DRAFT GUIDANCE

ON

APPROVAL OF CLINICAL TRIALS

& NEW DRUGS

DRAFT GUIDANCE

This guidance document is for feedback purposes only. Comments suggestions, if any, may please be submitted to the office of Drugs Controller General India within thirty days i.e. latest by 24th August 2011.

CENTRAL DRUGS STANDARD CONTROL ORGANIZATION

DIRECTORATE GENERAL OF HEALTH SERVICES

MINISTRY OF HEALTH & FAMILY WELFARE

GOVT. OF INDIA

JULY 2011

DOC # NDCT-20072011

1 ABBREVIATIONS AND DEFINITIONS

API	Active Pharmaceutical Ingredient
BA	Bio-availability
BE	Bio-equivalence
CRF	Case Record Form
CT	Clinical Trial
FDC	Fixed Dose Combination
ICF	Informed Consent Form
IND	Investigational New Drug
INR	Indian National Rupee
LD	Lethal Dose
NDA	New Drug Application
NDAC	New Drug Advisory Committee
PK / PD	Pharmacokinetic and Pharmacodynamic
CV	Curriculum vitae
NOC	No objection certificate
QC	Quality control

2 TABLE OF CONTENTS

3 BACKGROUND 4
4 SCOPE 5
5 GENERAL CONSIDERATIONS....5
6 FUTTHER CLARIFICATIONS 6
7 GUIDELINES ON DATA REQUIRED FOR APPROVAL OF CLINICAL TRIALS 8
8 GUIDELINES ON DATA REQUIRED FOR APPROVAL NEW DRUGS 20
8.1 New Chemical Entity – developed in India as an IND and not marketed anywhere in world 25
8.2 New Chemical Entity approved & marketed in other countries not approved in India....30
8.3 New Chemical Entity being developed in other countries and not marketed anywhere in world. ...36
8.4 A drug already approved - New claims. 37
8.4.1 New Indication 39
8.4.2 New Dosage Form/ New Route of Administration 43
8.4.3 Modified Release Dosage Form....48
8.5 Fixed Dose Combination 55
8.6 Already Aproved New Drug....55

ANNEXURE-A 59
ANNEXURE-B 61
ANNEXURE-C 63
ANNEXURE-D 66

DRAFT GUIDANCE ON APPROVAL OF CLINICAL TRIAL & NEW DRUG

3 BACKGROUND

Demonstration of safety and efficacy of the drug product for use in humans is essential before the drug product can be approved for import or manufacturing and marketing in the country. The Rules 122A, 122B and 122D, 122 DA, 122DAA, 122E of Drugs and Cosmetics Rules and Appendix I, IA and VI of Schedule Y, describe the information/data required for approval of clinical trial and/or to import or manufacture of new drug for marketing in the country. However, the requirements for approval of clinical trials and new drugs may vary depending on nature of new drugs. This guidance documents has been prepared to specify the general requirements for approval of clinical trial and different categories of New Drugs viz. Investigational New Drugs, New drugs substances, additional strength, additional indication, modified release form etc. This guidance will help the industry to submit the required documents in a more realistic manner, which in turn will also help reviewer of CDSCO to review such application in systematic manner. It is apparent that this structured application with comprehensive and rational contents will help the CDSCO to review and take necessary actions in a better way and would also ease the preparation of electronic submissions, which may happen in the near future at CDSCO.

4 SCOPE

These guidelines apply to approval of clinical trial and approval of manufacture/import for marketing of various categories of new drugs in the form of API and finished formulation which are considered as new drug as per Rule 122E of Drugs and Cosmetics Rules.

This guideline describes requirements for approval of clinical trials and new drugs and the procedure for review of technical dossiers of such applications by CDSCO under Rule 122 A, 122B, 122DA, 122DAA, 122E and Schedule-Y of Drugs and Cosmetics Rules.

(b) This guideline does not apply to biologicals and vaccines.

5 General Consideration:

This guideline is based on regulatory requirement for drug approval in India as prescribed under Drugs and Cosmetic Act and Rules made there under and its various amendments. For development of any new drug the applicant is required to obtain license in Form-29 from State Licensing Authority based on NOC obtained from CDSCO. Test batches of new drugs for development and generation of data of any new drug should be manufactured only after obtaining the license in Form-29.

An application for approval of clinical trial or marketing authorization may comprise:

- Entirely original data.
- Entirely data from the literature.
- Both original data and data from the literature ("hybrid").

- For New Drugs, it is likely that hybrid submissions will be the most common type.

Chemical and pharmaceutical data should always be original, unless there is sufficient justification with literature in case partial data is not original.

The office of DCG (I) grants approval of manufacture / import of new drugs for marketing in the country. This office is also responsible for grant of permission to conduct clinical trials of new drugs including Investigational New Drugs (IND).

New drugs as define under Rule 122-E of Drugs and Cosmetics Rules include unapproved drugs, modified or new claims, namely, indications, dosage forms (including sustained release dosage form) and route of administration of already approved drugs and combination of two or more drugs. A new drug shall continue to be considered as new drug for a period of four years from the date of its first approval or its inclusion in the Indian Pharmacopoeia, whichever is earlier.

No clinical trial for a new drug, whether for clinical investigation or any clinical experiment by any institution, shall be conducted except under, and in accordance with, the permission, in writing, of the Licensing Authority defined in clause (b) of Rule 21.

6 FURTHER CLARIFICATIONS

1. SOURCE OF BULK DRUG(S) FOR MANUFACTURING FINISHED FORMULATION

Documentations required related to source of bulk drug(s) /raw material(s) when the applicant is seeking approval for manufacturing of finished formulation only.

If the applicant has a manufacturing permission for bulk drugs, please provide a copy of the same. Otherwise, provide the consent letter from the approved source regarding supply of material.

CLARIFICATION: *In case if the applicant does not have an approval from DCGI to manufacture the Active Pharmaceutical Ingredient(s) (API), then the applicant can,*

- *Import the API → Applicant has to submit all relevant information and documents and comply with further requirements for import of API.*
- *Manufacture the API → Applicant has to submit all relevant information and documents and comply with further requirements for manufacture of API*
- *Obtain the API from another manufacturer which is not yet approved by DCGI → In such case, the respective manufacturer of the API has to file an application separately in Form 44 along with treasury challan of requisite amount with all relevant documents.*

Approval of manufacture of new drug API will be considered after approval of manufacture of its finished formulation.

7 Guidelines on data required to be submitted for approval of clinical trials (Phase-I/II/III/IV).

For new drug substances discovered in India, clinical trials are required to be carried out in India right from Phase I. For new drug

substances discovered in countries other than India, Phase I data as required along with the application. After submission of Phase I data generated outside India to the Licensing Authority, permission may be granted to repeat Phase I trials and/or to conduct Phase II trials and subsequently Phase III trials concurrently with other global trials for that drug. Phase III trials are required to be conducted in India before permission to market the drug in India is granted;

The data required will depend upon the purpose of the new drug application.

The number of study subjects and sites to be involved in the conduct of clinical trial will depend upon the nature and objective of the study. Phase I clinical trials should usually be 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. At least 2 subjects should be used on each dose.

Phase II clinical trials should normally be carried out on 10-12 patients at each dose level. These studies should usually be carried out at 3-4 centers by clinicians specialized on the concerned therapeutic areas and having adequate facilities to perform the necessary investigations for efficacy and safety.

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 generally be obtained on at least 500 patients distributed over 10-15 centres.

Permission to carry out these trials shall generally be given in stages, considering the data emerging from earlier Phase(s)

CDSCO will initially examine such applications, if any particular data is lacking same will be informed to the applicant or else the applications will be forwarded to the members of IND committee in case of Investigational New Drugs (INDs) or to the members of New Drug Advisory Committee (NDAC) in case of new chemical entities other than IND. However, in case of applications for grant of approval to conduct clinical trials with new dosage form, new indication, new route of administration etc. of approved drugs, the application will be examined by CDSCO. Wherever required, such applications may also be examined in consultation with expert / expert committees.

For conduct of clinical trials with a new drug, data required to be submitted will be similar as per Appendix I of Schedule Y. However, as per Clause 1(3) of Schedule Y to Drugs & Cosmetics Rules, for drugs indicated in life threatening / serious diseases or diseases of special relevance to the Indian health scenario, the toxicological & clinical data requirements may be abbreviated, deferred or omitted, as deemed appropriate by the Licensing Authority.

There is as such neither any definition of “life threatening / serious diseases” nor any list of such disease/disorders prescribed under the Drugs & Cosmetics Act & Rules. "Life-threatening” diseases are generally considered as diseases or conditions where the likelihood

of death is high unless the course of the disease is interrupted and diseases or conditions with potentially fatal outcomes. Diseases like Cancer, AIDS etc are generally considered as Serious /Life Threatening Diseases.

In cases of life threatening / serious diseases, it is desirable to expedite the development, evaluation, and marketing of new therapies intended to treat persons especially where no satisfactory alternative therapy exists. In such cases patients / clinicians are generally willing to accept greater risks or side effects from products that treat life-threatening/ serious diseases, than they would accept from products that treat less serious illnesses.

All such request for exemption of toxicological & clinical data requirements will be considered on the basis of examination and scrutiny of the adequacy of data in consultation with expert/expert committees.

