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MODERN PHARMACEUTICAL FORMULATIONS BASED ON THE TRADITIONAL THAI PHARMACOPOEIA

DP/THA/87/010

THAILAND

Technical report: Findings & recommendations*

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

Based on the work of Anthony D. Dayan,
Toxicologist

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Chemical Industries Branch

United Nations Industrial Development Organization
Vienna

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* This document has not been edited.

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1. Introduction

The visit was first suggested in 1988 by Mrs Sasithorn Wasuwat, Director of the Plant and Natural Products Division (PNPD) at the Thai Institute (TISTR). It had initially been arranged for early in 1989, but had had to be postponed until 1990 by Professor Dayan for personal reasons.

2. Objectives

It had previously been agreed in correspondence with Mrs Sasithorn and with UNIDO, Vienna that I would study the technical procedures and facilities used for toxicity testing by the staff of PNPD, that I would discuss in detail their current projects and short-term plans, and that I would offer immediate advice and suggestions by reviewing the role of toxicity testing in drug development and the current principles and procedures adopted by major Western firms to meet current national regulatory requirements whilst conforming to acceptable industrial practices.

In mid 1989, Mr Jakkrapong of PNPD spent three months in my department in London, learning a variety of experimental procedures, and visiting the toxicology departments of several large pharmaceutical and household products firms, a number of contract research companies and British regulatory authorities (Medicines Control Agency and Dept of Health).

3. Activities During my Visit

A detailed time table is given in Appendix 1.

The visit off-site were mainly arranged by PNPD, so that I could meet scientific colleagues with whom they are collaborating (e.g. Dr Wanee, National Cancer Institute, who has undertaken some bacterial mutagenicity tests), or who run relevant medical or laboratory services (clinical and forensic toxicology in Rambathibodi and Sirriraj Hospitals; several members of the Pathobiology and Pharmacology Departments and the Dean's and President's offices, Mathidol University; the National Laboratory Animals Centre and the Vaccine Development Centre, both on the Salaya campus of Mathidol University).

The extended visit and discussions with the Thai FDA (Mrs Chantana and her Division, and the Deputy Secretary) were arranged both because the FDA is the national regulatory authority for pharmaceutical and related products, and because that body has long been involved with other work I do for the International Programme on Chemical Safety (WHO).

Most of the time was spent in seminars and discussions at TISTR with the scientific staff of PNPD, or in an extended tour of the laboratories, animal rooms and production and formulation facilities. The majority of the staff took part in most of the activities, excluding only those who intermittently had duties elsewhere.

The staff list is shown in Appendix B. I met and talked to about 90% of them.

4. **Observations**

My comments here are confined to areas and equipment directly used for toxicological work.

I have considered the facilities shown to me in relation to those that would be required to meet the national regulatory standards and requirements of a major industrialised nation for a pharmaceutical or foodstuff, as I have repeatedly been told that that is the standard of work and reporting expected by the Thai FDA.

Toxicity testing in this context comprises a comprehensive and integrated set of experiments in animals and in in vitro systems to demonstrate a wide variety of possible functional, biochemical or pathological actions on the body, on the processes of reproduction, and on the genetic apparatus. It is equally necessary to investigate the biochemical metabolism of the test compound and its pharmacokinetics. All the results require careful statistical analysis, followed by critical expert judgement by a skilled toxicologist in order to prepare the comprehensive dossier required to obtain permission for clinical trials in man or eventually a product licence (NDA). This report must contain equally full accounts of the chemical, pharmaceutical and pharmacological work, and ultimately of the clinical studies.

a) **Facilities and Plant**

Toxicity work is done on parts of three floors of one fairly recent building at TISTR. On each floor one room is used as a dedicated animal room (respectively for mice, rats and rabbits or guinea pigs), and an adjacent room is used as a laboratory, e.g. for autopsies, biochemical tests etc, and in part as an office. There is a third office room on each floor.

The animal and laboratory accommodation is shared with the pharmacology function.

i Animal Rooms

Simple metal racks are used to hold standard, solid bottomed cages (rodents) containing sawdust, or wire grid cages (rabbits). There is natural lighting (mosquito screens on windows) and ventilation. Animals are individually identified by ear punching. Rats and mice (conventional) came from the National Centre in Bangkok, and rabbits from Kasesart University.

Tap water is supplied in bottles.

The diet is a locally made, commercial pellet, supplemented with clean grass from a TISTR lawn for rabbits.

Cages are changed x 2 or x 3 weekly and are washed by hand.

Sawdust (from a local wood firm) and diet are stored in bags in a closed room.

Total holding capacity possible up to 48 rabbits and 200-300 rats and mice in separate rooms.

ii Equipment

There are two electronic balances (shared) for weighing animals and a shared chemical balance for weighing chemicals.

One laboratory contains a semiautomatic diluter-spectrophotometer (Hitachi/Boehringer) for clinical chemistry tests (hospital model), a recent tissue processor, a modern embedding centre, microtome and photomicroscope. Staining was done manually. In another laboratory, where autopsies on rodents were done, there was an incubator and a laminar flow cabinet for microbiological testing.

