DRUG DEVELOPMENT IN INDIA

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Medicine has changed more in the last fifty years than perhaps in any comparable period during the history of mankind. Despite the enormous progress made, there is a lack of drugs which can prevent or effectively treat a large number of major illnesses. The quest for new drugs is essentially focused at two broad objectives. One is to develop a drug for a malady for which no prevention and/or cure is presently available. The second objective is to develop better drugs for those diseases where treatment though presently available, is sub-optimal either in terms of therapeutic efficacy or with regard to associated adverse reactions. The two objectives are not mutually exclusive as a major therapeutic breakthrough in terms of the discovery of a new drug often leads to further modifications in the drug structure with the ultimate development of better compounds. The discovery of pencillin was a major breakthrough and fulfilled to a large measure the first objective, development of newer synthetic pencillins with additional advantages of oral absorption and broader or more selective spectrum of activity, is an example of the achievement of second objective.

Drug Development Programme ; The Indian Scene (Fig. 1)

Drug industry has rapidly expanded in the country since the dawn of independence. From a turn over of about 50 crores in 1947, recent estimates put it around 470 crores during 1976. This is indeed a phenomenal growth. According to the Hathi Committee Report (1), the drug industry in India can be broadly divided into (i) organised sector and (ii) small scale sector. The organised sector has 116 units; of these there are 25 units with foreign equity of more than 50% and 26 units with a foreign equity of 50% or less. The small scale sector has approximately 2500 units; of these there are 9 units with foreign equity of more than 50% and 6 units with foreign equity of 50% or less. One of the essential problems in the Indian drug industry is a low turn over for the manufacture of basic drugs as against a much higher turn over for the manufacture of formulations. For example, in 1979, out of a total turn over of 1250 crores the value of bulk drug production was put at Rs. 200 crores while value of formulation was well over Rs. 1000 crores. The Hathi

Committee identified 117 basic drugs as urgently required for the maintenance of essential drug delivery and public health services in the country. Of these the Indian Drugs and Pharmaceuticals Ltd. (IDPL), a public sector undertaking, is at present manufacturing 40 items. It is planned to increase this to 51 items through suitable expansion of its manufacturing capacity. It may be of interest to note that the Indian public sector investment in the field of pharmaceuticals and chemicals was as much as 14.7% of the total investment of Rs. 8973 crore as on April 1, 1976. Inspite of this the indigenous capacity for the production of essential basic drugs is significantly short of the country's requirements.

