

²[SCHEDULE Y

REQUIREMENT AND GUIDELINES ON CLINICAL TRIALS FOR IMPORT AND
MANUFACTURE OF NEW DRUG.

I. Clinical Trials.

1.1. *Nature of trials.* - The clinical trials required to be carried out in the country before a new drug is approved for marketing depend on the status of the drug in other countries. If the drug is already approved/marketed, Phase III trials as required under Item 7 of Appendix 1 usually are required. If the drug is not approved/marketed trials are generally allowed to be initiated at one phase earlier to the phase of trials in other countries.

For new drug substances discovered in other countries phase I trials are not usually allowed to be initiated in India unless Phase I data as required under Item 5 of the said Appendix from other countries are available. However, such trials may be permitted even in the absence of Phase I data from other countries if the drug is of special relevance to the health problem of India.

For new drug substances discovered in India, clinical trials are required to be carried out in India right from phase I as required under Item 5 of the said Appendix though Phase III as required under Item 7 of the said Appendix, permission to carry out these trials is generally given in stages, considering the data emerging from earlier phase.

1.2. *Permission for trials.* - Permission to initiate clinical trials with a new drug may be obtained by applying in Form 12 for a test licence (TL) to import or manufacture the drug under the Rules. Data appropriate for the various phases of clinical trials to be carried out should accompany the application as per format given in Appendix I (items 1-4). In addition, the protocol for proposed trials, case report forms to be used, and the names of investigators and institutions should also be submitted for approval. The investigators selected should possess appropriate qualifications and experience and should have such investigations facilities as are germane to the proposed trials protocol.

Permission to carry out clinical trials with a new drug is issued along with a test licence in Form 11.

¹ Omitted as per G.O.I. Notification No. GSR 673(E) dt 27.10.1993.

² Ins. by G.O.I. Notification No. GSR 944(E) dt 21.9.1998.

It is desirable that protocols for clinical trials be reviewed and approved by the institution's ethical committee. Since such committees at present do not exist in all institutions, the approval granted to a protocol by the ethical committee of one institution will be applicable to use of that protocol in other institutions which do not have an ethical committee. In case none of the trial centers/institutions has an ethical committee, the acceptance of the protocol by the investigator and its approval by the Drugs Controller (India) or any officer as authorized by him to do so will be adequate to initiate the trials.

For new drugs having potential for use in children, permission for clinical trials in the paediatric age group is normally given after phase III trials as required under item 7 of the said Appendix in adults are completed. However, if the drug is of value primarily in a disease of children, early trials in the paediatric age group may be allowed.

1.3. *Responsibilities of Sponsor/Investigator.* - Sponsors are required to submit to the licensing authority as given under Rule 21 an annual status report on each clinical trial, namely, ongoing, completed, or terminated. In case a trial is terminated, reason for this should be stated. Any unusual, unexpected or serious adverse drug reaction (ADR) detected during a trial should be promptly communicated by the sponsor to the licensing authority under Rule 21 and the other investigators.

In all trials an informal, written consent required to be obtained from each volunteer/patient in the prescribed Forms (See Appendix V) which must be signed by the patient/volunteer and the chief investigator.

2. *Chemical and pharmaceutical information.*

Most of the data under the heading (See Appendix I, item 2) are required with the application for marketing permission. When the application is for clinical trials only, information covered in item 2.1 to 2.3 of Appendix I will usually suffice.

3. *Animal Toxicology.*

3.1. *Acute Toxicology.* - Acute toxicity studies (See Appendix I item 4.2) should be carried out in at least two species usually mice and rats using the same route as intended for humans. In addition, at least one more route should be used to ensure systemic absorption of the drug; this route may depend on the nature of the drug. Mortality should be looked for up to 72 hours after parenteral administration and up to 7 days after oral administration. Symptoms, signs and mode of death should be reported, with appropriate macroscopic and microscopic findings where necessary. LD 50s should be reported preferably with 95 per cent confidence limited, if LD 50s cannot be determined, reasons for this should be stated.