A domestic refrigerator/freezer was available. A haematology analyser (RBC, WCC, platelets, Hb and indices) is to be delivered in mid-1990.

Access to each staff lavatory was via a laboratory.

No dosing or bleeding was done whilst I was at TISTR, but I understand that conventional techniques of gavage, injection and ocular and cutaneous application are used and that rodents are bled in life by tail snip. Rodents were killed with carbon dioxide.

I was told that wet tissues, blocks and slides could be stored for at least two years.

All the rooms were clean and tidy and no 'animal smell' was detected. footwear was changed before entering the building and before entering each animal room.

There was one animal attendant.

iii Staff

Toxicity testing is the responsibility of Mr Jakkrapong and Miss Prapaipat and Miss Saipin. The latter works as a technician. Mr Jakkrapong has a few years of local experience of animal care, of a variety of acute toxicity and topical tests, and of a number of limited subacute oral toxicity studies. In 1989 he spent three months in the UK seeing various techniques in my (academic) department and making brief orientation visits to pharmaceutical, household products and contract research laboratories. Miss Prapaipat is a new graduate, who has joined the group as her first job.

iv Work Load

(Internal) I was told that there would shortly be a subacute (28 day) dermal toxicity test in the rabbit of the candidate anti-inflammatory lotion Plegasil, including biochemical, haematological and pathological investigations, as well as the essential topical observations.

Plans were being made for various topical irritancy and acute and subacute toxicity studies of candidate hypocholesterolaemic and antihypertensive plant extracts for oral administration, and for topical and sensitisation testing of preparations to treat jelly fish stings and fungal infections.

(External) In 1987 a teratology test in rat and rabbit was done by a colleague at the nearby Kasesart University, who was experienced in doing full autopsies on the dams, and external examination, Wilson slicing and skeletal preparations of fetuses.

A partial Ames test (TA98 and 100, +/- S9) on terpen-4-ol, a major constituent of Plegasil had been done by Dr Wanee, NCI, Who had provided a limited summary account of the findings. She had the other conventional Ames strains available (TA 1535, 1537 and 1538), but did not normally use them.

v Operations

The dosing solutions were made up and administered by any of the three toxicology staff.

All protocols were written by Mr Jakkrapong.

Results were recorded manually, including multiple transcriptions in certain instances. Macrophotography would be possible if requested, but had not been used.

Numerical data were sent to a central computer department for statistical analysis. The statistician did not appear to be involved in study design or interpretation of the findings.

American and British regulatory guidelines about animal numbers in tests were followed, and, to the extent possible, so were their recommendations for blood and pathological investigations. Blood film staining was done by Mss Prapaipat and Saipin. Previously all histological sections had been prepared, stained and examined by Mr Jakkrapong, but he was teaching Mss Prapaipat and Saipin to take over that technical work, and subsequently the former would begin to examine sections.

A form of project group management was employed, in that the toxicologists, pharmacologists and chemists met regularly to make work plans for toxicity tests. Interpretation of the findings and compilation of the final report was the responsibility of Mr Jakkrapong. Individual reports were submitted to Mrs Sasithorn as Director of PNPD.

Some clinical advice was obtained from Dr Sunthorn, who worked in PNPD one or two days a week. He is a retired senior physician and nuclear medicine expert, previously Director of the Sirriraj Hospital.

vi Reference Sources of Literature and Information Retrieval

There were recent editions of a few standard textbooks (mainly Thai translations from English and some local monographs on specific problems, and some student mammals) and photocopies of selected sections of certain more advanced works in the department. There were no current toxicology or pathology journals.

I was told that TISTR did not have an extensive library, but that visits were made to the library of the Science Faculty of Mathidol University, where there were modern standard works, some journals and access to computer searches of certain databases (via DIALOG).

The staff were familiar with Index Medicus, major texts on pharmacology, including Martindale and Goodman and Gilman, but they did not have regular access to major journals, such as Toxicology and Applied Pharmacology, Archives of Toxicology, Food and Chemical Toxicology, or to a corresponding range of medical and pathological periodicals. Selected papers could be obtained as photocopies.

Relevant WHO and IPCS publications on toxicology were not regularly seen in the department.

5. Assessment

a) General

I was very impressed by the enthusiasm and interest of all the staff, and I was afforded many personal and professional courtesies by everyone from the Governor of TISTR, Dr Smith, to the administrative staff.

It was a pleasure to find here such dedication and willingness in the nucleus of a drug development organisation, which was working very energetically to fuse the different disciplines (chemical analysis, pharmacognosy, pharmacology and toxicology). There was awareness of many of the limitations they faced and great eagerness to learn how to overcome deficiencies and areas of ignorance. The desire to advance must be considered in relation to the absence of experience of drug discovery and development, the constraints imposed by the available resources and the limitation entailed by the role envisaged for PNPD in TISTR in relation to that of the Government Pharmaceutical Organisation (of Thailand; GPO) and arrangements that might be made for clinical pharmacology advice and formal trials in man

The relation between the work of PNPD, the possible involvement of GPO and the formal regulatory control of pharmaceuticals and related products by the Thai FDA must also be considered.

