria (including, where applicable, confirmatory laboratory tests)

(vi) Duration and severity of disease to be treated

b. Non-eligibility Conditions - Specify all conditions that would make a subject unsuitable for study, such as:

(i) Known hypersensitivity to the investigational drug or to the control drug

(ii) Need for concomitant medication that would interfere with assessment of the investigational drug's safety or effectiveness

(iii) Complicating concomitant disease

(iv) Pregnancy or child-bearing potential

4. Number of Subjects

For a single study, note the number of subjects in whom the investigator expects to complete the study. For a multicenter study, give the minimum number of subjects in whom each investigator expects to complete all observations. The number of subjects specified in either of the foregoing instances must be predetermined through biostatistical consultation.

5. Design of Study

Explain the kind of study (e.g., parallel-group, crossover, paired patients, etc.), the kind of control, (placebo, active-drug, historical), and the level of "blinding" (double-blind, single-blind, open-label).

6. Drug Supplies

Describe the investigational drug materials (test drug, reference drug, placebo) to be supplied for study. Give the generic name and (if one exists) the trade name, identify the dosage form (capsules, tablets, injectable, etc.) and the strength, and explain the pharmaceutical method of blinding (e.g., by encapsulation in grossly indistinguishable opaque capsules). Also, note that the investigational drug materials will be furnished in a sealed envelope to be opened by the investigator only in case of emergency.

7. Duration of Study

Estimate how long the entire investigation is to take. Also, specify how long each subject is to be treated, noting permissible variations (if any) in duration of trials.

8. Investigational Procedure

a. Note pre-treatment requirements of medical history, physical examination, and laboratory tests.

b. If applicable, point out need for a washout or pre-drug period, and specify how long the period should be.

c. Describe the method that will be used for randomizing assignment of subjects to treatment groups in order to minimize bias. This will entail a full description of

the randomized coding and the "blind" labeling of the study drug(s) and placebo. Document by footnote the source of the randomization table employed.

d. Dosage: State the dosage. If this is not fixed, give permissible variations and specify the minimum and maximum adjustments allowable at any one time.

e. Concomitant Medication: List the specific medications that patients may not receive during the course of the study. State that other medications that are considered necessary for a patient's welfare may be used concurrently, but note that the administration of any such medications must be reported in the individual's case record.

f. Clinical Assessments: Specify what clinical assessments are to be made.* Describe how and precisely when these are to be made. Include a description of any scoring system to be used for quantifying the clinical assessments.

* (The clinically important variables should be assessed. Parameters of only marginal clinical significance should be omitted.)

g. Laboratory Measurements: Specify what laboratory tests (including any special diagnostic procedures) are to be carried out, and when these are to be performed. Note that the clinical laboratory to be used by the investigator must be identified, and must furnish a listing of its normal values for laboratory tests.

h. Adverse Reactions: Include a listing of expected adverse reactions. Explain how adverse reactions that occur during the study are to be recorded. Describe the procedure that the investigator is to follow in promptly reporting the occurrence of any serious adverse reaction.

i. Case Record Forms: State that special case record forms will be supplied and that, after completion, these forms - together with any other pertinent recordings - are to be returned, with copies retained by the investigator.

j. Dropouts: Emphasize that effort will be made to determine why a patient in the study fails to return for required visits or is dropped from the study. State that the reason(s), if determinable, will be set forth in the patient's case record.

9. Statistical Analysis Methods

Describe the statistical methods to be used in analyzing the data elicited by the study. State that the data will be analyzed and that any additional analysis of the data performed independently by the investigator is to be submitted.

10. Disposition of Unused Drug Supplies

State that all unused investigational drug materials must be returned on termination of the study. in the case of a blind study, state too, that the sealed decoding information also must be returned.

11. Signature and Dating

Provide space for the principal investigator's signed approval, address, institutional affiliation (if appropriate), and dating.

Need for Corroborative Clinical investigation

A plan for clinical trial will not generally be regarded as a reasonable one, unless it provides for adequate and well-controlled study by two or more independent, competent investigators. A multicenter clinical trial is viewed, of course, as a single study, even though it involves several independent clinical investigators.