3.2 *Long term toxicity:* - Long term toxicity (*see* appendix 1, item 1.3) should be carried out in at least two mammalian species, of which one should be a non rodent. The duration of study will depend on whether the application is for marketing permission or for clinical trial, and in the latter case, on the phase of trials (*see* Appendix III). If a species is known to metabolize the drug in the same way as humans, it should be preferred.

In long-term toxicity studies the drug should be administered 7 days a week by the route intended for clinical use in humans. The number of animals required for these studies, i.e. the minimum number on which data should be available, is shown in Appendix IV.

A control group of animals given the vehicle along should always be included and three other groups should be given graded dose of the drug; the highest dose should produce observable toxicity, the lowest dose should not cause observable toxicity, but should be comparable to the intended therapeutic dose in humans of a multiple of it, e.g. 2.5 to make allowance for the sensitivity of the species; the intermediate dose should cause some symptoms, but not gross toxicity or death, and may be placed logarithmically between the other two doses.

The variables to be monitored and recorded in long-term toxicity studies should include behavioral, physiological, biochemical, and microscopic observations.

3.3. *Reproduction studies.* - Reproduction studies (*see* Appendix I, item 4.4) need to be carried out only if the new drug is proposed to be studied or used in women or childbearing age. Two species should generally be used, one of them being a non-rodent if possible.

- a. *Fertility Studies.* - The drug should be administered to both males and females, beginning a sufficient number of days before mating. In females the medication should be continued after mating and the pregnant one should be treated throughout pregnancy. The highest dose used should not affect general health or growth of the animals. The route of administration should be the same as for therapeutic use in humans. The control and the treated group should be similar size and large enough to give at least 20 pregnant animals in the control group of rodents and at least 8 pregnant animals in the control group of non-rodents. Observations should include total examination of the litters from both the groups, including spontaneous abortions, if any.
- b. *Teratogenicity studies.* - The drug should be administered throughout the period of organogenesis, using three dose levels. One of the doses should cause minimum maternal toxicity and one should be proposed dose for clinical use in humans or a multiple of it. The route of administration should be the same as for human therapeutic use. The control and the treated group should consist of at least 20 pregnant females in case of non-rodents, on each dose used. Observations should include the number of implantation sites; resorptions if any; and the number of fetuses with their sexes, weights and malformations, if any.
- c. *Perinatal studies.* - The drug should be administered throughout the last third of pregnancy and then through lactation of weaning. The control of each treated group should have at least 12 pregnant females and the dose which causes low foetal loss should be continued throughout lactation weaning. Animals should be sacrificed and observations should include macroscopic autopsy and where necessary, histopathology.

3.4. *Local toxicity.* - These studies (*see* Appendix I, item 4.5) are required when the new drug is proposed to be used topically in humans. The drug should be applied to an appropriate site to determine local effects in a suitable species such as guinea pigs or rabbits, if the drug is absorbed from the site of applications, appropriate systemic toxicity studies will be required.

3.5 *Mutagenicity and Carcinogenicity.* - These studies (*see* Appendix 1, item 4.5) are required to be carried out if the drug or its metabolite is related to a known carcinogen or when the nature and action of the drug is such as to suggest a carcinogenic/mutagenic potential. For carcinogenicity studies, at least two species should be used. These species should not have a high incidence of spontaneous tumors and should preferably be known to metabolize the drug in the same manner as humans. At least three dose level should be used; the highest dose should be sublethal out cause observable toxicity; the lowest dose should be comparable to the intended human therapeutic dose or a multiple of it, e.g. 2.5 X; to make intermediate dose to be placed logarithmically between the other two doses. A control group should always be included. The drug should be administered 7 days a week or a fraction of the life span comparable to the fraction of human life span over which the drug is likely to be used therapeutically. Observations should include macroscopic changes observed at autopsy and detailed histopathology.