b) Principles of Drug Development

Development of a drug into a medicine requires identification and characterisation of a desirable pharmacological activity, an ordered series of toxicity tests, appropriate mutagenicity studies (and possibly complex reproduction and carcinogenicity experiments), careful pharmacokinetic and drug metabolism investigations and critical assessment of all those data, obtained according to comprehensive national guidelines, mostly before clinical trials in healthy humans and patients. The latter are followed by further non-clinical work and definitive clinical studies, culminating in a large dossier, which must be approved by the Thai FDA (or the corresponding official body in any other country) before a Product Licence (NDA) is obtained, after which the new medicine can be prescribed and sold. In parallel, chemical and pharmaceutical development is required to define the compound, to make useful formulations and to prove their stability. Throughout these laboratory and industrial activities there must be medical consideration of the clinical need for the potential medicine, of the professional and public view of existing competitor

products, and careful commercial-industrial assessment of the financial viability of the eventual product in the market place, including its protection as intellectual property.

The stated policy of regulatory authorities, including the Thai FDA, is that products of natural origin will be evaluated by the same criteria of quality, safety and efficacy as synthetic chemicals, the only distinction being the possible lessening of certain requirements if a new product of natural origin is identical to or very close to one for which there is already a good history of prolonged safe use.

A product might be developed as a 'herbal' or 'health food' rather than a prescription medicine, in which case there will be similar but possibly less onerous (in Thailand) requirements for evidence of quality, safety and efficacy, but it would be unwise to anticipate much reduction without the prior agreement of the national regulatory agency.

To make a Thai product available in any industrialised country would require it to meet all their comprehensive data requirements, which will be identical to those for any new synthetic chemical medicine.

c) Organisation of Drug Development at TISTR

Although not one of my formal objectives, my experience of the pharmaceutical industry suggests several points of concern, subject to my correct understanding of the administrative arrangements.

i PNPD is considered to be responsible for development of natural products, or extraction, identification and development of responsible chemical, up to and including sufficient clinical work in patients to demonstrate a useful therapeutic activity. The GPO will then decide whether to take over, either arranging definitive industrial development and clinical studies, followed by a Product Licence application, or by making a collaborative arrangements with an industrial firm (local or multinational).

I understand that the GPO is not involved prior to the stage just described.

ii PNPD appears not to have close regular liaison with a medical expert able to advise on the medical value of projects, on the state of competitor products, or on the appropriateness of the preclinical work in relation to medical requirements for gaining official approval for work in healthy man or patients.

iii The chemical analysis and quality control of a natural or synthetic product, the related pharmaceutical development and its associated stability tests and quality control work are a major continuum that cannot efficiently be separated into 'early' or 'late' components to be passed between separate organisations that have not had any prior involvement.

iv Similarly, the toxicity work represents an ordered programme that must also be planned and completed over a prolonged period if it is to be effectively co-ordinated to permit different phases of work in man to be done without administrative

ordinated to permit different phases of work in man to be done without administrative interruptions.

The same requirement for orderly progression and reporting applied to the pharmacological studies.

v The apparent separation of responsibilities will make difficult to devise an effective strategy for the protection of intellectual property, and without that it must be questioned whether projects can become financially viable.

For these reasons I consider that there is need to introduce appropriate medical and industrial-commercial liaison at an early stage in the inception and conduct of projects, including arrangements for giving strategic advice.

d) State of the Toxicological Function at TISTR

There is a promising base but much is required to meet regulatory standards. The most striking deficiencies in relation to conventional drug development are the absence of facilities to do toxicity testing in a second species (the dog or perhaps a primate), the lack of any drug metabolism and pharmacokinetics function, and the lack of a Good Laboratory Practice (GLP) system of controls. All these are essential if any preparation is to meet the Thai FDA requirements for any treatment of man, unless full development work is restricted to slightly modified versions of traditional plant extracts, or studies are to be limited to identifying pharmacological actions and interesting chemicals. The reliance on an external academic scientist for basic mutagenicity testing would be acceptable only if she is able and willing to conform to specific regulatory requirements. The full test results and interpretation are essential to gain even clinical trial approval.

The same caution about an external scientist applies to reproduction toxicity testing, although that is less important at an early stage of development, as females should anyway be excluded from initial human trials.

In addition to the lack of a GLP system, the existing Toxicology Group has some specific needs for equipment and expert training, and it must have ready access to certain types of journal and monographs. If its work is to be acceptable to a regulatory authority, it must have direct pharmaceutical analytical support to verify the composition and stability of preparations being tested to provide regulatory data.

The Toxicology Group is very small and there is a risk that it might be swamped by technical procedures rather than its proper scientific role of experimental design and interpretation, and project organisation, unless only a few substances reach the stage of being test. Its members need, in any case, additional experience in general, as well as of specific areas. It is now time to develop its capabilities in an ordered fashion, as discussed below in Section 6.

vi Conclusions and Recommendations

Three areas are considered here - general aspects, the toxicology function, and specific projects.

A General

i) At least a skeleton mechanism and organisation for considering all the activities involved in full development of a project to compilation of a regulatory dossier to obtain permission for human volunteer and clinical trial (TND) work should be devised, especially including liaison with a skilled clinical pharmacologist, who would also advise on the medical prospects of such potential medicines.

ii) An analogous and related system is required for industrial-commercial liaison and advice, including consideration of intellectual property protection.