Details of Animal Pharmacology & Animal Toxicology studies required to be carried out will be as per Appendix IV & Appendix III of Schedule Y of Drugs and Cosmetics Rules respectively. Depending upon the nature of new drugs and disease(s) specific additions/deletions may be made to the said requirements.

For permission of such clinical trials the documents required to be submitted are as follows:

1. Form 44
2. Treasury Challan of INR 50,000 (for Phase- I) / 25,000/- (for Phase-II/III clinical trials).
3. Source of bulk drugs /raw materials.

Clarification:

- Import the API - Applicant can import small quantity of the API under Form-11 for which separate application in Form-12 alongwith Treasury Challan and all relevant documents should be submitted.

- Manufacture the API - Applicant can manufacture small quantities under license in Form-29 obtained from State Licensing Authority.

- Obtain the API from another manufacturer which is not yet approved by DCGI - In such case, the respective manufacturer of the API has to file an application separately seeking NOC to manufacture small quantities for clinical trial purpose. Based on NOC from CDSCO license in Form-29 is required to be obtained from the concerned State Licensing Authority before manufacturing the trial batches.

4. Chemical and pharmaceutical information including:

Information on active ingredients:

Drug information (Generic Name, Chemical Name or INN) & Physicochemical Data including:

i. Chemical name and Structure - Empirical formula, Molecular weight

ii. Analytical Data: Elemental analysis, Mass spectrum, NMR spectra, IR spectra, UV spectra, Polymorphic identification

iii. Stability Studies: Data supporting stability in the intended container closure system for the duration of the clinical trial.

Data on Formulation:

i. Dosage form,

ii. Composition,

iii. Master manufacturing formula,

iv. Details of the formulation (including inactive ingredients),

v. In process quality control check,

vi. Finished product specification & Method of Analysis,

vii. Excipient compatibility study,

viii. Validation of the analytical method.

ix. Stability Studies: Data supporting stability in the intended container closure system for the duration of the clinical trial.

Note: While adequate chemical and pharmaceutical information should be provided to ensure the proper identity, purity, quality & strength of the investigational product, the amount of information needed may vary with the Phase of clinical trials, proposed duration of trials, dosage forms and the amount of information otherwise available.

5. **Animal Pharmacology**

i. Summary
ii. Specific pharmacological actions
iii. General pharmacological actions
iv. Follow-up and Supplemental Safety Pharmacology Studies

v. Pharmacokinetics: absorption, distribution; metabolism; excretion

6. **Animal Toxicology**

i. General Aspects
ii. Systemic Toxicity Studies
iii. Male Fertility Study
iv. Female Reproduction and Developmental Toxicity Studies
v. Local toxicity
vi. Allergenicity/Hypersensitivity
vii. Genotoxicity
viii. Carcinogenicity

A. <u>For Phase I Clinical Trials</u>

Systemic Toxicity studies

(i) Single dose toxicity studies

(ii) Dose Ranging Studies

iii) Repeat-dose systemic toxicity studies of appropriate duration to support the duration of proposed human exposure. (As per Clause1.8 of Appendix-III of Schedule Y to Drugs & Cosmetics Rules.

Male fertility study

In-vitro genotoxicity tests

Relevant local toxicity studies with proposed route of clinical application (duration depending on proposed length of clinical exposure)

Allergenicity / Hypersensitivity tests (when there is a cause for concern or for parenteral drugs, including dermal application)

Photo-allergy or dermal photo-toxicity test (if the drug or a metabolite is related to an agent causing photosensitivity or the nature of action suggests such a potential)

B. <u>For Phase II Clinical Trials</u>

Provide a summary of all the non-clinical safety data (listed above) already submitted while obtaining the permissions for Phase I trial, with appropriate references.

In case of an application for directly starting a Phase II trial - complete details of the nonclinical safety data needed for obtaining the permission for Phase I trial, as per the list provided above must be submitted.

Repeat-dose systemic toxicity studies of appropriate duration to support the duration of proposed human exposure

In-vivo genotoxicity tests.

Segment II reproductive/developmental toxicity study (if female patients of child bearing age are going to be involved)

C. <u>For Phase III Clinical Trials</u>

Provide a summary of all the non-clinical safety data (listed above) already submitted while obtaining the permissions for Phase I and II trials, with appropriate references.

In case of an application for directly initiating a Phase III trial - complete details of the non-clinical safety data needed for obtaining the permissions for Phase I and II trials, as per the list provided above must be provided.

Repeat-dose systemic toxicity studies of appropriate duration to support the duration of proposed human exposure

Reproductive/developmental toxicity studies

Segment I (if female patients of child bearing age are going to be involved), and Segment III (for drugs to be given to pregnant or nursing mothers or where there are indications of possible adverse effects on foetal development)

Carcinogenicity studies (when there is a cause for concern or when the drug is to be used for more than 6 months).

D. <u>For Phase IV Clinical Trials</u>

Provide a summary of all the non-clinical safety data (listed above) already submitted while obtaining the permissions for Phase I, II and III trials, with appropriate references.

In case an application is made for initiating the Phase IV trial, complete details of the non-clinical safety data needed for obtaining the permissions for Phase I, II and III trials, as per the list provided above must be submitted.

7. **Human / Clinical pharmacology (Phase I)**

   i. Summary
   ii. Specific Pharmacological effects
   iii. General Pharmacological effects
   iv. Pharmacokinetics, absorption, distribution, metabolism, excretion
   v. Pharmacodynamic / early measurement of drug activity

8. **Therapeutic exploratory trials (Phase II)**

   i. Summary
   ii. Study report(s) as given in Appendix II

9. **Therapeutic confirmatory trials (Phase III)**

   i. Summary
   iii. Individual study reports with listing of sites and Investigators as given in Appendix II.

10. **Special studies**

   i. Summary
   ii. Bio-availability / Bio-equivalence.
   iii. Other studies e.g. geriatrics, paediatrics, pregnant or nursing women

11. **Regulatory status in other countries**

   A. Countries where the drug is

      i. Marketed

ii. Approved
iii. Approved as IND
iv. Withdrawn, if any, with reasons

B. Restrictions on use, if any, in countries where marketed/approved

.12. **Prescribing information** (of the drug circulated in other countries, if any)

13. **Application in Form -12 alongwith T-Challan of requisite fees** (in case of import of investigational products)

NOTE:

- For new drug substances discovered in India, for Phase I clinical trials data as per the items 1, 2, 3, 4, 5, 6, 7 (data, if any, from other countries) & 11 as mentioned above is required to be submitted.
- For new drug substances discovered in countries other than India, for Phase I clinical trials data as per the items 1, 2, 3, 4, 5, 6, 7 (data from other countries) & 11 as mentioned above is required to be submitted.
- A legal undertaking in the form of an affidavit should be submitted by the applicant (competent person from the Company) stating that the data submitted alongwith the application is scientifically valid and authentic.

14. The Proposed Protocol For Conducting The Clinical Trial

The proposed protocol should contain the information as mentioned below:

i. Title Page

(a) Full title of the clinical study,

(b) Protocol / Study number, and protocol version number with date

(c) The IND name/number of the investigational drug

(d) Complete name and address of the Sponsor and contract research organization if any

(e) List of the Investigators who are conducting the study, their respective institutional affiliations and site locations

(f) Name(s) of clinical laboratories and other departments and/or facilities participating in the study.

ii. Table of Contents

A complete Table of Contents including a list of all Appendices.

Background and Introduction

(a) Preclinical experience.

(b) Clinical experience.

Previous clinical work with the new drug should be reviewed here and a description of how the current protocol extends existing data should be provided. If this is an entirely new indication, how this drug was considered for this should be discussed. Relevant information regarding pharmacological, toxicological and other biological properties of the drug, and previous efficacy and safety experience should be described.

iii. Study Rationale

This section should describe a brief summary of the background information relevant to the study design and protocol methodology. The reasons for performing this study in the particular population included by the protocol should be provided.

iv. Study Objective(s): (primary as well as secondary) and their logical relation to the study design**.**

v. Study Design

(a) Overview of the Study Design: Including a description of the type of study (i.e., double-blind, multicentre, placebo controlled, etc.), a detail of the specific treatment groups and number of study Subjects in each group and investigative site, Subject number assignment, and the type, sequence and duration of study periods.

(b) Flow chart of the study

(c) A brief description of the methods and procedures to be used during the study.

(d) Discussion of Study Design: This discussion details the rationale for the design chosen for this study.

vi. Study Population:

The number of Subjects required to be enrolled in the study at the investigative site and by all sites along with a brief description of the nature of the Subject population required is also mentioned.

vii. Subject Eligibility

(a) Inclusion Criteria

(b) Exclusion Criteria

viii. Study Assessments – plan, procedures and methods to be described in detail

ix. Study Conduct: stating the types of study activities that would be included in this section would be: medical history, type of physical examination, blood or urine testing, electrocardiogram (ECG), diagnostic testing such as pulmonary function tests, symptom measurement, dispensation and retrieval of medication, Subject cohort assignment, adverse event review, etc. Each visit should be described separately as Visit 1, Visit 2, etc. Discontinued Subjects: Describes the circumstances for Subject withdrawal,

dropouts, or other reasons for discontinuation of Subjects . State how dropouts would be managed and if they would be replaced Describe the method of handling of protocol waivers, if any. The person(s) who approves all such waivers should be identified and the criteria used for specific waivers should be provided. Describes how protocol violations will be treated, including conditions where the study will be terminated for non-compliance with the protocol.

x. Study Treatment

(a) Dosing schedule (dose, frequency, and duration of the experimental treatment) Describe the administration of placebos and/or dummy medications if they are part of the treatment plan. If applicable, concomitant drug(s), their doses, frequency, and duration of concomitant treatment should be stated.