Case Record Forms

The case record form to be used in clinical investigation of a new drug must be designed to enable the investigator to maintain all pertinent information about each study subject, including the following:

> "Age, sex, conditions treated, dosage, frequency of administration of the drug, results of all relevant clinical observations and laboratory examinations, adequate information about any other treatment given, and a full statement of any adverse effects and useful results observed, together with an opinion as to whether such effects or results are attributable to the drug under investigation."

RESPONSIBILITIES OF SPONSOR AFTER FILING AN IND

When an IND has been filed with the Regulatory Agency and the clinical studies of the drug are ongoing, the sponsor has assumed a number of additional responsibilities. Set forth in the investigational-drug regulations, these added responsibilities include:

a. Maintenance of records of distribution of the new drug, showing the investigator to whom shipped, and the date, quantity, and batch number of each such shipment of delivery.

b. Monitoring the progress of the investigation, and evaluating the evidence of the drug's safety and effectiveness as it is obtained from the investigator.

c. Filing IND progress reports of the investigation at intervals not to exceed one year.

d. Reporting to the Regulatory Agency and to all investigators any findings that suggest significant hazards associated with use of the drug. If a finding is alarming, it must be reported immediately and investigation of the drug discontinued until the finding is adequately evaluated and a decision reached that it is safe to proceed.

e. Stopping the investigation and recalling all clinical supplies of the new drug (with appropriate notification to the Regulatory Agency and all investigators), if investigative findings give rise to substantial doubt about the safety of continuing clinical study of the drug.

f. Discontinuance of shipments or deliveries of the drug to any investigator who fails to maintain or make available adequate records of his investigation.

g. Avoidance of unduly proionged distribution of an investigational new drug.

h. Obtaining from the investigator, in the case of a study involving institutionalized subjects, documentation that an institutional Review Committee has given initial and continual approval of the study.

RESPONSIBILITIES OF CLINICAL INVESTIGATORS

FDA regulations detail the obligations of clinical investigators who undertake studies of investigational new drugs. For each such study, the principal investigator is expressly responsible for the following:

a. Assurance that the study drug is administered only by him, or by a qualified individual under his direct supervision who has been named in the signed "Statement of investigator".

b. Conduct of the study in accordance with the submitted protocol.

c. Maintenance of adequate records of the disposition of all supplies of the new drug; on discontinuance or completion of the study, returning to the sponsor any unused supply of the drug.

d. Maintenance of adequate and accurate case records for all subjects, including those used as controls.

e. Furnishing the sponsor with progress reports of the study at intervals not exceeding one year, and with an adequate final report shortly after the study's completion.

f. Prompt reporting to the sponsor of serious adverse effects that may be attributable to the drug, and immediate reporting of any alarming adverse effect.

g. Maintenance of drug disposition records and of case records for two years following either approval of an NDA for the drug or (if an NDA is not approved) discontinuance of the study.

h. Obtaining informed consent from all subjects, or their representatives, unless this is not feasible or, in the investigator's judgement, is contrary to the best interests of the subjects.

i. Assurance that, for an investigation involving institutionalized subjects, an Institutional Review Committee has reviewed and approved the study.

MONITORING CLINICAL INVESTIGATIONS

The sponsor shares with the clinical investigator responsibility for the manner in which the clinical studies of a new drug are performed. The sponsor's share of this responsibility has to do with the monitoring of the clinical studies. Described below are particulars of investigational drug studies that should be monitored by the sponsor. In this description, the term "sponsor" should be understood to mean the sponsor's authorized representative (the MRP) who is charged with the monitoring function.

1. Principal Investigator's Involvement in Study

FDA regulations provide that the investigational new drug must be administered by the principal investigator or by a qualified individual under his direct supervision, whom he must name in his signed "Statement of Investigator". The principal investigator also is responsible for the study's being conducted in accordance with the protocol and for the accurate reporting of the results.

The sponsor, therefore, must make reasonable efforts to determine, both in advance of and during the study, that the principal investigator's interest and time do, in fact, permit his personal involvement in the study. Further, the sponsor should review the role of any other individual who has a key part in the performance of the study.

2. Study Facilities

Taking into account the protocol and the type of the investigational drug, the sponsor should assure himself that the location where the subjects are to be seen and tests conducted will be adequate for proper conduct of the study. After onset of the investigation, the sponsor

also should confirm the suitability of the study facilities. If the clinical laboratory to be used by the Investigator is not certified, assurance of the laboratory's reliability should be sought.