This should include clarification of the role and responsibilities of the GPO in relation to subsequent manufacture and sale of products after gaining a licence from the Thai FDA. It must be realised that a significant change in the composition or formulation of a medicine due to the move from pilot plant to industrial manufacture may force repetition of extensive toxicity, pharmacy and clinical studies, with great cost in time and resources. To avoid this it is important to prevent too complete a separation of 'early' and 'late' development. They are a continuum.

I suggest that advice on these aspects might be obtained by short-term consultation with a senior R&D manager from a multinational pharmaceutical firm.

Formal collaboration should be considered with a local expert in clinical pharmacology, who would have to be prepared effectively to act as the 'Medical Director' does in a conventional pharmaceutical firm. If someone with that specific type of skill is not available, could limited training be offered to a local clinician with appropriate interests and some experience of drug trials in man?

B Toxicology Function

i) Overall Progress

It must be realised that the existing staff and facilities cannot meet current national requirements for human studies of novel drugs as I understand them, because of the absence of the major functions noted in 5(d) above.

The possibilities are to restrict development to projects that do not depart much from traditional plant extracts (except for pharmacological and chemical work with no possibility of clinical studies), to make the massive investment required to initiate these mandatory activities, or, as successfully done in the recent past by the Japanese, to make formal collaborative agreements with multinational firms for joint development of specific materials. PNPD would offer potentially valuable and partly explored activity (including some toxicity testing) in return for joint full development, including training of PNPD staff and an appropriate financial return on any substance that became a successful medicine.

I strongly recommend that consideration be given to such collaborative agreements, subject to the appropriate national and legal considerations.

Again, advice from a senior pharmaceutical R &D manager might be valuable on this possibility and usual terms and conditions of joint ventures of this type.

ii) Specific Needs

a) Staff Training and Numbers

Both Mr Jakkrapong, and later Miss Prapaipat, would benefit from further experience of scientific toxicology and drug development work. This will require extended absence overseas, for example by work for a PhD (scientific toxicology) and attachment to the R&D group of a pharmaceutical firm (drug development, which can only be learnt 'on the job').

If the pharmacological and chemical work is as successful as it promises to be, then, even if medical and industrial realism reduces the number of projects, the need for subacute and related toxicity studies will increase to the point where additional staff will eventually be required.

b) Major Facilities

Mixing lavatories and laboratories is unsatisfactory and potentially dangerous. Can anything be done to improve the building?

The existing animal rooms are probably just about adequate for current use, given the latitude and climate of Bangkok, and the availability only of conventional standard rodents.

If standards and throughput are to rise in a few years, rooms with air conditioning, controlled lighting and barriered access should be considered, as should facilities for work on radioactively labelled and other types of hazardous chemicals.

c) Major Functions

1. It is essential now that GLP controls be instituted as soon as possible.

I recommend that a short visit by an expert adviser be considered, or that Mr Jakkrapong be sent overseas for about one month to learn in detail how to devise and enforce the system, especially its requirements for written Standard Operating Procedures and controlled record keeping.

2. An adequate system for full Ames mutagenicity testing must be devised.

I suggest that an effective way might be for the PNPD microbiologist to be trained in the Ames and the related micronucleus test (a further regulatory requirement) by an overseas attachment for about 6 months. On her return, consideration should be given as to whether she could do the necessary technical work in the present university laboratory to avoid duplication of expensive equipment and special facilities. This possibility should be explored, because the amount of work required now is unlikely to justify establishing the special facility at TISTR.

3. Analyses of dosing materials in toxicity tests is essential.

Either chemical analyses or, less suitably, standardisation by bioassay will be required for every formal test done for regulatory purposes. This has implications for other members of PNPD.

4. Equipment. It is essential in any subacute toxicity test that ophthalmoscopy be done, that urine be analysed and that certain blood clotting factors be investigated.

I recommend that an indirect ophthalmoscope be obtained and that Mr Jakkrapong and Miss Prapaipat be trained in its use. The latter could be done by liaison with an ophthalmologist in a local medical school.

I recommend that metabolic cages be obtained and used.

I recommend that a small, semi-automated blood coagulometer be obtained and instruction in its use be given by an haematologist in a local medical school, or, less satisfactorily, that in every subacute study at least the prothrombin time be measured by a test tube method.

I further recommend that planning now be undertaken to recruit and train staff and provide the facilities for basic pharmacokinetic work (overall balance and assessment of half-life of excretion from blood of the specific chemical or a marker substance).

d) Other Needs

1. Regular access to major toxicology, pathology and medical journals is essential, and so is bench-side availability of the principal specialist monographs.

I recommend that certain journals and books be provided within PNPD, e.g. the periodicals mentioned in Section 4.6 and monographs on laboratory animal pathology and haematology.

I recommend that certain journals and books be provided within PNPD, e.g. the periodicals mentioned in Section 4.6 and monographs on laboratory animal pathology and haematology.