4. *Animal pharmacology.*

Specific pharmacological actions (*see* Appendix I, item 3.2) are those with therapeutic-potential for humans. These should be described according to the animal models and species used. Wherever possible, dose-response relationships and ED 50s should be given. Special studies to elucidate mode of action may also be described.

General pharmacological action (*see* Appendix I, item 3.3) are effects on other organs and systems, specially cardiovascular, respiratory and central nervous systems.

Pharmacokinetic data help relate drug effect to plasma concentration and should be given to the extent available.

5 *Human/Clinical Pharmacology (Phase I).*

The objective of phase I of trials (*see* Appendix I, item 5) is to determine the maximum tolerated dose in humans; pharmacodynamic effects; adverse reactions, if any, with their nature and intensity; and pharmacokinetic behaviour of the drug as far as possible. These studies are carried out in healthy adult males, using clinical, physiological and biochemical observations. At least 2 subjects should be used on each dose.

Phase I trials are usually carried out by investigators trained in clinical pharmacology and having the necessary facilities to closely observe and monitor the subjects. These may be carried out at one or two centers.

6. *Explanatory trials (Phase II).*

In phase II trial (*see* appendix I, item 6) a limited number of patients are studied carefully to determine possible therapeutic use, effective dose range and further evaluation of safety and pharmacokinetics. Normally 10-12 patients should be studied at each dose level. These studies are usually limited to 3-4 centres and carried out by clinicians specialized in the concerned therapeutic areas and having adequate facilities to perform the necessary investigations for efficacy and safety.

1. *Confirmatory trials (Phase III).*

The purpose of these trials (*see* Appendix I, item 7) is to obtain sufficient evidence about the efficacy and safety of the drug in a larger number of patients, generally in comparison with a standard drug and/or a placebo as appropriate. These trials may be carried out by clinicians in the concerned therapeutic areas, having facilities appropriate to the protocol. If the drug is already approved/marketed in other countries, phase III data should generally be obtained on at least 100 patients distributed over 3-4 centres primarily to confirm the efficacy and safety of the drug, in Indian patients when used as recommended in the product monograph for the claims made.

If the drug is a new drug substance discovered in India and not marketed in any other country, phase III data should be obtained at least 500 patients distributed over 10-15 centres. In addition, data on adverse drug reactions observed during clinical use of the drug should be collected in 1000-2000 patients; such data may be collected through clinicians who give written consent to use the drug as recommended and to provide a report on its efficacy and adverse reactions in the treated patients. The selection of clinicians for such monitoring and supply of drug to them will need approval of the licensing authority under Rule 21.

2. *Special Studies.*

A. These include studies on solid oral dosage form, such as, bio-availability and dissolution studies. These are required to be submitted on the formulations manufactured in the country. (*see* Appendix I, items 8.2 and 8.3).

B. These include studies to explore additional aspects of the drug, e.g. use in elderly patients or patients with renal failure, secondary or ancillary effects, interactions, etc. (*See* Appendix 8.2 and 8.3).

3. *Submission of Reports (Appendix II).*

The reports of completed clinical trials shall be submitted by the applicant duly signed by the investigator with a stipulated period of time. The applicant should do so even if he is no longer interested to market the drug in the country unless there are sufficient reasons for not doing so.

4. *Regulatory status in other countries.*

It is important to state if any restrictions have been placed on the use of the drug in any other country, e.g. dosage limited, exclusion of certain age groups, warnings about adverse drug reaction, etc. (*See Appendix I, item 9.2*).

Likewise, if the drug has been withdrawn from any country specially by a regulatory directive, such information should be furnished along with reasons and their relevance, if any, to India (*See appendix I, item 9.1 (d)*).

5. *Marketing information.*

The product monograph should comprise the full prescribing information necessary to enable a physician to use the drug properly. It should include description, actions, indications, dosage precaution, drug interactions, warnings and adverse reactions.