(b) Study drug supplies and administration: A statement about who is going to provide the study medication and that the investigational drug formulation has been manufactured following all regulations Details of the product stability, storage requirements and dispensing requirements should be provided.

(c) Dose modification for study drug toxicity: Rules for changing the dose or stopping the study drug should be provided.

(d) Possible drug interactions.

(e) Concomitant therapy: The drugs that are permitted during the study and the conditions under which they may be used are detailed here. Describe the drugs that a Subject is not allowed to use during parts of or the entire study. If any washout periods for prohibited medications are needed prior to enrolment, these should be described here.

(f) Blinding procedures: A detailed description of the blinding procedure if the study employs a blind on the Investigator and/or the Subject.

(g) Unblinding procedures: If the study is blinded, the circumstances in which unblinding may be done and the mechanism to be used for unblinding should be given.

xi. Adverse Events (As per Annexure-A):

Description of expected adverse events should be given.

Procedures used to evaluate an adverse event should be described.

xii. . Ethical Considerations: Give the summary of:

(a) Risk/benefit assessment:

(b) Ethics Committee review and communications.

(c) Informed consent process.

(d) Statement of Subject confidentiality including ownership of data and coding procedures.

xiii. Study Monitoring and Supervision:

A description of study monitoring policies and procedures should be provided along with the proposed frequency of site monitoring visits, and who is expected to perform monitoring.

Case Record Form (CRF) completion requirements, including who gets which copies of the forms and any specifics required in filling out the forms CRF correction requirements, including who is authorized to make corrections on the CRF and how queries about study data are handled and how errors, if any, are to be corrected should be stated.

Investigator study files, including what needs to be stored following study completion should be described.

xiv. Investigational Product Management

(a) Give Investigational product description and packaging (stating all Ingredients and the formulation of the investigational drug and any placebos used in the study)

(b) The precise dosing required during the study.

(c) Method of packaging, labelling, and blinding of study substances.

(d) Method of assigning treatments to Subjects and the Subject identification code numbering system.

(e) Storage conditions for study substances.

(f) Investigational product accountability: Describe instructions for the receipt, storage, dispensation, and return of the investigational products to ensure a complete accounting of all investigational products received, dispensed, and returned/destroyed.

(g.)Describe policy and procedure for handling unused investigational products.

xv. Data Analysis:

Provide details of the statistical approach to be followed including sample size, how the sample size was determined, including assumptions made in making this determination, efficacy endpoints (primary as well as secondary) and safety endpoints.

Statistical analysis: Give complete details of how the results will be analyzed and reported along with the description of statistical tests to be used to analyze the primary and secondary endpoints defined above. Describe the level of significance, statistical tests to be used, and the methods used for missing data; method of evaluation of the data for treatment failures, non-compliance, and Subject withdrawals; rationale and conditions for any interim analysis if planned.

Describe statistical considerations for Pharmacokinetic (PK) analysis, if applicable.

xvi. Undertaking by the Investigator (As per Annexure B)

xvii. Appendices:

- Provide a study synopsis,
- copies of the informed consent documents (patient information sheet, informed consent form etc.) as per **Annexure C**;
- CRF and other data collection forms;
- a summary of relevant pre-clinical safety information and any other documents referenced in the clinical protocol.

8 GUIDELINES ON DATA REQUIRED FOR APPROVAL FOR MARKETING OF NEW DRUG

No new drug shall be imported (Rule 122 A) or manufactured (Rule-122 B) except under, and in accordance with, the permission granted by the Licensing Authority as defined in clause (b) of rule 21 (i.e. DCGI).

For permission to import or manufacture of new drug substances and its formulations for marketing in the country, applicant is required to file application in Form 44 along with prescribed fees in the form of treasury Challan and all relevant data as per Schedule Y to Drugs and Cosmetics Rules which include chemical & pharmaceutical information, animal pharmacological & toxicological data, clinical data of safety & efficacy regulatory status in other countries etc and results of clinical trials on local population. The local clinical trials are required to carried out as per Guidelines mentioned at Item No. 7

above and the report of the same should be submitted as per the format specified in **Annexure-D.**

However, in case of new drugs approved in other countries, the requirement of submitting the results of local clinical trials for approval of a new drug may not be necessary if the drug is of such a nature that the licensing authority may, in public interest decide to grant such permission on the basis of data available from other countries.

The criteria of considering the clause of "public interest", may be as follows:

1. In case the drug is indicated for serious/life threatening conditions.
2. If the drug is indicated for a disease of special relevance to the Indian health scenario.
3. The drug is indicated for a disease for which there is no or limited satisfactory therapeutic options.
4. If the drug is indicated for a rare disease or a disease in which patient population is scanty and conducting clinical trial will take long time.
5. Existence of significant unmet medical needs or significant public health issue
6. The drug under evaluation is offering added significant advantage over the existing treatment modalities for a specific disease.

Further the submission of requirements relating to Animal toxicology, Reproduction studies, Teratogenic Studies, Perinatal Studies, Mutagenicity and Carcinogenicity data may be modified or relaxed in

case of new drugs approved and marketed for several years in other countries and adequate published evidence regarding the safety of the drug is available. Although, Drugs & Cosmetics Rules does not specifically mention about the period of marketing of a new drug in other countries which can be considered as “several years”, it may be however be clarified that for relaxation or modification of the animal toxicology data requirements of a new drug as mentioned above, the drug should be marketed in other countries for a period of more than two years and adequate evidence regarding safety of the drug in published journals should be made available to CDSCO. Such relaxation or modification of requirement of toxicological data will be considered by CDSCO on case-by-case basis in consultation with experts/experts committee.

Also, as per Clause 1(3) of Schedule Y to Drugs & Cosmetics Rules, for drugs indicated in life threatening / serious diseases or diseases of special relevance to the Indian health scenario, the toxicological & clinical data requirements may be abbreviated, deferred or omitted, as deemed appropriate by the Licensing Authority.

There is as such neither any definition of “life threatening / serious diseases” nor any list of such disease/disorders prescribed under the Drugs & Cosmetics Act & Rules. "Life-threatening” diseases are generally considered as diseases or conditions where the likelihood of death is high unless the course of the disease is interrupted and diseases or conditions with potentially fatal outcomes. Diseases like Cancer, AIDS etc are generally considered as Serious /Life Threatening Diseases.

In cases of life threatening / serious diseases, it is desirable to expedite the development, evaluation, and marketing of new therapies

intended to treat persons especially where no satisfactory alternative therapy exists. In such cases patients / clinicians are generally willing to accept greater risks or side effects from products that treat life-threatening/ serious diseases, than they would accept from products that treat less serious illnesses.

CDSCO will initially examine such applications, if any particular data is lacking same will be informed to the applicant or else the applications will be forwarded to the members of IND committee in case of Investigational New Drugs (INDs) or to the members of New Drug Advisory Committee (NDAC) in case of new chemical entities other than IND and new fixed dose combinations (FDC's). However, in case of applications for grant of approval of new dosage form, new indication, new route of administration etc. of approved drugs, the application will be examined by CDSCO. Wherever required, such applications may also be examined in consultation with expert / expert committees.

Further, all requests for exemption of toxicological & clinical data requirements will be considered on the basis of examination and scrutiny of the adequacy of data and in consultation with expert/expert committees.

A legal undertaking in the form of an affidavit should be submitted by the applicant (competent person from the Company) stating that the data submitted alongwith the application is scientifically valid and authentic.

New Drugs can be divided into the following groups and data required for approval for marketing is described below:

8.1 New Chemical Entity – developed in India as an IND and not marketed anywhere in world.

8.2 New Chemical Entity approved & marketed in other countries not approved in India.

8.3 New Chemical Entity being developed in other countries and not marketed anywhere in world.

8.4 A drug already approved by the Licensing Authority mentioned in Rule 21 for certain claims, which is now proposed to be marketed with modified or new claims, namely, indications, dosage, dosage form (including sustained release dosage form) and route of administration.

8.5 A fixed dose combination of two or more drugs, individually approved earlier for certain claims, which are now proposed to be combined for the first time in a fixed ratio, or if the ratio of ingredients in an already marketed combination is proposed to be changed, with certain claims, viz. indications, dosage, dosage form (including sustained release dosage form) and route of administration.

8.6 A New Drug already approved in the country (within four years of approval of new drugs).

8.1 New Drugs – developed in India as an IND and not marketed anywhere in world.

For such New Drugs to be approved for marketing, data required to be submitted will be similar as per Appendix I of Schedule Y which is similar to data required for any new chemical entity (NCE). For

such New Drugs the clinical trials are required to be carried out right from Phase I.

CDSCO will initially examine such applications, if any particular data is lacking same will be informed to the applicant or else the applications will be forwarded to the members of IND committee.