2. Closer collaboration with an expert statistician would be helpful.

Would it be possible for the Computer Centre to nominate one of its staff to specialise in the design and analysis of biological experiments?

It would be valuable, too, if the toxicologists were provided with hand calculators and encouraged to do their own initial testing once they were familiar with the techniques.

4. It may be helpful to examine the ECG in the rat in certain subacute toxicity tests. A suitable machine and training should be provided if possible.

e) Additional and Miscellaneous Points

1. The Toxicology Group does a limited amount of testing under contract for local firms.

This should be encouraged as a source of work, funding and contacts. Its capabilities might be appropriately advertised at meetings of the Thai Toxicology Society and to the Pharmaceutical Manufacturers' Group of the Federation of Thai Industries.

2. There are several groups of toxicologists and especially toxicological pathologists in various Science, Medical and Veterinary faculties in Bangkok.

It would be to the advantage of all of the pathologists if they were to meet informally from time to time to compare slides.

3. The Toxicology Group and, from personal enquiry, many other laboratories in Bangkok use automated clinical chemistry and haematology analysers, which are only standardised by use of commercially available high and low value control materials.

This is not adequate and consideration should be given to a 'External Quality Assurance Scheme,' involving regular circulation of 'unknown' samples, central collation of results and their return to participants. This greatly improves analytical accuracy.

From experience in the UK and USA, it may well be that TISTR/PNPD could start a very profitable small business by providing the unknown samples and organising the system.

4. In view especially of the proximity of TISTR to Kasesart University, and the extensive use of plant products to treat veterinary parasitic diseases, should consideration be given to collaborative screening of PNPD materials as veterinary therapeutics?

In any case, an informal link with the veterinary pathologists should be encouraged.

C. Specific Projects (see outline record in Appendix 4)

The following summarises our detailed discussions.

1. Plegasil

At present most attention is being given to this anti-inflammatory preparation, as a critical subacute dermal toxicity test in the rabbit should be done shortly.

In detailed discussions, it was agreed that a chemical fingerprint and bioassay of the anti-inflammatory activity would be done as quality control measures on the present and all subsequent batches of Plegasil, using part of the batch as a working standard. Without such methods there is no means at present of standardising or characterising any batch of Plegasil, of ensuring consistency of activity, or of determining its stability.

Summary data from Dr Wanee's mutagenicity testing have raised a question about the possible mutagenicity of a major constituent terpinen-4-ol. I consider that the available information is inconclusive and that the test should be repeated in a standard manner as soon as possible, using pure terpinen-4-ol, and preferably in parallel with a full test on Plegasil (all 5 Ames strains). If both are negative, then there is no cause for concern. If the oil is positive then there must be doubt about its safety until that activity can be shown not to concern man, or unless it can be excluded by a different refining process. If pure terpinen-4-ol itself is positive, the same considerations apply to any oil containing it.

2. The other topical agents would be developed according to the general plan in the appendix.

3. Hypocholesterolaemic Agent

I was told that it was being prepared as a spray dried aqueous extract of hibiscus petals and that there was a long history of safe consumption of hibiscus flower infusions in Thailand and elsewhere. Further, the Thai FDA would permit development and licensure as a 'health food' of such an extract with a specific medical claim.

Under these unique circumstances the development plan shown was agreed.

For development of a more conventional modified extract, or a pure substance isolated from it, the model "internal drug" was agreed.

4. The general approach to cosmetics etc. was also agreed.

Stress was placed on the importance of chemical and pharmaceutical QC standardisation and on the need to start such approaches and to devise the necessary techniques as soon as possible once a candidate development material has been identified. The late stage of development of Plegasil without such controls illustrates the problems caused by the separation between PNPD's work and the role of the GPO as presumptive manufacturer.

vii Thanks

In my brief time at TISTR I was warmly befriended by all the staff of PNPD, especially Mr Jakkrapong, Mrs Pattama, Miss Prapaipat and Dr Wilaiportn, Mrs Sasithorn, Miss Chuleratana, Dr Montree, Mr Taweesak and Dr Sunthorn and all helped greatly to make my visit so interesting and pleasant.

Mr Kortas of UNIDO/UNDP, too, successfully minimised the inconveniences of administrative hiccups.

I thank them and their colleagues.

Summary

1. Professor A D Dayan, Dept of Toxicology, St Bartholomew's Hospital Medical College, London, visited the Pharmaceutical and Natural Products Division, Thai Institute of Science and Technological Research, Bangkok, from 19 February to 11 March 1990, to advise on their toxicological capability fro the development of pharmaceutical products from traditional Thai medicines.

2. After reviewing the position of the Toxicology Group, it is concluded that the current organisation is not well adapted to successful trials of new medicines and that certain major functions are lacking which are essential for successful drug development.

3. It is recommended that:

a) consideration be given to joint ventures with multinational pharmaceutical firms to gain experience and income, and to compensate for the complete absence of certain facilities essential for full drug development.

b) close liaison with an experienced clinical pharmacology expert is needed.

c) continuing liaison is necessary with an expert capable of advising on the industrial-commercial-intellectual property aspects of projects.

d) the Toxicology Group must institute a GLP system as soon as possible, especially the record keeping and checking procedures.

e) advanced scientific training and experience of pharmaceutical industry toxicology is required.

f) consideration should be given to training a PNPD staff member in the Ames and other mutagenicity tests, and to arranging for that work to be done in Dr Wanee's or some other laboratory.

g) analytical support for toxicity tests is needed.

h) metabolic cages, an indirect ophthalmoscope and a blood coagulometer, and training in their use, are all immediate needs.