The drafts of label and carton texts should comply with provisions of Rules 96 and 97 of the said rules.

*[12 *Post-marketing surveillance study.*

On approval of a new drug, the importer or the manufacturer shall conduct post-marketing surveillance study of that new drug after getting the protocols and the names of the investigators approved by the Licensing Authority as defined under clause (b) of Rule 21 during the initial period of two years of marketing.]

* Ins. by G.O.I. Notification No. 900(E) dt 12.12.2001.

APPENDIX I

Data required to be submitted with application for permission to market a New Drug

1. INTRODUCTION

A brief description of the drug and the therapeutic class to which it belongs.

2. CHEMICAL AND PHARMACEUTICAL INFORMATION.

- 2.1. Chemical name, code name or number, if any, non-proprietary or generic name, if any, structure, physio-chemical proportion.
- 2.2 Dosage form and its composition.
- 2.3 Specifications of active and inactive ingredients.
- 2.4. Tests for identification of the active ingredient and method of its assay.
- 2.5. Outline of the method of manufacture of the active ingredient.
- 2.6 Stability data

3. ANIMAL PHARMACOLOGY

- 3.1. Summary
- 3.2. Specific pharmacological actions.
- 3.3 General pharmacological actions.
- 3.4. Pharmacokinetics, absorption, distribution, metabolism, excretion.

4. ANIMAL TOXICOLOGY (*See* Appendix III and IV)

- 4.1. Summary
- 4.2 Acute Toxicity
- 4.3. Long Term Toxicity
- 4.4 Reproduction Studies.
- 4.5 Local Toxicity
- 4.6. Mutagenicity and Carnicogenicity.

5. HUMAN/CLINICAL PHARMACOLOGY (PHASE I).

- 5.1. Summary
- 5.2 Specific Pharmacological effects.
- 5.3 General Pharmacological effects.
- 5.4. Pharmacokinetics, absorption, distribution, metabolism, excretion.

6. EXPLANATORY CLINICAL TRIALS (PHASE II).

- 6.1. Summary
- 6.2 Investigatorwise reports.

7.. CONFIRMATORY CLINICAL TRIALS (PHASE III)

- 7.1. Summary
- 7.2 Investigatorwise reports

8. SPECIAL STUDIES

- 8.1. Summary
- 8.2. Bioavailability and dissolution studies.
- 8.3. Investigatorwise reports.
- 9. REGULATORY STATUS IN OTHER COUNTRIES.
 - 9.1. Countries where –
 - (a) Marketed
 - (b) Approved.
 - (c) Under trial, with phase.
 - (d) Withdrawn, if any, with reasons.
 - 9.2. Restrictions on use, if any, in countries where marketed/approved.
 - 9.3. Free sale certificate from country of origin.

10. MARKETING INFORMATION.

- 4.1. Proposed product monograph
- 4.2. Drafts of labels and cartons.
- 4.3. Sample of pure drug substance, with testing protocol.

Notes: (1) All items may not be applicable to all drugs, for explanation, see text of Schedule Y.

- (2) For requirements of data to be submitted with application for clinical trials see text of Schedule Y, Section 1 and also Appendices II and III.

*[APPENDIX 1-A
[See Rules 122-A and 122-B)

*Data required to be submitted by an applicant for grant of permission to import
manufacture an already approved new drug.*

1. INTRODUCTION

A brief description of the drug and the therapeutic class.

* Ins. by G.O.I. Notification No. GSR 900(E) dt 12.12.2001.