For new drug permission of such New Drugs the documents required to be submitted are as follows:

1. Form 44
2. Treasury Challan of INR 50,000.
3. Source of bulk drugs /raw materials.

Clarification:

- Manufacture the API - Applicant has to also to file application for API alongwith all relevant documents and comply with further requirements for manufacture of API
- Obtain the API from another manufacturer which is not yet approved by DCGI - In such case, the respective manufacturer of the API has to file an application separately in Form 44 along with treasury Challan of requisite amount with all relevant documents. Such application will be processed simultaneously with the application for the New Drug. Approval of the API will be considered after approval of its formulation.

4. Chemical and pharmaceutical information including:

a) Information on active ingredients:

Drug information (Generic Name, Chemical Name or INN) & Physicochemical Data including:

i. Chemical name and Structure - Empirical formula, Molecular weight

ii. Physical properties - Description, Solubility, Rotation, Partition coefficient, Dissociation constant
iii. Analytical Data: Elemental analysis, Mass spectrum, NMR spectra, IR spectra, UV spectra, Polymorphic identification
iv. Complete monograph specification including: Identification, Identity/ quantification of impurities, Enantiomeric purity, Assay
v. Validations: Assay method, Impurity estimation method, Residual solvent/other volatile impurities (OVI) estimation method
vi. Stability Studies (refer Appendix IX of Schedule Y):
vii. Final release specification,
viii. Reference standard characterization,
ix. Material safety data sheet.
x. Certificate of Analysis

b) **Data on Formulation:**

i. Dosage form,
ii. Composition,
iii. Master manufacturing formula,
iv. Details of the formulation (including inactive ingredients),
v. In process quality control check,
vi. Finished product specification & Method of Analysis,
vii. Excipient compatibility study,
viii. Validation of the analytical method.
ix. Comparative evaluation with international brand(s) or approved Indian brands, if applicable.

x. Pack presentation ,
xi. Dissolution ,
xii. Assay ,
xiii. Impurities ,
xiv. Content uniformity ,
xv. PH ,
xvi. Force degradation study ,
xvii. Stability evaluation in market intended pack proposed storage conditions ,
xviii. Packing specifications ,
xix. Process validation.

6. **Animal Pharmacology**

i. Summary
ii. Specific pharmacological actions
iii. General pharmacological actions
iv. Follow-up and Supplemental Safety Pharmacology Studies
v. Pharmacokinetics: absorption, distribution; metabolism; excretion

7. **Animal Toxicology**

i. General Aspects
ii. Systemic Toxicity Studies
iii. Male Fertility Study
iv. Female Reproduction and Developmental Toxicity Studies
v. Local toxicity
vi. Allergenicity/Hypersensitivity
vii. Genotoxicity

viii. Carcinogenicity

8. **Human / Clinical pharmacology (Phase I)**
   i. Summary
   ii. Specific Pharmacological effects
   iii. General Pharmacological effects
   iv. Pharmacokinetics, absorption, distribution, metabolism, excretion
   v. Pharmacodynamic / early measurement of drug activity
9. **Therapeutic exploratory trials (Phase II)**
   i. Summary
   ii. Study report(s) as given in Appendix II
10. **Therapeutic confirmatory trials (Phase III)**
   i. Summary
   ii. Individual study reports with listing of sites and Investigators as given in Appendix II.
11. **Special studies**
   i. Summary
   ii. Bio-availability / Bio-equivalence.
   iii. Other studies e.g. geriatrics, paediatrics, pregnant or nursing women
12. **Regulatory status in other countries**

C. Countries where the drug is

   i. Marketed
   ii. Approved
   iii. Approved as IND
   iv. Withdrawn, if any, with reasons

D. Restrictions on use, if any, in countries where marketed/approved

E. Undertaking in respect of GMP status of manufacturing facility.

13. A. **Prescribing information**

Proposed full prescribing information containing the following information:

generic name; composition; dosage form/s, indications; dose and method of administration; use in special populations (such as pregnant women, lactating women, paediatric patients, geriatric patients etc.); contra-indications; warnings; precautions; drug interactions; undesirable effects; overdose; pharmacodynamic and pharmacokinetic properties; incompatibilities; shelf-life; packaging information; storage and handling instructions.

B. **Draft Specimen of label & Carton**

14. **Copy of License in Form-29**

15. **Samples and Testing Protocol/s**

Samples of pure drug substance and finished product (an equivalent of 50 clinical doses, or more number of clinical Doses, if prescribed by the Licensing Authority), with testing Protocol/s, full impurity profile and release specifications.

NOTE: Details of Animal Pharmacology & Animal Toxicology studies required to be carried out will be as per Appendix IV & Appendix III of Schedule Y of Drugs and Cosmetics Rules respectively. Depending upon the nature of new drugs and disease(s) specific additions/deletions may be made to the above requirements.

8.2 New Chemical Entity approved & marketed in other countries not approved in India.

For such New Drugs to be approved for marketing, data required to be submitted will be similar as per Appendix I of Schedule Y which is similar to data required for any new chemical entity (NCE).

Generally, the new drugs which are approved in one or more countries like USA, UK, Canada, European Union, Japan, and Australia will be considered for approval of manufacture/import & marketing of the drug in the country unless there are specific reasons as follows:

1. The drug is indicated for serious/life threatening conditions.
2. The drug is indicated for a disease of special relevance to the Indian health scenario.
3. The drug is indicated for a disease for which there is no or limited satisfactory therapeutic options.
4. The drug is indicated for a rare disease or a disease in which patient population is scanty and conducting clinical trial will take long time.
5. Existence of significant unmet medical needs or significant public health issue
6. The drug under evaluation is offering added significant advantage over the existing treatment modalities for a specific disease.

For such new drugs, Phase III studies need to be carried out locally primarily to generate evidence of efficacy and safety of

the drug in Indian patients when used as recommended in the prescribing information. Prior to conduct of Phase III studies in Indian subjects, Licensing Authority may require pharmacokinetic studies to be undertaken to verify that the data generated in Indian population is in conformity with the data already generated abroad.

As per the provisions given in the Drugs & Cosmetics Rules requirement of submitting results of local clinical trials may not be necessary, if the drug is of such a nature that the licensing authority may in public interest decide to grant such permissions on the basis of data available from other countries.

Applicants seeking such waiver of local clinical trials of new drugs should submit formal request to CDSCO alongwith adequate justification and data.

CDSCO will initially examine such applications, if any particular data is lacking same will be informed to the applicant or else the applications will be forwarded to the members of New Drug Advisory Committee (NDAC). Decision on requests for waiver of local clinical trials before approval of new drugs for marketing in the country will be taken as per recommendation of NDAC.

For approval of such New Drugs the documents required to be submitted are as follows:

1. Form 44
2. Treasury Challan of INR 50,000.
3. Source of bulk drugs /raw materials.

Clarification: The applicant can either import or manufacture the API by themselves or they can obtain the same from some other indigenous source:

- Import the API - Applicant has to file application alongwith all relevant documents and comply with further requirements for import of API.
- Manufacture the API - Applicant has to file application alongwith all relevant documents and comply with further requirements for manufacture of API
- Obtain the API from another manufacturer which is not yet approved by DCGI - In such case, the respective manufacturer of the API has to file an application separately in Form 44 along with treasury Challan of requisite amount with all relevant documents. Such application will be processed simultaneously with the application for finished formulation. Approval of the API will be considered after approval of its formulation.

4. Chemical and pharmaceutical information including:

a) Information on active ingredients:

Drug information (Generic Name, Chemical Name or INN) &
Physicochemical Data including:

i. Chemical name and Structure - Empirical formula, Molecular weight

ii. Physical properties - Description, Solubility, Rotation, Partition coefficient, Dissociation constant

iii. Analytical Data: Elemental analysis, Mass spectrum, NMR spectra, IR spectra, UV spectra, Polymorphic identification

iv. Complete monograph specification including: Identification, Identity/ quantification of impurities, Enantiomeric purity, Assay

v. Validations: Assay method, Impurity estimation method, Residual solvent/other volatile impurities (OVI) estimation method

vi. Stability Studies (refer Appendix IX of Schedule Y): Final release specification, Reference standard characterization, Material safety data sheet.

5. Data on Formulation:

i. Dosage form,

ii. Composition,

iii. Master manufacturing formula,

iv. Details of the formulation (including inactive ingredients),

v. In process quality control check,

vi. Finished product specification & Method of Analysis,

vii. Excipient compatibility study,

viii. Validation of the analytical method.

ix. Comparative evaluation with international brand(s) or approved Indian brands, if applicable.

x. Pack presentation,

xi. Dissolution,

xii. Assay,

xiii. Impurities,

xiv. Content uniformity,

xv. pH ,

xvi. Force degradation study,

xvii. Stability evaluation in market intended pack at proposed storage conditions,

xviii. Packing specifications,

xix. Process validation.