3. Informed Patient Consent

The law in the U.S.A. stipulates that, before administering an investigational new drug to human beings, the investigator must "obtain the consent of such human beings or their representatives except when it is not feasible or when, in his professional judgement, it is contrary to the best interests of such human beings".

Informed consent implies a fair representation to the patient of the investigational nature of the new drug, the purpose of the study, the possible risks involved, the benefits that might be expected, the alternative treatments available, the opportunity to withdraw without prejudice, and a meaningful explanation of the procedures to be followed.

Informed consent must be obtained in writing in phase 1 and phase 2 studies. In phase 3 studies, the investigator may obtain such consent orally, taking into account the physical and mental state of the patient. If only oral consent is obtained, a notation to that effect should be made in the patient's case record.

As part of his monitoring duties, the sponsor should obtain a copy of the "informed consent" form that the investigator plans to use in the study. During the study, when a patient's consent has been obtained orally or, for reasons mentioned above, has not been obtained, the sponsor should confirm that the investigator has included an appropriate notation in the patient's case record.

4. Institutional Review Committee

Where an investigational drug is to be used in institutionalized patients, the sponsor should assure himself that a properly constituted Institutional Review Committee does exist. Further, he should obtain for his files copies of the Committee's communications to the investigator, indicating approval of the study initially and at subsequent intervals not exceeding one year.

5. Compliance with Protocol

FDA regulations require the investigator to adhere to the protocol of study that has been agreed upon in advance by both sponsor and investigator, and submitted to FDA. Although some latitude is permissible, particularly in phase 1 and phase 2 studies, significant deviations from the protocol must be reported to the sponsor, who in turn is obligated to report such deviations to FDA.

During the course of the study, therefore, the sponsor should periodically ascertain that the procedures detailed in the protocol are actually being followed, including adherence to subject eligibility criteria, treatment and re-visit schedules, specified clinical assessments and laboratory measurements, and follow-up of study drop-outs. The sponsor

also should periodically evaluate the availability to the investigator of suitable patients, and the effort being made by the investigator to complete the study as planned.

6. Adverse Reactions

The sponsor should advise the investigator of legal and regulatory requirements related to adverse reaction reporting. The investigator must determine whether the seriousness of a reaction warrants removal of any patient from study but, in any event, should institute appropriate diagnostic and therapeutic measures and keep the reacting patient under observation for as long as medically indicated.

The investigator should notify the sponsor promptly when a patient has been removed from study because of an adverse reaction. The sponsor, in turn, is required to report adverse drug reactions to FDA.

7. Accuracy of Study Records

It is good monitoring practice to check periodically patients' study record forms against their regular office or hospital records. This is particularly desirable with respect to information concerning patient-identification, concurrent diagnoses and therapy, laboratory data, dates of treatment with study drug(s), and patient-status before and at the end of the investigation. The sponsor also should encourage the investigator to make study-record entries at the time of patient visits, rather than at some later time, in order to minimize inaccuracies and omission of information.

8. Drug Accountability

The sponsor should assure himself during the study that the investigator's new-drug supplies are being stored in a safe place and dispensed only by authorized individuals, and that accurate records of the disposition of all receipts of the new drug are being kept. On completion of the study, the sponsor must arrange for the investigator to return all unused supplies of the new drug.

9. Evaluation of Safety and Efficacy Data

As case records are received from the investigator, the sponsor should carefully review these for accuracy and completeness. Records with illegible entries or missing data should be returned promptly to the investigator for appropriate correction. In his initial review of case records, the sponsor should be sure to include a check on the kind and frequency of reported adverse effects, the number of patients lost or withdrawn from study, and the reasons for drop-outs.

As soon as possible following completion of an investigator's study of a new drug, the sponsor should prepare a detailed report based on his evaluation of the study data, stating his conclusions regarding the study's support of the safety and effectiveness of the new drug. A copy of this report should be made available promptly to the investigator for validation.

10. Retention of Study Records

The investigator is required to retain all records of his investigation for at least two years after either approval of an NDA for the drug or -- if an NDA is not approved -- termination of the IND. The sponsor, however, should urge the investigator to keep on file for at least five years the full name, last known address, and telephone number of each subject who received the investigational drug since such information would be useful if later follow-up of subjects should be indicated.