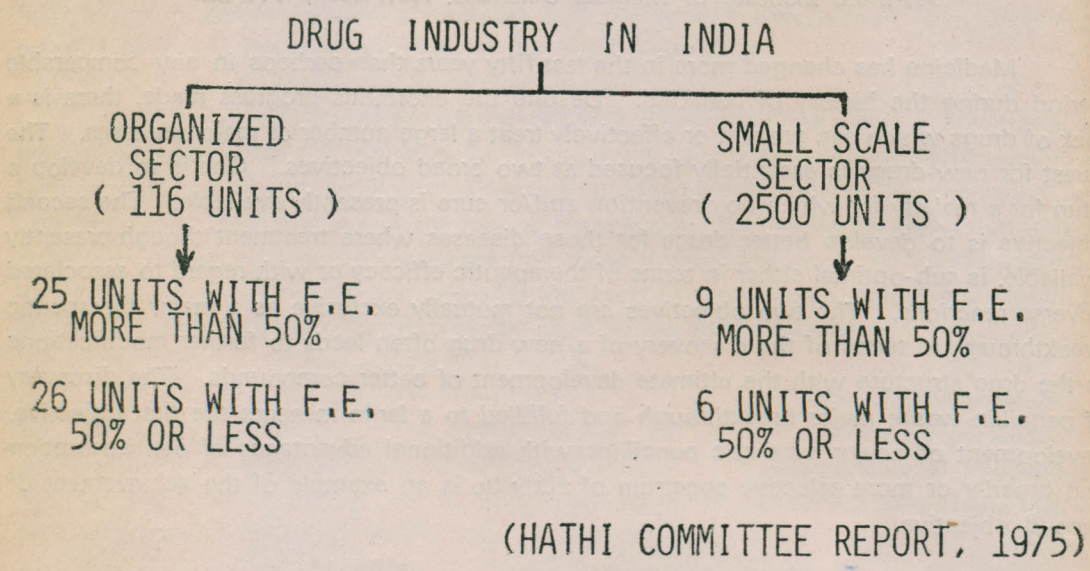

Fig. 1

The first priority for the pharmaceutical industry, therefore, is to develop indigenous know-how and technology for the production of basic drugs as identified in the Hathi Committee Report. This can only be done if there is a shift of emphasis from the production of formulations to that of essential drugs. This necessarily implies a certain amount of sacrifice on the part of the industry as the margin of profit in the manufacture of basic drugs is less than that for the formulations. This type of drug development programme does not need the help of clinical pharmacology, as all these drugs have been in use for a considerable period of time, and have passed through various phases of clinical evaluation. The only need is of the study of bioavailability of these drugs when manufactured by different units in the country. Bioavailability means the availability of drugs in the biological system to elicit the therapeutic response. A drug produces therapeutic effect when the concentration or the quantity of the drug attains minimal critical level at the site of responsive tissue. The term bioavailability or therapeutic equivalence refers

to the rate and extent to which the pharmacologically active ingredient becomes available in the biological system in order to elicit the desired therapeutic response. The essential need for the study of bioavailability is the development of improved methods for the analysis of drugs in biological fluids, particularly methods that are sensitive, specific and precise. This however, is a separate subject and shall not be discussed further.

Development of New Drugs :

Having emphasised the importance of producing basic drugs as the priority area for the drug development programme in India, the need for the research efforts in the development of new drugs in terms of the already defined objectives (p.1) remains to be highlighted. The definition of a new drug in the Indian context includes :

(i) a drug whose composition is such that it is not generally recognized among experts as safe and efficacious for use in the disease conditions recommended or suggested. Essentially, this would be a new compound developed in India or abroad but not yet administered in human subjects ;

(ii) a drug which, during the course of investigations, has been found to be safe and efficacious but which has not been used otherwise than during the investigations to any large extent or for any appreciable length of time. Generally, this would include a new compound developed abroad where early clinical trials have been completed and the drug has already been released for therapeutic trials ;

(iii) a recommended new therapeutic use of a known drug which has already been proved to be safe and efficacious in other disease condition(s), on the basis of which a marketing permission has previously been accorded.

(iv) a known safe and effective drug, already released for use, for which it is now intended to change the vehicle, or formulation, or the route of administration; and

(v) a combination of two or more drugs, one or more of which have previously been shown to be safe and effective, or that the combination has previously been considered as safe and effective but the proportion of its components is now intended to be changed.

Under the Drugs and Cosmetics Act, no new drug can be imported or manufactured in the country unless it has been approved by the Drug Controller of India. In order to obtain such an approval essential, information including data for establishing the safety and therapeutic efficacy of the drug, needs to be provided. The following excerpts are

from the proforma available from the Drug Controller of India for this purpose; the essential information required includes :

(i) The chemical description of the drug.

(ii) The description of the pharmaceutical form/forms in which it is proposed to be marketed and the route of administration, the proposed dosage and the claims to be made for such a drug.

(iii) A detailed statement of the composition of the drug giving the amount of each ingredient whether active or not, contained in a stated quantity of the drug.

(iv) Details of the method of manufacture, the details should include the raw-material used in various stages, the precautions taken to see that the raw-materials or intermediates are not present as impurities in the final product.

(v) Analytical specifications including the tests for identity, purity and method of assay for the bulk drug as well as the formulations. In case of a combination containing 2 or more active ingredients, the analytical methods should be capable of identifying and determining wherever possible the strength of all the active ingredients individually. The specifications should also include limits for impurities.

(vi) Reports of preclinical testing in animals in respect of toxicology, and if available, efficacy.

(vii) If the drug has already been used in clinical studies outside India, relevant information on human tolerance, efficacy, dosage range and route of administration. If information is available on human pharmacokinetics, pharmacodynamics and mechanism of action, it should also be made available.

Early Clinical Evaluation of New Drugs :
The Role of Clinical Pharmacology.

With regard to the drug development programme the eseential role of clinical pharmacology pertains to the early clinical evaluation of new drugs. These studies are conventionally divided into phase I, phase II, phase III and field trials. As there is a continuous spectrum of interaction between different phases, a precise delineation of each step has not always been possible; hence the recent concept of phase I, phase II (a) and II (b) and field trials. It is perhaps more important to understand the objectives at each level rather than to get involved in pure semantics.