6. Animal Pharmacology

i. Summary

ii. Specific pharmacological actions
iii. General pharmacological actions
iv. Follow-up and Supplemental Safety Pharmacology Studies
v. Pharmacokinetics: absorption, distribution; metabolism; excretion

7. Animal Toxicology

i. General Aspects
ii. Systemic Toxicity Studies
iii. Male Fertility Study
iv. Female Reproduction and Developmental Toxicity Studies
v. Local toxicity
vi. Allergenicity / Hypersensitivity
vii. Genotoxicity
viii. Carcinogenicity

8. Human / Clinical pharmacology (Phase I)

i. Summary
ii. Specific Pharmacological effects
iii. General Pharmacological effects
iv. Pharmacokinetics, absorption, distribution, metabolism, excretion
v. Pharmacodynamic / early measurement of drug activity

9. Therapeutic exploratory trials (Phase II)

i. Summary
ii. Study report(s) as given in Appendix II

10. Therapeutic confirmatory trials (Phase III)

i. Summary
ii. Individual study reports with listing of sites and Investigators as given in Appendix II

11. Special studies

i. Summary

ii. Bio-availability / Bio-equivalence.

iii. Other studies e.g. geriatrics, paediatrics, pregnant or nursing women

12. Regulatory status in other countries

a) Countries where the drug is

i. Marketed

ii. Approved

iii. Approved as IND

iv. Withdrawn, if any, with reasons

b) Restrictions on use, if any, in countries where marketed/approved

c) Free sale certificate (FSC) or Certificate of Pharmaceutical Product (COPP), as appropriate.

13. A. **Prescribing information**

Proposed full prescribing information containing the following information:

generic name; composition; dosage form/s, indications; dose and method of administration; use in special populations (such as pregnant women, lactating women, paediatric patients, geriatric patients etc.); contra-indications; warnings; precautions; drug interactions; undesirable effects; overdose; pharmacodynamic and pharmacokinetic properties; incompatibilities; shelf-life; packaging information; storage and handling instructions.

B. **Draft Specimen of label & Carton**

14. **Copy of License in Form-29**

15. **Samples and Testing Protocol/s**

Samples of pure drug substance and finished product (an equivalent of 50 clinical doses, or more number of clinical Doses, if prescribed by the Licensing Authority), with testing Protocol/s, full impurity profile and release specifications.

NOTE: *Details of Animal Pharmacology & Animal Toxicology studies required to be carried out will be as per Appendix IV & Appendix III of Schedule Y of Drugs and Cosmetics Rules respectively. Depending upon the nature of new drugs and disease(s) specific additions/deletions may be made to the above requirements.*

8.3 New Chemical Entity being developed in other countries and not marketed anywhere in world.

For approval of such New Drugs, the clinical trial may be required to be carried out right from Phase I depending on the status of development of the molecule in other countries. However, approval of such new drug for manufacture/import for marketing in the country will generally be considered after the drug is approved in one or more countries like USA, UK, Canada, European Union, Japan, and Australia unless there are specific reasons as follows:

1. The drug is indicated for serious/life threatening conditions.
2. The drug is indicated for a disease of special relevance to the Indian health scenario.
3. The drug is indicated for a disease for which there is no or limited satisfactory therapeutic options.

4. The drug is indicated for a rare disease or a disease in which patient population is scanty and conducting clinical trial will take long time.

5. Existence of significant unmet medical needs or significant public health issue

6. The drug under evaluation is offering added significant advantage over the existing treatment modalities for a specific disease.

For such New Drugs to be approved for marketing, data required to be submitted will be similar as per data requirements as stipulated for Category 8.2 given above.

CDSCO will initially examine such applications, if any particular data is lacking same will be informed to the applicant or else the applications will be forwarded to the members of New Drug Advisory Committee (NDAC).

8.4 A drug already approved by the Licensing Authority mentioned in Rule 21 for certain claims, which is now proposed to be marketed with modified or new claims, namely, indications, dosage, dosage form (including sustained release dosage form) and route of administration.

Such types of new drug applications differ from the new drug application as mentioned above at 8.1 to 8.3 in that they allow the applicant and regulatory authority to rely at least in part, on the safety and/or efficacy data of a previously approved drug. However, additional nonclinical and/or clinical data is necessary to substantiate the new claims of

the approved drug. The additional data needed for establishing the safety and efficacy of such new drugs will usually be determined on case-by-case basis depending on the type of new claims being made.

Requirements of Animal Pharmacological, Animal Toxicological & clinical data may be abbreviated / relaxed / omitted if all the below mentioned conditions are satisfied:

1. If the drug is already approved by various agencies and is being marketed in major countries for the proposed new claim (s).
2. There are evidences of no difference in metabolism of drug due to ethnic differences.
3. Availability of adequate clinical data supporting the benefit-risk ratio in favour of the drug in the proposed new claim (s).
4. The package insert from marketed countries shows that there is no added safety concern if the drug is allowed to be given to Indian patients for the new claim (s).

Requirements of Animal Toxicological & clinical data may be abbreviated / relaxed / omitted if the proposed new claim is for serious life threatening disease or disease of special relevance to Indian health scenario.

CDSCO will examine the adequacy of such applications for the purpose of granting approval for manufacture/import of such new drugs. Wherever required the matter may also be examined in consultation with experts/expert committees.

Requests for waiver of requirements of Animal Toxicological & clinical data will be examined in consultation with expert/expert committees.

8.4.1 A drug already approved by the Licensing Authority mentioned in Rule 21 proposed to be marketed with new indication

In such cases when application is for an already approved drug which is proposed to be marketed with a new indication the documents required to be submitted are as follows:

1. Form 44
2. Treasury Challan of INR 50,000 / 15,000 as the case may be.
3. Source of bulk drugs /raw materials: For those raw materials, which are approved and considered new drugs - If the applicant has a manufacturing license for bulk drugs, a copy of the same needs to be submitted. Otherwise, provide the consent letter from the approved source regarding supply of raw material.

Clarification: In case if the applicant does not have an approval from DCGI to manufacture Active Pharmaceutical Ingredient (API) which is considered as new drug, applicant can,

- Import the API - Applicant has to file application alongwith all relevant documents and comply with further requirements for import of API.
- Manufacture the API - Applicant has to file application alongwith all relevant documents and comply with further requirements for manufacture of API

- *Obtain the API from another manufacturer which is not yet approved by DCGI - In such case, the respective manufacturer of the API has to file an application separately in Form 44 along with treasury Challan of requisite amount with all relevant documents. Such application will be processed simultaneously with the application for the finished formulation. Approval of the API will be considered after approval of its formulation.*

4. **Chemical and pharmaceutical information including:**

Data requirements in respect of Chemical and Pharmaceutical information may be omitted depending on whether the applicant has already obtained permission from CDSCO for the same dosage form of the new drug for approved indication. If the applicant has already obtained permission from CDSCO for the same dosage form of the new drug for approved indication, no further chemical and pharmaceutical data is required to be submitted.

If the applicant has not obtained such permission, complete chemical & pharmaceutical data is required to be submitted alongwith the application. Details of such data required are as follows:

a) **Information on active ingredients:**

Drug information (Generic Name, Chemical Name or INN) & Physicochemical Data including:

i. Chemical name and Structure - Empirical formula, Molecular weight
ii. Physical properties - Description, Solubility, Rotation, Partition coefficient, Dissociation constant

iii. Analytical Data: Elemental analysis, Mass spectrum, NMR spectra, IR spectra, UV spectra, Polymorphic identification

iv. Complete monograph specification including: Identification, Identity/ quantification of impurities, Enantiomeric purity, Assay

v. Validations: Assay method, Impurity estimation method, Residual solvent/other volatile impurities (OVI) estimation method

vi. Stability Studies (refer Appendix IX of Schedule Y): Final release specification, Reference standard characterization, Material safety data sheet.

5. **Data on Formulation:**

i. Dosage form,

ii. Composition,

iii. Master manufacturing formula,

iv. Details of the formulation (including inactive ingredients),

v. In process quality control check,

vi. Finished product specification & Method of Analysis,

vii. Excipient compatibility study,

viii. Validation of the analytical method.

ix. Comparative evaluation with international brand(s) or approved Indian brands, if applicable.

x. Pack presentation ,

xi. Dissolution ,

xii. Assay ,

xiii. Impurities ,

xiv. Content uniformity ,

xv. pH ,

xvi. Force degradation study ,

xvii. Stability evaluation in market intended pack at proposed storage conditions ,

xviii. Packing specifications ,

xix. Process validation.

6. **Animal Pharmacology Data (as per Schedule-Y)**
7. **Animal Toxicology Data (as per Schedule-Y)**
8. **Human / Clinical pharmacology (Phase I) Data**
9. **Therapeutic exploratory trials (Phase II)**
   i. Summary
   ii. Study report(s) as given in Appendix II
10. **Therapeutic confirmatory trials (Phase III)**
   i. Summary
   ii. Individual study reports with listing of sites and Investigators as given in Appendix II.
11. **Special studies**
   i. Summary
   ii. Bio-availability / Bio-equivalence.
   iii. Other studies e.g. geriatrics, paediatrics, pregnant or nursing women
12. **Regulatory status in other countries for proposed indication**

a) Countries where the drug is

i. Marketed
ii. Approved
iii. Approved as IND
iv. Withdrawn, if any, with reasons

b) Restrictions on use, if any, in countries where marketed/approved

c) Free sale certificate (FSC) or Certificate of Pharmaceutical Product (COPP), as appropriate

.