During the clinical study of an investigational drug, the sponsor's contacts with the investigator -- by personal visit, correspondence, and telephone -- should be frequent enough to ensure that the study is progressing according to the protocol and in compliance with FDA's investigational drug regulations. The sponsor should keep an accurate account of his findings at each on-site visit and in each telephone conference with the investigator. Any procedural corrections that are indicated by the sponsor's findings should be reiterated to the investigator in a follow-up letter, so that a record of such changes is available.

Appendix VI

COMPONENT PARTS OF AN NDA

Itemized below, are the component parts of a new drug application. This listing is intended mainly to highlight the parts of an NDA for which Medical Research has total and consultative responsibilities. Medical Research (in the person of the delegated MRP) is fully responsible for the items that are checkmarked and CAPITALIZED, and consultatively responsible for the items that are checkmarked and underscored:

Part 1: Table of Contents

Parts 2 and 3: Summary and Evaluation

A. Chemistry

1. Structural formula or descriptive for any new-drug substance.
2. Relationship to chemically or pharmacologically related drugs.
3. Description of dosage form and quantitative composition.

B. Scientific rationale and purpose drug is to serve

√1. CLINICAL PURPOSE

2. Highlights of pre-clinical studies

√3. HIGHLIGHTS OF CLINICAL STUDIES

√4. CONCLUSIONS

C. Reference number of IND under which drug was investigated, and of any IND, NDA, or master file that is incorporated by reference for support.

D. Pre-clinical Studies

1. Pharmacology

2. Toxicology and pathology

√E. CLINICAL STUDIES

√1. SPECIAL STUDIES

√2. DOSE-RANGE STUDIES

√3. CONTROLLED CLINICAL STUDIES

√4. OTHER CLINICAL REPORTS

√5. CLINICAL LABORATORY STUDIES RELATED TO EFFECTIVENESS

√6. CLINICAL LABORATORY STUDIES RELATED TO SAFETY

√7. SUMMARY OF CLINICAL LITERATURE

√8. OVERALL RESULTS AND CONCLUSIONS

√9. Annotated Product Information sheet

Part 4: Labeling

4a. Label(s), carton(s), etc.

√4e. Product information sheet

Part 5: Statement whether drug is limited in its labeling to Rx

Part 6: Full list of articles used as components of drug

Part 7: Full statement of composition of drug

Part 8: Full description of methods, facilities, and controls for manufacture, processing, and packing of drug.

Part 9: Samples of drug and articles used as components

Part 10: Full reports of pre-clinical investigations

Part 11: √a. List of all clinical investigators supplied with drug; also volume and page references to submitted reports, or explanation of omission of reports

√b. Explanation of omission of any reports of clinical investigations of drug

Part 12: Full reports of clinical investigations

12c. Detailed listing of domestic clinical studies, and statement where data are available for inspection. For each investigator's study:

(i) Investigator's curriculum vitae

(ii) Protocol of study

(iii) Normal values for tests by investigator's laboratory

(iv) Master drug-code (if applicable)

(v) Investigator's summary of study

(vi) Case Reports

12d. Drug Experience Reports

(i) List adverse experiences by investigator and cross-reference to any narrative description in Part 12c.

12e. Data from other sources

(i) Detailed listing of <u>foreign</u> clinical studies, and statement where data are available for inspection.

(ii) √Scientific literature:

<u>Annotated bibliography, with copies of published reports not available to FDA</u> (consult with Library)

Copies of unpublished manuscripts

√12f. <u>If drug is combination of previously investigated or marketed drugs: Summary of pre-existing information from pre-clinical and clinical investigations and experience with the components, plus adequate bibliography</u> (consult with Library).

12g. Composition or method of manufacture of new drug used in each reported investigation, if it differs from that described in Parts 6-8.

Appendix VII

SENIOR SEMINAR LECTURE

TYPICAL LECTURE SCHEDULE

ALLERGY LECTURE

Allergy is an inherited or acquired side-effect of the body's immune system. In inherited allergies, the individual is genetically endowed (born with) a hypersensitivity to a particular foreign subjects (e.g., plant pollens). In acquired cases, the allergic reaction is precipitated by an environmental cause (e.g., organ transplants).

In either situation, the foreign substance can be an antigen or a hapten. An antigen is almost always a high molecular weight protein (e.g., bacteria, pollens, foods) which can, by itself, initiate the allergic response. A hapten is generally a non-protein of low molecular weight (e.g., drugs, dust, animal dander) which cannot initiate the allergic response until it is united with a protein such as the plasma proteins of the body.