The objectives of phase I clinical trials are essentially focused at establishing the safety of the drug under reference (human tolerance), and at the study of pharmacokinetics including absorption, distribution, biotransformation and excretion of the drug. An essential pre-requisite for undertaking phase I studies is the availability of adequate animal data. The existing rules regarding pre-clinical toxicology as framed by the Drug Controller of India, are shown in Table I. In essence, available data should include acute toxicology, and sub-acute or chronic toxicity

TABLE I : Drug regulation in India : Animal toxicity requirements.

Category	*Duration of human administration*	*Phase**	*Subacute or chronic toxicity*
Oral or parenteral	Several days upto 2 wk	CP, CT, MP	2 species; 2 wk
		CP	2 species; 4 wk
		CT, MP	2 species; 3 wk
		CP	2 species; 4 wk
	Up to 3 mo	CT	2 species; 3 mo
		MP	2 species; 6 mo
	6 mo to unlimited	CT, MP	2 species; 6 mo
Dermal	Short-term application	CP	1 species; single 24-hr exposure followed by 2-wk observation
	Long-term	CT, CP, MP	1 species; number of applications and duration commensurate with the preparation and the duration of use; the occlusive irritant test may be sufficient
Inhalation (general anesthetics)		CP, CT, MP	4 species; 5 days (3 hr/day)
Ophthalmic, otic, nasal	Single application		Irritation tests, graded doses, 1 species; 3-wk
	Multiple application	CP, CT	daily applications, as in clinical use
		MP	1 species; duration commensurate with period of drug administration
Vaginal or rectal		CP, CT, MP	1 species; duration and number of applications determined by proposed use

CP : Clinical Pharmacology; CT : Clinical Trials; MP : Marketing

studies in atleast two species one of which being a non-rodent species. The period of sub-acute or chronic administration of drug in the animal species is related to the likely duration of human administration. In addition there should be adequate data regarding dose-range and pharmacokinetics in the animal species. The clinical investigator must be completely satisfied with the available data and should carefully weigh the potential benefits against the likely side effects following human administration. An additional safeguard can be the clearance from the institutional Ethics Review Committee. Such a committee is in existence at the All-India Institute of Medical Sciences for the last two years. The members of this Committee except one, do not belong to the Institute; amongst them is a retired judge of the High Court who primarily looks at the ethical and legal aspects of the studies intended to be undertaken. These latter aspects must receive continuing attention. All clinical investigators conducting drug evaluation studies should be familiar with the guidelines as enunciated in the Declaration of Helsinki and adopted by the World Medical Association at its meeting in June 1964. The major areas of concern expressed by the WHO Group on Principles for the Clinical Evaluation of Drugs (2) in relation to the ethical aspects of clinical trials include the following:

a. consent of subjects,
b. safety of subjects,
c. reward of subjects,
d. payment of costs,
e. remuneration of investigators,
f. compensation for injury;
g. subjects with limited civil rights (mentally retarded children, psychiatric patients, prisoners).

These have been reiterated in a subsequent report from the WHO (3). Without going into the details of each one of these areas it may be stated in general terms that an informed consent from every subject who volunteers for study should be obtained, that the subject must volunteer without any fear of the investigator (as may happen in the case of medical students) or any undue financial incentive, and that every possible precaution should be observed in order to ensure utmost safety and welfare of the subject.

The main objective of phase II clinical trials include the establishment of clinical efficacy, delineation of the most effective dosage schedule, and better definition of drug pharmacodynamics. The studies concerning drug pharmacokinetics which are primarily undertaken during phase I, may be further extended into phase II. For both phase I

and phase II studies, it is essential to design an appropriate protocol. It is not intended to discuss here in any detail the protocol design for early clinical studies. However, the following constitute focal points for consideration in such a protocol :

a. Selection of subjects,
b. Number of subjects,
c. Initial dose,
d. Maximum dose,
e. Record of subjective and objective parameters,
f. Drug levels in body fluids and
g. Evaluation of organ system toxicity.