13. A. **Prescribing information**

Proposed full prescribing information containing the following information:

generic name; composition; dosage form/s, indications; dose and method of administration; use in special populations (such as pregnant women, lactating women, paediatric patients, geriatric patients etc.); contra-indications; warnings; precautions; drug interactions; undesirable effects; overdose; pharmacodynamic and pharmacokinetic properties; incompatibilities; shelf-life; packaging information; storage and handling instructions.

B. **Draft Specimen of label & Carton**

14. **Copy of License in Form-29**

8.4.2 **A drug already approved by the Licensing Authority mentioned in Rule 21 and proposed to be marketed as a 'new dosage form / new route of administration'.**

In such cases when application is for an already approved drug which is proposed to be marketed with a new dosage form the documents required to be submitted are as follows:

1. Form 44
2. Treasury Challan of INR 50,000 / 15,000 as the case may be.

3. Source of bulk drugs /raw materials. For those ingredients which are approved and considered new drugs - If the applicant has a manufacturing license for bulk drugs, please provide a copy of the same. Otherwise, provide the consent letter from the approved source regarding supply of material.

Clarification: In case if the applicant does not have an approval from DCGI to manufacture Active Pharmaceutical Ingredient (API) which is considered as new drug, applicant can,

- Import the API - Applicant has to file application alongwith all relevant documents and comply with further requirements for import of API.
- Manufacture the API - Applicant has to file application alongwith all relevant documents and comply with further requirements for manufacture of API
- Obtain the API from another manufacturer which is not yet approved by DCGI - In such case, the respective manufacturer of the API has to file an application separately in Form 44 along with treasury Challan of requisite amount with all relevant documents. Such application will be processed simultaneously with the application for the finished formulation. Approval of the API will be considered after approval of its formulation.

4. Chemical and pharmaceutical information including:

a) **Information on active ingredients:**

Drug information (Generic Name, Chemical Name or INN) & Physicochemical Data including:

i. Chemical name and Structure - Empirical formula, Molecular weight

ii. Physical properties - Description, Solubility, Rotation, Partition coefficient, Dissociation constant

iii. Analytical Data: Elemental analysis, Mass spectrum, NMR spectra, IR spectra, UV spectra, Polymorphic identification

iv. Complete monograph specification including: Identification, Identity/ quantification of impurities, Enantiomeric purity, Assay

v. Validations: Assay method, Impurity estimation method, Residual solvent/other volatile impurities (OVI) estimation method

vi. Stability Studies (refer Appendix IX of Schedule Y): Final release specification, Reference standard characterization, Material Safety data sheet.

5. Data on Formulation:

i. Dosage form,

ii. Composition,

iii. Master manufacturing formula,

iv. Details of the formulation (including inactive ingredients),

v. In process quality control check,

vi. Finished product specification & Method of Analysis,

vii. Excipient compatibility study,

viii. Validation of the analytical method.

ix. Comparative evaluation with international brand(s) or approved Indian brands, if applicable.
x. Pack presentation ,
xi. Dissolution ,
xii. Assay ,
xiii. Impurities ,
xiv. Content uniformity ,
xv. pH ,
xvi. Force degradation study ,
xvii. Stability evaluation in market intended pack at proposed storage conditions ,
xviii. Packing specifications ,
xix. Process validation.

6. **Animal Pharmacology Data (as per Schedule-Y)**
7. **Animal Toxicology Data (as per Schedule-Y)**
8. **Human / Clinical pharmacology (Phase I) Data (as per Schedule-Y)**
9. **Therapeutic exploratory trials (Phase II)**
   i. Summary
   ii. Study report(s) as given in Appendix II
10. **Therapeutic confirmatory trials (Phase III)**
   i. Summary
   ii. Individual study reports with listing of sites and Investigators.
11. **Special studies**
   i. Summary
   ii. Bio-availability / Bio-equivalence.
   iii. Other studies e.g. geriatrics, paediatrics, pregnant or nursing women

12. Regulatory status in other countries

a) Countries where the drug is

i. Marketed
ii. Approved
iii. Approved as IND
iv. Withdrawn, if any, with reasons

b) Restrictions on use, if any, in countries where marketed/approved

c) Free sale certificate (FSC) or Certificate of Pharmaceutical Product (COPP), as appropriate

13. A. **Prescribing information**

Proposed full prescribing information containing the following information:

generic name; composition; dosage form/s, indications; dose and method of administration; use in special populations (such as pregnant women, lactating women, paediatric patients, geriatric patients etc.); contra-indications; warnings; precautions; drug interactions; undesirable effects; overdose; pharmacodynamic and pharmacokinetic properties; incompatibilities; shelf-life; packaging information; storage and handling instructions.

B. **Draft Specimen of label & Carton**

14. **Copy of License in Form-29**

15. **Samples and Testing Protocol/s**

Samples of pure drug substance and finished product (an equivalent of 50 clinical doses, or more number of clinical Doses, if prescribed by the Licensing Authority), with testing Protocol/s, full impurity profile and release specifications.

.

8.4.3 A drug already approved by the Licensing Authority mentioned in Rule 21 now proposed to be marketed as a 'Modified release dosage form'.

When a modified release product is the first market entry of the modified release type both comparative clinical trials and bioequivalence study comparing the modified release formulation with the immediate release formulation is required to be conducted.

When the modified release product is approved and marketed in other major countries, comparative bioequivalence study of the test product versus the innovator's modified release is required to be conducted.

For modified release dosage form In vivo bioequivalence/bioavailability studies are recommended which should be designed to ensure that:

i . The product meets the modified release label claims

ii. The product does not release the active drug substance at a rate and extent leading to dose dumping

iii. There is no significant difference between the performance of the modified release product and the reference immediate release product administered by same route in multiple doses (of an equivalent daily amount) or to the reference modified release product.

Iv There must be a significant difference between the performance of modified release product and the conventional release product when used as reference product.

For In vivo bioequivalence/bioavailability studies of modified release doses forms study design will be single dose or single and multiple dose based on the modified release products that are likely to accumulate or unlikely to

accumulate both in the fasted and non-fasting state. If the effect of food on the reference product is not known (or it is known that food affects its absorption), two separate two-way cross-over studies, one in the fasted state and the other in the fed state, may be carried out. If it is known with certainty (e.g. from published data) that the reference product is not affected by food, then a three-way cross-over study may be appropriate with:

A. The reference product in the fasting state
B. The test product in the fasted state, and
C. The test product in the fed state.

Modified release formulations which are not likely to accumulate

Modified release formulations which are unlikely to accumulate are used at dose intervals that are not likely to lead to accumulation (AUC_{0-t} /$AUC_{0-\alpha} \geq$ 0.8).

When the modified release product is the first market entry of that type of dosage form, the reference product should normally be the innovator's immediate- release formulation. The comparison should be between a single dose of the modified release formulation and doses of the immediate-release formulation which it is intended to replace. The later must be administered according to the established dosing regimen.

When the modified release product is the second or subsequent entry on the market, comparison should be with the reference modified release product for which bioequivalence is claimed.

Studies should be performed with single dose administration in the fasting state as well as following an appropriate meal at a specified time.

The following pharmacokinetic parameters should be calculated from plasma (or relevant biological matrix) concentrations of the drug and/or

major metabolite(s): AUC_{0-t} , $AUC_{0-\infty,}$ and C_{max} (Where the comparison is with an existing modified release product), and k_{el}

The 90% confidence interval (Test/Reference) of the geometric mean of log transformed AUC (for both AUC_{0-t} and AUC_{0-t}) should be within the range 80 to 125% both in the fasting state and following the administration of an appropriate meal at a specified time before taking the drug.

Modified release formulations which are likely to accumulate

Modified release formulations which are likely to accumulate are used at dose intervals that are likely to lead to accumulation (AUC_{0-t} /$AUC_{0-\alpha}$ < 0.8).

Studies should be performed with single dose administration in the fasting state as well as following an appropriate meal. In addition, studies are required at steady state. The following pharmacokinetic parameters should be calculated from single dose studies: AUC0-t, AUC0-t $AUC_{0-\infty}$, C max(where the comparison is with an existing modified release product), and k el The following parameters should be calculated from steady state studies: AUC0-t(ss) C max C min C pd and degree of fluctuation.

When the modified release product is the second or subsequent modified release entry, single dose and steady state comparisons should normally be made with the reference modified release product for which bioequivalence is claimed. The 90% confidence interval for the ratio of geometric means (Test: Reference drug) of AUC (for both AUC0-t and AUC0-t and C max(where the comparison is with an existing modified release product) determined using log-transformed data should generally be within the range 80 to 125% when the products are compared after single dose administration in both the fasting state and the fed state.

The documents required to be submitted for approval of new dosage forms are as follows:

1. Form 44
2. Treasury Challan of INR 50,000 / 15,000 as the case may be.
3. Source of bulk drugs /raw materials. For those ingredients which are approved and considered new drugs - If the applicant has a manufacturing license for bulk drugs, please provide a copy of the same. Otherwise, provide the consent letter from the approved source regarding supply of material.

   Clarification: In case if the applicant does not have an approval from DCGI to manufacture Active Pharmaceutical Ingredient (API) which is considered as new drug, applicant can,

   - Import the API - Applicant has to file application alongwith all relevant documents and comply with further requirements for import of API.
   - Manufacture the API - Applicant has to file application alongwith all relevant documents and comply with further requirements for manufacture of API

- Obtain the API from another manufacturer which is not yet approved by DCGI - In such case, the respective manufacturer of the API has to file an application separately in Form 44 along with treasury Challan of requisite amount with all relevant documents. Such application will be processed simultaneously with the application for the finished formulation. Approval of the API will be considered after approval of its formulation.