Other recommendations to aid progress are made and possibilities are raised for additional activities by the Toxicology Group, PNPD and TISTR.

There is an excellent beginning, which needs help to grow to maturity.

APPENDIX 2

Tentative Topics on Toxicology Discussion

21 Feb. 1990	09.00 - 12.00 am.	Lecture on "Guidelines of Toxicity Study for Drug Registration"
	01.00 - 04.30 pm.	Discussion
22 Feb. 1990	09.00 - 12.00 am.	Discussion on guidelines for general toxicity study - acute study - repeated administration study
27 Feb. 1990	09.00 - 12.00 am.	Discussion on guidelines for special toxicity study - Mutagencity study - Carcinogenicity study - Reproductive study - Immunotoxicpgy - skin and eye irritation test - sensitization test
28 Feb. 1990	09.00 - 12.00 am.	Lecture on "Pharmacokinetics"
	01.00 - 04.30 pm.	Discussion
05. March 1990	09.00 - 12.00 am.	Lecture on "Internpretation and Extrapolation from Animal to Man"
	01.00 - 04.30 pm.	Discussion
06. March 1990	09.00 - 12.00 am.	Discussion on safety evaluation of cosmetic and household products
	01.00 - 04.30 pm.	Discussion on health food for Registration
08. March 1990		Conclusion and Recommendation
09. March 1990	09.00 am.	Dr. Maltarou, Mahiod. Univeristy (Careinogenesis expert)
		Discussions and visit chemical analytical facility.

APPENDIX 3

Tentative Toxicology Programme

Prof. A. D. Dayan

19 February - 11 March 1990

Thailand Institute of Scientific and Technological Research

19 Feb. 1990	Arrival
20 Feb. 1990	Visit TISTR (2.00 p.m.) - meet the TISTR Governer and PNPD Group - visit UNDP (9.00)
21 - 23 Feb. 1990	Toxicology discussion
24 - 25 Feb. 1990	Holiday
26 Feb. 1990	Visit Food and Drug Administration
27 Feb. 1990	Toxicology discussion Visit National Cancer Institute of Ramathibodi Hospital
28 Feb. 1990	Toxicology discussion
1 - 2 March 1990	Visit Mahidol University,
3 - 4 March 1990	Holiday
5 - 6 March 1990	Toxicology discussion
7 March 1990	Seminar on "General Toxicological Task need for Drug Development" at 02.00 - 03.30 p.m. TISTR
8 March 1990	Toxicology discussion
9 March 1990	Report
10 March 1990	Holiday
11 March 1990	Departure

APPENDIX 4

CONCLUSION AND RECOMMENDATION

(for general discussion 8.3.1990)