2. CHEMICAL AND PHARMACEUTICAL INFORMATION.

- 2.1. Chemical name, code name or number, if any, non-proprietary or generic name, if any, structure, physico-chemical properties.
- 2.2. Dosage form and its composition

- 2.3. Test specifications.
 - (a) active ingredients.
 - (b) Inactive ingredients
- 2.4. Tests for identification of the active ingredients and method of its assay.
- 2.5. Outline of the method of manufacture of active ingredients.
- 2.6. Stability data.
3. Marketing information.
 - 3.1 Proposed package insert/promotional literature
 - 3.2 Draft specimen of the label and carton.
4. Special studies conducted with approval of Licensing Authority.
 - 4.1. Bioavailability/Bioequivalence and comparative Dissolution Studies, for oral dosage form,
 - 4.2. Sub-acute animal toxicity studies for intravenous infusions and injectables.]

APPENDIX II

Format for submission of clinical Trial Reports.

- ___ Title of the trial
- ___ Name of investigator and institution
- ___ Objectives of the trial
- ___ Design of study: Open, single-blind or double blind, non-comparative or comparative, parallel group or crossover.
- ___ Number of patients, with criteria selection and exclusion, whether written, informed consent, was obtained.
- ___ Treatments given – drugs and dosage forms, dosage regimens, method of allocation of patients to treatments, method of verifying compliance, if any
- ___ Observations made before, during and at the end of treatment, for efficacy and safety, with methods used.
- ___ Results : exclusions and dropouts, if any, with reasons, description of patients with initial comparability of groups where appropriate, clinical patients with initial comparability of groups where appropriate, clinical and laboratory observations on efficacy and safety, adverse drug reactions.

- Discussion of results ; relevance to objectives, correlation with other reports/data, if any, guidance for further study, if necessary.
- Summary and conclusion.

APPENDIX III

Animal toxicity requirements for clinical trials and marketing of a New Drug.

Route of administration	Duration of administration	Human Phase	Long term toxicity requirements.
1	2	3	4
	Single dose of several doses in one day.	I-III MP	2 sp; 2 wk
Oral or Parenteral or Transdermal	Up to 2 wk	I, II	2 sp ; Up to 4 wk
		III MP	2 sp; Up to 3 mo
		I, II	2 sp; 4 wk
	Up to 3 wk	III	2 sp; 3 mo
		MP	2 sp; Up to 6 mo
	Over 3 mo	I, II	2 sp; 3 mo
		III: MP	2 sp; 6 mo
Inhalation (general Anaesthetics)		I: III MP	4 sp; 5d(3h/d)
Aerosole	Repeated or Chronic use	I; II	1-2 sp; 3h/exp.
		III	1-2 sp; Up to 6 wk (2 exp/d)
		MP	1-2 sp; 24 wk (2 exp/d)
Dermal	Short term or long Term application	I: II	1 sp; single 24h exp; then 2 wk observation
		III: MP	1 sp. number and duration of applications commensurate with duration of use.
Ocular or Otic or Nasal	Single or Multiple Applications.	I: II	Irrigation test; Graded doses.
		III	1 sp; 3 wk; daily applications as in clinical use.

		MP	1 sp; number and or duration of application commensurate with duration of use.
Vaginal or Rectal	Single or Multiple Application	I : II III : MP	1 sp; number and duration of applications commensurate with duration of use.

Abbreviations : Sp-species, wk- week, d- day, h-hour, mo-month, MP-Marketing Permission, exp-exposure, I,II,III – Phases of clinical trial (*see* Appendix I, item No.5-8).

Note: - (1) Animal toxicity data available from other countries are acceptable and do not need to be repeated/duplicated in India.

(2) Requirements for fixed dose combinations are given in Appendix VI.

APPENDIX IV

Number of animals for long term Toxicity Studies.