4. **Chemical and pharmaceutical information including:**

a) **Information on active ingredients:**

Drug information (Generic Name, Chemical Name or INN) & Physicochemical Data including:

i. Chemical name and Structure - Empirical formula, Molecular weight

ii. Physical properties - Description, Solubility, Rotation, Partition coefficient, Dissociation constant

iii. Analytical Data: Elemental analysis, Mass spectrum, NMR spectra, IR spectra, UV spectra, Polymorphic identification

iv. Complete monograph specification including: Identification, Identity/ quantification of impurities, Enantiomeric purity, Assay

v. Validations: Assay method, Impurity estimation method, Residual solvent/other volatile impurities (OVI) estimation method

vi. Stability Studies (refer Appendix IX of Schedule Y): Final release specification, Reference standard characterization, Material Safety Data Sheet.

5. **Data on Formulation:**

i. Dosage form,

ii. Composition,

iii. Master manufacturing formula,

iv. Details of the formulation (including inactive ingredients),

v. In process quality control check,

vi. Finished product specification & Method of Analysis,
vii. Excipient compatibility study,
viii. Validation of the analytical method.
ix. Comparative evaluation with international brand(s) or approved Indian brands, if applicable.
x. Pack presentation ,
xi. Dissolution ,
xii. Assay ,
xiii. Impurities ,
xiv. Content uniformity ,
xv. pH ,
xvi. Force degradation study ,
xvii. Stability evaluation in market intended pack at proposed storage conditions ,
xviii. Packing specifications ,
xix. Process validation.

6. Summary of Animal Pharmacology & Toxicological Data

7. A. Summary of Phase I, Phase II & Phase III clinical trials data generated with immediate release formulation of the drug

B. Report of clinical trials carried out with the modified release dosage form

i. Summary
ii. Individual study reports with listing of sites and Investigators as per appendix-II of Schedule Y.

C. Report of Bioequivalence study (ies) carried out with the modified release dosage form

8. Regulatory status in other countries

a) Countries where the drug is

i. Marketed

ii. Approved

iii. Approved as IND

iv. Withdrawn, if any, with reasons

b) Restrictions on use, if any, in countries where marketed/approved

c) Free sale certificate (FSC) or Certificate of Pharmaceutical Product (COPP), as appropriate

9. A. Prescribing information

Proposed full prescribing information containing the following information:

generic name; composition; dosage form/s, indications; dose and method of administration; use in special populations (such as pregnant women, lactating women, paediatric patients, geriatric patients etc.); contra-indications; warnings; precautions; drug interactions; undesirable effects; overdose; pharmacodynamic and pharmacokinetic properties; incompatibilities; shelf-life; packaging information; storage and handling instructions.

B. **Draft Specimen of label & Carton**

10. Copy of License in Form-29

11. Samples and Testing Protocol/s

Samples of pure drug substance and finished product (an equivalent of 50 clinical doses, or more number of clinical Doses,

if prescribed by the Licensing Authority), with testing Protocol/s, full impurity profile and release specifications.

8.5 A fixed dose combination of two or more drugs, individually approved earlier for certain claims, which are now proposed to be combined for the first time in a fixed ratio, or if the ratio of ingredients in an already marketed combination is proposed to be changed, with certain claims, viz. indications, dosage, dosage form (including sustained release dosage form) and route of administration.

Separate guidelines for Fixed Dose Combinations have already been posted on CDSCO website.

8.6 A New Drug already approved in the country (within four years of approval of new drugs).

1. Form 44
2. Treasury Challan of INR 15,000 if all the active ingredients are approved in India for more than one year, or INR 50,000 in case any of the active ingredients is approved for less than one year.
3. **Source of bulk drugs /raw materials**: For those ingredients which are approved and considered new drugs - If the applicant has a manufacturing license for bulk drugs, a copy of the same is needs to be submitted. Otherwise, provide the consent letter from the approved source regarding supply of material.

   Clarification: In case if the applicant does not have an approval from DCGI to manufacture Active Pharmaceutical

Ingredient (API) which is considered as new drug, applicant can,

- Import the API - Applicant has to file application alongwith all relevant documents and comply with further requirements for import of API.
- Manufacture the API - Applicant has to file application alongwith all relevant documents and comply with further requirements for manufacture of API
- Obtain the API from another manufacturer which is not yet approved by DCGI - In such case, the respective manufacturer of the API has to file an application separately in Form 44 along with treasury Challan of requisite amount with all relevant documents. Such application will be processed simultaneously with the application for API. Approval of the formulation will be considered after approval of the API.

4. **Chemical and pharmaceutical information including:**

Information on active ingredients:

a) Brief Chemical & pharmaceutical data

Data on Formulation

a) Master manufacturing formula
b) Details of the formulation (including inactive ingredients)
c) Finished product specification
d) In process quality control check
e) Certificate of analysis including identification, pH, content uniformity, impurities, assay etc.
f) Comparative Dissolution data in case oral dosage form as appropriate

g) Stability study evaluation as per requirements of schedule Y

5. Regulatory status of the drug including names of the company's marketing the drug in the country
6. Bioavailability/Bioequivalence study reports (for oral dosage forms)

Note: In following circumstances equivalence may be assessed by the use of in vitro dissolution testing:

a. Drugs for which the applicant provides data to substantiate all of the following:

i. Highest dose strength is soluble in 250 ml of an aqueous media over the pH range of 1-7.5 at 37°C

ii. At least 90% of the administered oral dose is absorbed on mass balance determination or in comparison to an intravenous reference dose.

iii. Speed of dissolution as demonstrated by more than 80% dissolution within 15 minutes at 37°C using IP apparatus 1, at50 rpm or IP apparatus 2, at 100 rpm in a volume of 900 ml or less in each of the following media:

a. 0.1 N hydrochloric acid or artificial gastric juice (without enzymes)
b. a pH 4.5 buffer
c. a. pH 6.8 buffer or artificial intestinal juice (without enzymes)

b. Different strengths of the drug manufactured by the same manufacturer, where all of the following criteria are fulfilled:

i. The qualitative composition between the strengths is essentially the same;

ii. The ratio of active ingredients and excipients between the strengths is essentially the same, or, in the case of small strengths, the ratio between the excipient is the same;

iii. The method of manufacture is essentially the same;

iv. An appropriate equivalence study has been performed on at least one of the strengths of the formulation (usually the highest strength unless a lower strength is chosen for reasons of safety); and

v. In case of systemic availability - pharmacokinetics have been shown to be linear over the therapeutic dose range.

c. In vitro dissolution testing may also be suitable to confirm unchanged product quality and performance characteristics with minor formulation or manufacturing changes after approval.

7. In case of Injectable formulation, sub-acute toxicity data conducted with the applicants' product has to be provided.

8. Prescribing information

Proposed full prescribing information containing the following information:

generic name; composition; dosage form/s, indications; dose and method of administration; use in special populations (such as pregnant women, lactating women, paediatric patients, geriatric patients etc.); contra-indications; warnings; precautions; drug interactions; undesirable effects; overdose; pharmacodynamic and

pharmacokinetic properties; incompatibilities; shelf-life; packaging information; storage and handling instructions.

9. Draft of labels and carton

10. Copy of License in Form-29

Annexure A

Data Elements For Reporting Serious Adverse Events Occurring In A Clinical Trial

1. Patient Details

Initials & other relevant identifier (hospital/OPD record number etc.)*

Gender

Age and/or date of birth

Weight

Height

2. Suspected Drug(s)

Generic name of the drug*.

Indication(s) for which suspect drug was prescribed or tested.

Dosage form and strength. 546 Drugs and Cosmetics Rules, 1945

Daily dose and regimen (specify units - e.g., mg, ml, mg/kg).

Route of administration.

Starting date and time of day.

Stopping date and time, or duration of treatment

3. Other Treatment(s)

Provide the same information for concomitant drugs (including non prescription/OTC drugs) and non-drug therapies, as for the suspected drug(s).

4. Details of Suspected Adverse Drug Reaction(s)

Full description of reaction(s) including body site and severity, as well as the criterion (or criteria) for regarding the report as serious. In addition to a description of the reported signs and symptoms, whenever possible, describe a specific diagnosis for the reaction.*

Start date (and time) of onset of reaction.

Stop date (and time) or duration of reaction.

De-challenge and re-challenge information.

Setting (e.g., hospital, out-patient clinic, home, nursing home).

5. Outcome

Information on recovery and any sequelae; results of specific tests and/or treatment that may have been conducted.

For a fatal outcome, cause of death and a comment on its possible relationship to the suspected reaction; any post-mortem findings.

Other information: anything relevant to facilitate assessment of the case, such as medical history including allergy, drug or alcohol abuse; family history; findings from special investigations etc.

6. Details about the Investigator*

Name

Address

Telephone number

Profession (speciality)

Date of reporting the event to Licensing Authority:

Date of reporting the event to Ethics Committee overseeing the site:

Signature of the Investigator

Note: Information marked * must be provided."