A. CONCLUSION

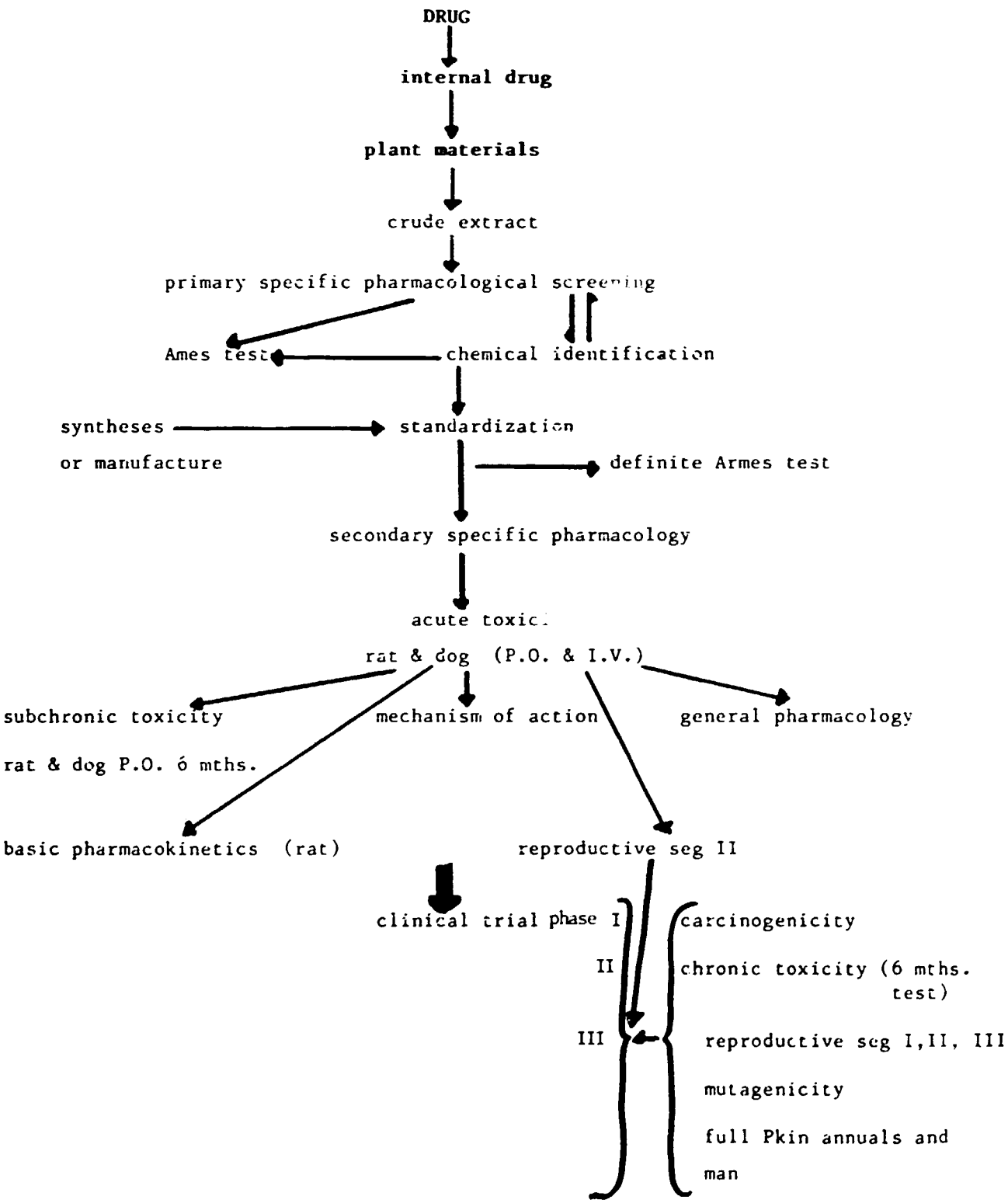
Development Programme

- Drug
  - internal drug
  - topical drug
- Health food with specific claim
- cosmetics, toiletries and household products.

B. RECOMMENDATION

1. Improve capability of microbiological lab in order to take responsibility in mutagenicity study especially Ames test.
2. Set up methods for standardization (Q.C.) of the active fractions/ active compounds (bioassay/chemical assay)
3. Facility of toxicology lab, present and future
4.
5.
6.

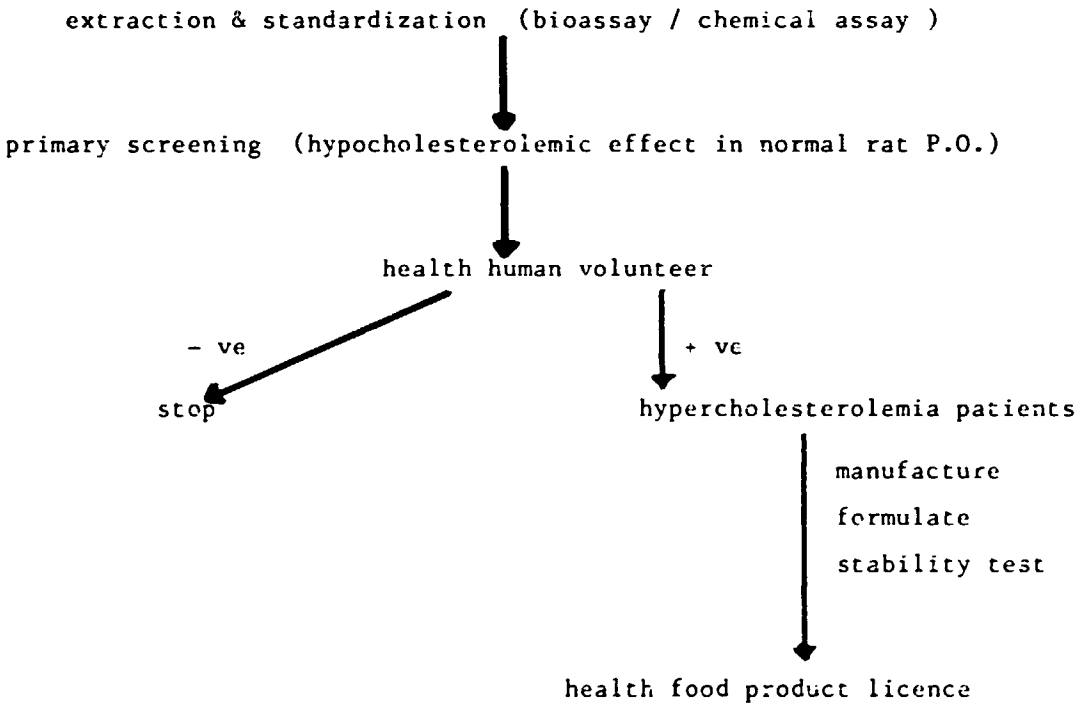
Standardise Complex process by Bioassay.