Phase III or controlled therapeutic trials constitute the next stage in the drug development programme. Bradford Hill (4) has defined the controlled therapeutic trials as follows :

> "a carefully, and ethically, designed experiment with the aim of answering some precisely framed question. In its most rigorous form, it demands equivalent groups of patients concurrently treated in different ways. These groups are constructed by the random allocation of patients to one or other treatment; such an allocation may sometimes preferably be made within more but smaller homogeneous subgroups composing the total groups. Sometimes carefully matched pairs of patients may provide the contrast. In some instances patients may form their own controls, different treatments being applied to them in random order and the effects compared. In principle the method is applicable with any disease and any treatment. It may also be applied on any scale; it does not necessarily demand large numbers of patients. It should be designed to promote rather than hinder the traditional method in medicine of acute observation of disease by the clinician at the bedside."

Besides giving information regarding the efficacy of a particular drug treatment administered at a pre-decided dosage level to a group of patients, in comparison with either a placebo treated or another drug treated group, these studies may also yield useful data in relation to the mechanism of action, contra-indications, as well as the development of drug tolerance, resistance and drug dependence.

The two essential pre-requisites for undertaking controlled therapeutic trials are (i) availability of additional animal data and (ii) a properly designed protocol.

The additional animal data should include the results of completed long-term toxicity studies as well as the results of special toxicological studies. The latter have assumed considerable significance during the last decade and include the study of teratogenic, carcinogenic and mutagenic effects. Special techniques and procedures are now available

which are useful in the assessment of potential teratogenic and carcinogenic risks associated with the use of new drugs. In all fairness it must be stated, however, that inspite of intensive research carried out over the last several years, there are still no fool-proof methods available for assessing the carcinogenicity of drugs. The problems of testing and evaluation of drugs for carcinogenicity have been summarised in a WHO Report (5); similarly the guidelines for testing of drugs for mutagenicity have been discussed in another WHO Report (6).

The protocol for therapeutic trials is essentially different from that used in phase I and phase II studies. It is extremely important that major time and effort should be devoted to the development of a most appropriate protocol for a particular therapeutic trial. In essence, such a protocol must clearly state the objectives of the study, the criteria for the selection of patients and number of patients in each group, experimental design and the duration of the study, end points or cut off points, relevant laboratory investigations to be undertaken, operational plan, and finally the necessary financial requirements. It hardly needs emphasis that the clinical investigator for such a study as well as the institution where the study is to be undertaken, should be chosen with great care. In a multi-centre trial, it is mandatory to nominate a co-ordinator who should visit all the participating centres, discuss the details of protocols with each investigator, and get acquainted with the out-patient, in-patient, and laboratory facilities available at each centre. Finally, a biostatistician should always be consulted while designing the protocol so that data record forms are designed in such a way as to ensure final computation and analysis without any difficulty.

Even if a drug has been cleared for usage outside India, the permission for its release in the country requires limited clinical trials so as to evaluate the recommendations for the dosage schedules as well as to confirm the safety of the drug in Indian population. It is, however, expected that all the data including pre-clinical animal pharmacology and toxicology as well as the results of clinical pharmacology evaluation and therapeutic trials as submitted to the drug regulatory agency in the country where the drug has been cleared for marketing, will be made available to the Drug Controller of India. Only on the basis of available data can the permission be given for conducting limited clinical trials in India. If such data cannot be made available then appropriate studies may have to be conducted in India for the purpose of satisfying the drug regulations. Mere evidence of the fact that the drug has been cleared for use abroad does not necessarily imply that a similar permission will be obtainable in this country. The reasons for such regulations are based on sound scientific evidence concerning the genetic and racial differences in biotransformation of drugs thereby producing at times unexpected adverse reactions. Furthermore, a variation in dosage schedules may be necessary in view of the differences in body weight, intestinal

absorption, hepatic metabolism, drug transport especially if the drug is bound with albumin, and variations in urinary drug excretion dependent on the pH.

The results of each study at the end of phase I or phase II or therapeutic trials should be submitted to the Drug Controller; any adverse drug reaction observed during any of the phased studies should also be reported. If all the studies, completed satisfactorily, indicate both safety as well as efficacy of the drug then the question of giving marketing permission is considered. At this time one of the important questions relates to the cost of the drug. This is as it should be, because in a country like India where resources are limited for health care delivery system, cost effectiveness and the risk – benefit ratio, constitute important considerations.