Antigens and haptens have a variety of sources, and in descending order of frequency, they are as follows:

(1) inhalants - e.g., pollens
(2) contactants - e.g., poison ivy
(3) ingestants - e.g., foods
(4) injectants - e.g., drugs
(5) infectants - e.g., bacteria

All allergic reactions follow a two stage sequence, viz, sensitization and challenge. Sensitization coincides with the first exposure to the alien antigen or hapten, and, at this time, no allergic symptoms generally occur. Challenge is associated with subsequent and repeated contact with the foreign substance, and this usually precipitates the allergic responses.

A. Immediate Allergy Characteristics

(1) During sensitization, the antigen stimulates the formation of antibodies. Antibodies are proteins of the gamma globulin class produced by the body to combat a foreign invader. These antibodies are synthesized by special cells known as plasmablasts which are contained in the lymph nodes, liver, spleen and bone marrow. The latter organs are collectively known as the reticulo-endothelial system (RES) which is the body's first line of defense against alien invasion. These cells produce antibodies at the rate of 100 molecules per second which, subsequently, circulate in the bloodstream.

(2) During subsequent exposure (challenge) to antigen, the circulating antibodies attack the antigen within seconds or minutes, and the allergic symptoms are elicited.

(3) The antigen-antibody union causes the release of numerous substances within the body such as prostaglandins, serotonin, bradykinins and histamine, and all these agents contribute toward the development of symptoms. However, it is generally believed that histamine is responsible for most of the allergic damage.

(4) The histamine released from blood basophils and tissue mast cells elicits the clinical symptoms via:

(a) smooth muscle contriction of bronchioles (causing asthma), intestines (causing nausea, vomiting, diarrhea, cramps) and arterioles (especially in brain membranes, causing headache).

(b) increase in capillary permeability (leakage) resulting in hypotension (low blood pressure) and increased mucous secretions (watery eyes, runny nose, chest congestion).

(c) formation of edema leading to swelling and inflammation (e.g., hives).

Examples of immediate allergies are:

(1) Seasonal rhinitis - e.g., rose fever

(2) Perennial rhinitis - e.g., animal dander

(3) Atopy*

(a) urticaria (hives)
(b) atopic dermatitis (eczema)
(c) asthma
(d) hayfever

*NOTE: Atopy is a "strange" or "out of place" condition. This means that the stimulus (route of exposure of antigen) is unrelated to the body's response site, e.g., eating strawberries (ingestion route) results in hives (dermal response). In general, atopic diseases are familial (inherited), i.e., a father may have eczema while his son may have urticaria and his daughter may have asthma.

There is no cure for immediate allergic reactions and treatment is restricted to the relief of symptoms. The usual therapy consists of one or more of the following drug ciasses:

(1) Antihistamines - mechanism involves antagonism of some effects of histamine at the target tissue.

(2) Glucocorticoids - mechanism involves alleviation of the associated inflammatory response and/or suppression of antibody formation by the RES.

(3) Sympathomimetics (e.g., epinephrine) - to relax the constricted bronchioles and constrict arterioles to combat hypotension and congestion.

B. Delayed Allergy Characteristics

(1) in this type, circulating antibodies are not produced. Rather, during sensitization, the RES manufacturers special cells known as lymphocytes. These lymphocytes divide about once every 10 hours: therefore, they are not as numerous as antibodies.

(2) During subsequent exposure (challenge) to antigen, the lymphocytes attack the antigen. However, because they are fewer in number, it takes hours or days to neutralize the antigen. Accordingly, the allergic symptoms are delayed in onset.

(3) The antigen-lymphocyte union does not release histamines; therefore, allergic symptoms are not histamine mediated.

Examples of delayed allergies are:

(1) Poison ivy

(2) Contact dermatitis

(3) Transplants and Grafts

(4) Tuberculin sensitivity

(5) Autoimmune diseases (e.g., rheumatism)

Therapy includes:

(1) Glucocorticoids

(2) Anticancer drugs — to alleviate inflammatory responses and/or to suppress antibody formation

(3) X-Rays

NOTE: Since histamine is not involved in the delayed allergy, antihistamines are ineffective.