	2 - 6 Weeks				7 - 26 Weeks			
Group	Rodents (rats)		Non-Rodents (dogs)		Rodents (Rats)		Non-Rodents (dogs)	
	M	F	M	F	M	F	M	F
Control	6 – 10	6 – 10	2 – 3	2 – 3	15 – 30	15 – 30	4 – 6	4 – 6
Low dose	6 – 10	6 – 10	2 – 3	2 – 3	15 – 30	15 – 30	4 – 6	4 – 6
Intermediate dose	6 – 10	6 – 10	2 – 3	2 – 3	15 – 30	15 – 30	4 – 6	4 – 6
High dose	6 – 10	6 – 10	2 – 3	2 – 3	15 – 30	15 – 30	4 – 6	4 – 6

APPENDIX V

Patient consent form for participation in a Phase I Clinical Trial

The clinical trial involves the study of a new agent in volunteers/patients suffering from

The drug which will be administered to volunteers/patients has been found to be safe in animal toxicity tests and other experimental data. The volunteers /patients will be required to

undergo, if necessary, all routine examinations including taking of X-ray, ECG, EEG etc. at intervals. The volunteers/patients may be asked to collect stool and urine, and there may be need to draw blood or any other body fluid on several occasions to test the effects of concentrations of the drug. The volunteers/patients are free to withdraw from the trial at any stage.

Authorisation

I have read/been briefed on the above project summary and I voluntarily agree to participate in the project. I understand that participation in this study may or may not benefit me. Its general purpose, potential benefits, possible hazards, and inconveniences have been explained to my satisfaction, I hereby give my consent for this treatment.

Name of the volunteer/patient

Signature or thumb impression
of the volunteer/patient.

Signature of Chief Investigator
Date:

Patient consent form for participation in Phase II and Phase III Clinical Trial: -

I..... exercising my free power of choice, hereby give my consent to be included as a subject in the clinical trial of a new drug, namely..... for the treatment of I understand that I may be treated with this drug for the diseases. I am suffering fromI have been informed to my satisfaction, by the attending physician the purpose of the clinical trial and the nature of drug treatment and follow up including the laboratory investigation to monitor and safeguard my body functions.

I am also aware of my right to opt out of the trial at any time during the course of the trial without having to give the reasons for doing so.

Signature of the attending physician.

Date:

Signature of the patient
Date:

APPENDIX VI

Fixed Dose Combination (FDC) fall into four groups and their data requirements accordingly.

(a) The first group of FDC includes those in which one or more of the active ingredients is a new drug. Such FDC are treated in the same way as any other new, drug, both the clinical trials and for marketing permission (*See* Rule 122-E, item (a).)

(b) The second group of FDC includes those in which active ingredients already approved/ marketed individually are combined for the first time, for a particular claim and where the ingredients are likely to have significant interaction of a pharmacodynamic or pharmacokinetic nature (*see* Rule 122-E, item (c)). For permission to carry out clinical trials with such FDC, a summary of available pharmacological, toxicological and clinical data on the individual ingredients should be submitted, with rationale for combining them in the proposed ratio. In addition, actual toxicity data (LD 50) and pharmacological data should be submitted on the individual ingredients as well as their combination in the proposed ratio. If the clinical trials have been carried out with the FDC in other countries, reports of such trials should be submitted. If the FDC is marketed abroad, the regulatory status in other countries should be stated. (*See* Appendix , item 9).

For marketing permission, the reports of clinical trials carried out with the FDC in India should be submitted. The nature of trials depending on the claims to be made and the data already available.

(c) The third group of FDC includes those which are already marketed, but in which it is proposed either to change the ratio of active ingredients or to make a new therapeutic claim.

For such FDC, the appropriate rationale should be submitted to obtain a permission for the clinical trials, and the reports of trials should be submitted to obtain a marketing permission. The nature of trials will depend on the claims to be made and the data already available.

(d) The fourth group of FDC includes those whose individual active ingredients have been widely used in particular indication for years, their concomitant use is often necessary and no claim is proposed to be made other than convenience, and a stable acceptable dosage from the ingredients are unlikely to have significant interaction of a pharmacodynamic or pharmacokinetic nature.

No additional animal or human data are generally required for these FDC, and marketing permission may be granted if the FDC has an acceptable rationale.