DRUG
internal drug
plant materials
crude extract
primary specific pharmacological screening
Ames test
chemical identification
syntheses
or manufacture
standardization
definite Armes test
secondary specific pharmacology
acute toxic.
rat & dog (P.O. & I.V.)
subchronic toxicity
rat & dog P.O. ó mths.
mechanism of action
general pharmacology
basic pharmacokinetics (rat)
reproductive seg II
clinical trial phase I
II
III
carcinogenicity
chronic toxicity (6 mths. test)
reproductive seg I,II, III
mutagenicity
full Pkin annuals and man

Health food with specific claim (hypocholesterolemic effect)

(adequate record of prior human use with safety)

applicable only under prior regulations proceedures



Cosmetics toiletries and household products

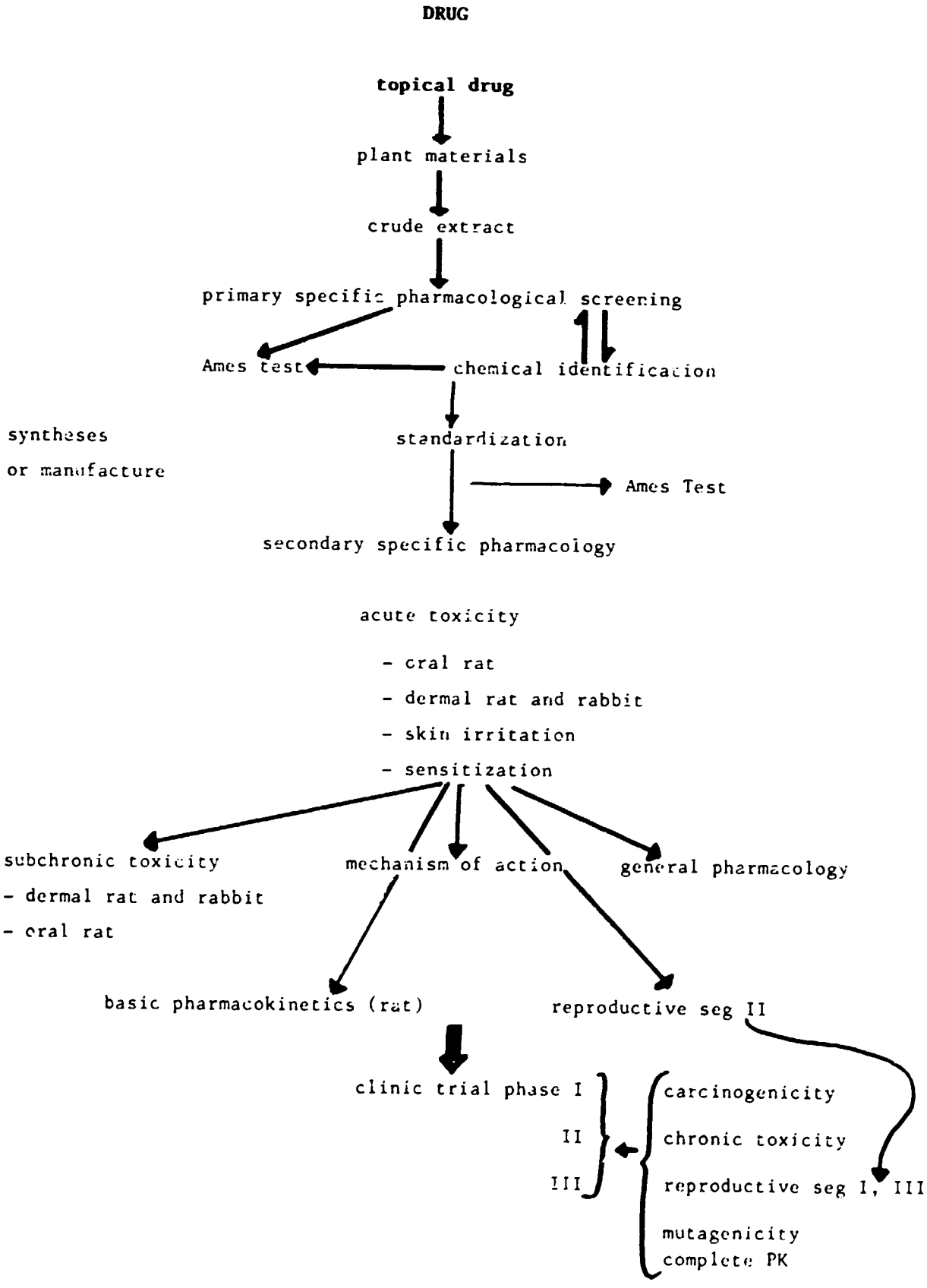
1. known ingredient, novel mixture

at least - acute toxicity test
oral
dermal
irritation
ocular irritation
sensitization

2. a novel ingredient, Be certain of 'novelty'

full set of development programme

- subac dermal tox
oral ''


DRUG
topical drug
plant materials
crude extract
primary specific pharmacological screening
Ames test
chemical identification
syntheses
or manufacture
standardization
Ames Test
secondary specific pharmacology
acute toxicity
- oral rat
- dermal rat and rabbit
- skin irritation
- sensitization
subchronic toxicity
- dermal rat and rabbit
- oral rat
mechanism of action
general pharmacology
basic pharmacokinetics (rat)
reproductive seg II
clinic trial phase I
II
III
carcinogenicity
chronic toxicity
reproductive seg I, III
mutagenicity
complete PK