Once permission is granted for the marketing of the drug, there is no mechanism at present which would ensure monitoring of the adverse drug reactions as may become manifest because of the long-term usage of drug in a large segment of population. Such an arrangement does exist in certain countries, but not in India. It is, however, important that this should be so and after the grant of permission for marketing the drug should be on a 'probation' or a 'parole' for a period of 2–3 years before the safety of its continuing usage can be confirmed. In the event of any evidence to the contrary such information should provide the necessary feed back to the pharmaceutical industry so as to encourage appropriate modifications in the parent molecule leading to the development of safer or more effective compound(s). At times only small changes in the formulation are necessary in order to ensure optimal bioavailability, purity and stability. However, if a change in the vehicle or excepient is contemplated it becomes imperative to submit data on bioavailability as well as on the safety of the new dosage form to the Drug Controller. This should not be considered as an unduly rigorous attitude on the part of drug regulatory agency; it helps to ensure public safety. The drug development programme pathways are shown in Fig. 2.

SUMMARY AND CONCLUSIONS

The drug development process is complex. It takes about 5–7 years before a compound synthesised in the laboratory can be made available to the general practitioner for therapeutic usage. Furthermore, only a few of the compounds developed and synthesised in the laboratory with possible hope of therapeutic application, satisfactorily pass through all the stages of development process. Complete development of a new drug may cost 10–15 million rupees and needs the technical expertise of the highest order. Obviously this calls for tremendous financial and human resources. It is, therefore, imperative that

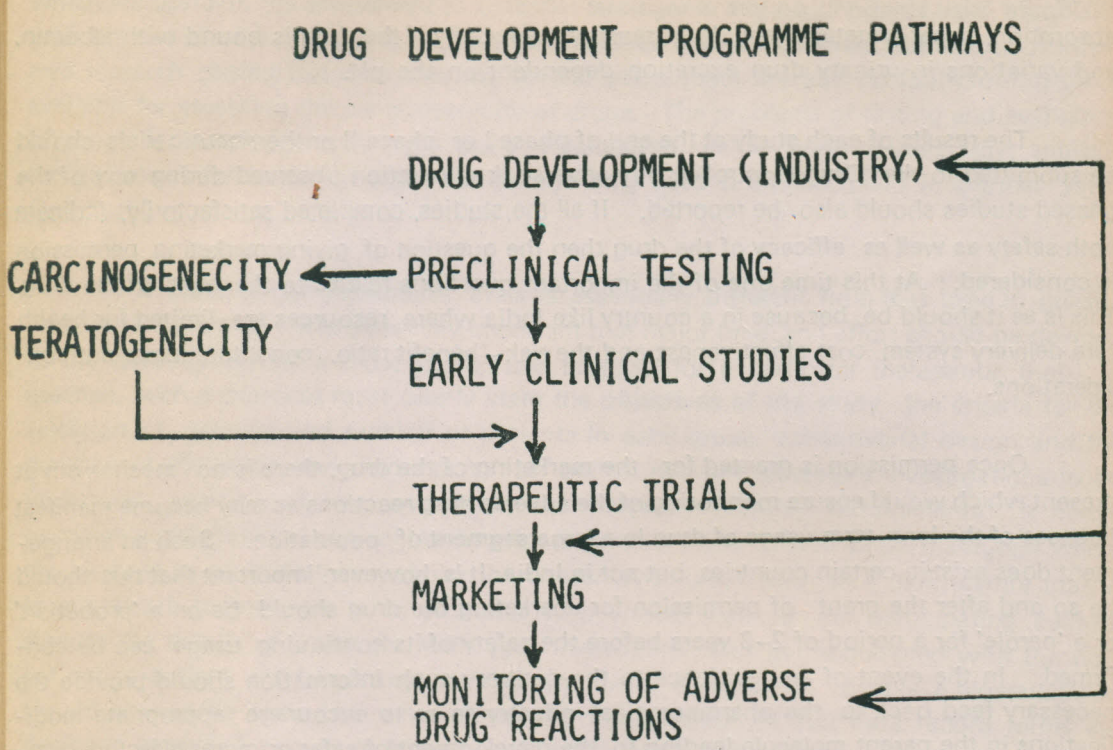

Fig. 2

research investments are properly planned and wisely made. It should be a well co-ordinated team effort with deep considerations of economic management. Clinical pharmacology plays an essential and a meaningful role in this process and its interactions with the pharmaceutical industry should be such as to ensure therapeutic efficacy and safety of new drugs.

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