Annexure-B

UNDERTAKING BY THE INVESTIGATOR

1. Full name, address and title of the Principal Investigator (or Investigator(s) when

there is no Principal Investigator)

2. Name and address of the medical college, hospital or other facility where the clinical trial will be conducted: Education, training & experience that qualify the Investigator for the clinical trial (Attach details including Medical Council registration number, and / or any other statement(s) of qualification(s))

3. Name and address of all clinical laboratory facilities to be used in the study.

4. Name and address of the Ethics Committee that is responsible for approval and continuing review of the study.

5. Names of the other members of the research team (Co- or sub-Investigators) who will be assisting the Investigator in the conduct of the investigation (s).

6. Protocol Title and Study number (if any) of the clinical trial to be conducted by the Investigator.

7. Commitments:

(i) I have reviewed the clinical protocol and agree that it contains all the necessary information to conduct the study. I will not begin the study until all necessary Ethics Committee and regulatory approvals have been obtained.

(ii) I agree to conduct the study in accordance with the current protocol. I will not implement any deviation from or changes of the protocol without agreement by the Sponsor and prior review and documented approval / favourable opinion from the Ethics Committee of the amendment, except where necessary to eliminate an immediate hazard(s) to the trial Subjects or when the change(s) involved are only logistical or administrative in nature.

(iii) I agree to personally conduct and/or supervise the clinical trial at my site.

(iv) I agree to inform all Subjects, that the drugs are being used for investigational purposes and I will ensure that the requirements relating to obtaining informed consent and ethics committee review and approval specified in the GCP guidelines are met.

(v) I agree to report to the Sponsor all adverse experiences that occur in the course of the investigation(s) in accordance with the regulatory and GCP guidelines.

(vi) I have read and understood the information in the Investigator's brochure, including the potential risks and side effects of the drug.

(vii) I agree to ensure that all associates, colleagues and employees assisting in the conduct of the study are suitably qualified and experienced and they have been informed about their obligations in meeting their commitments in the trial.

(viii) I agree to maintain adequate and accurate records and to make those records available for audit / inspection by the Sponsor, Ethics Committee, Licensing Authority or their authorized representatives, in accordance with regulatory and GCP provisions. I will fully cooperate with any study related audit conducted by regulatory officials or authorized representatives of the Sponsor.

(ix) I agree to promptly report to the Ethics Committee all changes in the clinical trial activities and all unanticipated problems involving risks to human Subjects or others. 539 Drugs and Cosmetics Rules, 1945

(x) I agree to inform all unexpected serious adverse events to the Sponsor as well as the Ethics Committee within seven days of their occurrence.

(xi) I will maintain confidentiality of the identification of all participating study patients and assure security and confidentiality of study data.

(xii) I agree to comply with all other requirements, guidelines and statutory obligations as applicable to clinical Investigators participating in clinical trials

8. Signature of Investigator with Date

ANNEXURE C

INFORMED CONSENT

1. Checklist for study Subject's informed consent documents

1.1 Essential Elements:

1. Statement that the study involves research and explanation of the purpose of the research

2. Expected duration of the Subject's participation

3. Description of the procedures to be followed, including all invasive procedures and

4. Description of any reasonably foreseeable risks or discomforts to the Subject

5. Description of any benefits to the Subject or others reasonably expected from research. If no benefit is expected Subject should be made aware of this.

6. Disclosure of specific appropriate alternative procedures or therapies available to the Subject.

7. Statement describing the extent to which confidentiality of records identifying the subject will be maintained and who will have access to Subject's medical records

8. Trial treatment schedule(s) and the probability for random assignment to each treatment (for randomized trials)

9. Compensation and/or treatment(s) available to the Subject in the event of a trial related injury

10. An explanation about whom to contact for trial related queries, rights of Subjects and in the event of any injury

11. The anticipated prorated payment, if any, to the Subject for participating in the trial

12. Subject's responsibilities on participation in the trial

13. Statement that participation is voluntary, that the subject can withdraw from the study at any time and that refusal to participate will not involve any penalty or loss of benefits to which the Subject is otherwise entitled

14. Any other pertinent information

1.2 Additional elements, which may be required

(a) Statement of foreseeable circumstances under which the Subject's participation may be terminated by the Investigator without the Subject's consent.

(b) Additional costs to the Subject that may result from participation in the study.

(c) The consequences of a Subject's decision to withdraw from the research and procedures for orderly termination of participation by Subject.

(d) Statement that the Subject or Subject's representative will be notified in a timely manner if significant new findings develop during the course of the research which may affect the Subject's willingness to continue participation will be provided.

(e). A statement that the particular treatment or procedure may involve risks to the subject (or to the embryo or foetus, if the Subject is or may become pregnant), which are currently unforeseeable

(f) Approximate number of Subjects enrolled in the study

2. Format of informed consent form for Subjects participating in a clinical trial

Informed Consent form to participate in a clinical trial

Study Title:

Study Number:

Subject's Initials: _____ Subject's Name:_____

Date of Birth / Age: _____

Please initial box (Subject)

(i) I confirm that I have read and understood the information sheet dated _____for the above study and have had the opportunity to ask questions.	[ ]
(ii) I understand that my participation in the study is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected.	[ ]
(iii) I understand that the Sponsor of the clinical trial, others working on the Sponsor's behalf, the Ethics Committee and the regulatory authorities will not need my permission to look at my health records both in respect of the current study and any further research that may be conducted in relation to it, even if I withdraw from the trial. I agree to this access. However, I understand that my identity will not be revealed in any information released to third parties or published.	[ ]
(iv) I agree not to restrict the use of any data or results that arise from this study provided such a use is only for scientific purpose(s)	[ ]
(v) I agree to take part in the above study	[ ]

Signature (or Thumb impression) of the Subject/Legally Acceptable Representative:_____

Date: _____/_____/_____

Signatory's Name:_____

Signature of the Investigator: _____ Date: _____/_____/_____

Study Investigator's Name:_____

Signature of the Witness _____ Date:_____/_____/_____

Name of the Witness: _____

ANNEXURE-D

STRUCTURE, CONTENTS AND FORMAT FOR CLINICAL STUDY REPORTS

1. Title Page:

This page should contain information about the title of the study, the protocol code, name of the investigational product tested, development Phase, indication studied, a brief description of the trial design, the start and end date of patient accrual and the names of the Sponsor and the participating Institutes (Investigators).

2.,Study Synopsis (1 to 2 pages)

A brief overview of the study from the protocol development to the trial closure should be given here. This section will only summarize the important conclusions derived from the study.

3. Statement of compliance with the 'Guidelines for Clinical Trials on Pharmaceutical Products in India: GCP Guidelines' issued by the Central Drugs Standard Control Organization, Ministry of Health, Government of India.

4. List of Abbreviations and Definitions

5. Table of contents

6. Ethics Committee:

This section should document that the study was conducted in accordance with the ethical principles of Declaration of Helsinki. A detailed description of the Ethics Committee constitution and date(s) of approvals of trial documents for each of the participating sites should be provided. A declaration should state that EC notifications as per Good Clinical Practice Guidelines issued by Central Drugs Standard Control Organization and Ethical Guidelines for Biomedical Research on Human Subjects, issued by Indian Council of Medical Research have been followed.

7. Study Team:

Briefly describe the administrative structure of the study (Investigators, site staff, Sponsor designates, Central laboratory etc.).

8. Introduction:

A brief description of the product development rationale should be given here.

9. Study Objective:

A statement describing the overall purpose of the study and the primary and secondary objectives to be achieved should be mentioned here.

10. Investigational Plan:

This section should describe the overall trial design, the Subject selection criteria, the treatment procedures, blinding / randomization techniques if any, allowed/ disallowed concomitant treatment, the efficacy and safety criteria assessed, the data quality assurance procedures and the statistical methods planned for the analysis of the data obtained.

Trial Subjects:

A clear accounting of all trial Subjects who entered the study will be given here. Mention should also be made of all cases that were dropouts or protocol deviations. Enumerate the patients screened, randomised, and prematurely discontinued. State reasons for premature discontinuation of therapy in each applicable case.

12. Efficacy evaluation

The results of evaluation of all the efficacy variables will be described in this section with appropriate tabular and graphical representation. A brief description of the demographic characteristics of the trial patients should also be provided along with a listing of patients and observations excluded from efficacy analysis.

13. Safety Evaluation:

This section should include the complete list

13.1 all serious adverse events, whether expected or unexpected and

13.2 unexpected adverse events whether serious or not (compiled from data received as per Appendix XI).

The comparison of adverse events across study groups may be presented in a tabular or graphical form. This section should also give a brief narrative of all important events considered related to the investigational product.

14. Discussion and overall Conclusion:

Discussion of the important conclusions derived from the trial and scope for further development.

15. List of References:

16. Appendices:

List of Appendices to the Clinical Trial Report

(a) Protocol and amendments

(b) Specimen of Case Record Form

(c) Investigators' name(s) with contact addresses, phone, e-mail etc.

(d) Patient data listings

(e) List of trial participants treated with investigational product

(f) Discontinued participants

(g) Protocol deviations

(h) CRFs of cases involving death and life threatening adverse event cases

(i) Publications from the trial

(j) Important publications referenced in the study

(k) Audit certificate, if available

(l) Investigator's certificate that he/she has read the report and that the report accurately describes the conduct and the results of the study