IJMPR 2023, 7(4), 14-28

International Journal of Modern Pharmaceutical Research
www.ijmpronline.com

ISSN: 2319-5878
IJMPR
Review Article
SJIF Impact Factor: 5.273

A REVIEW ARTICLE ON CENTRAL DRUGS STANDARD OF CONTROL ORGANIZATION (CDSCO)

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Received on: 04/02/2023
Revised on: 24/02/2023
Accepted on: 15/03/2023

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ABSTRACT

In India import, manufacturing, sale and distribution of drugs is regulated under Drugs and Cosmetics Act 1940 and Drugs and Cosmetic rules 1945. At present, bulk drug. Any substance falling within the definition of drug (Section 3b of the Act) required to be registered before import into the country. The application for registration and import can be made to the Licensing Authority under the Act i.e., to the Drugs controller General (1) at CDSCO, FDA Bhawan, New Delhi by the Local Authorized Agent of the foreign manufacturer having either manufacturing or sale Licensing or by the foreign manufacturers having a wholesale License in the country. This document 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 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. SUGAM is e-Governance system to discharge various functions performed by CDSCO under Drugs and Cosmetics Act 1940. The software system developed is an online web portal where applicants can apply for NOCs, licenses, registration certificates, permissions and approvals. It provides an online interface for applicants to track their applications, respond to queries and download the permissions issued by CDSCO. It also enables CDSCO officials to process the applications online and generate the permissions online and generate MIS reports. Demonstration of safety and efficacy of the drug product for use in humans is 1essential before the drug product can be approved for import or manufacturing and marketing in the country. The Rules 122A, 122B and 122D, 122DA, 122E of Drugs and Cosmetics Rules and Appendix 1, 1A and 6 of schedule Y, describe the information or data required for approval of clinical trial and/ or to import or manufacture of new drug for marketing in the country.[1]

KEYWORDS: Drug Control General of India, Clinical trials, phases of clinical trials, Ethics committee, Indian Drug regulatory process, National Drug Advisory Committee, Technical Review committee.

INTRODUCTION

The central drug standard and control organization (CDSCO) is the main regulatory body of India for regulation of pharmaceutical, medical devices and clinical trials. CDSCO is the central drug authority for discharging function assigned to the Central Government under the Drugs and Cosmetics Act.

Head office of CDSCO is located in New Delhi and functioning under the control of Directorate General of Health Services, Ministry of Health and Family welfare Government of India. It is a National Regulatory authority of India. It also has six zonal offices, four sub zonal offices, thirteen port offices and seven laboratories spread across the country.

The Drugs and Cosmetics Act 1940 and Rules 1945 have entrusted various responsibilities to central and state regulators for regulation of drugs and cosmetics. It envisages uniform implementation of the provisions of the Act and Rules made there under for ensuring the safety, rights and well-being of the patients by regulating the drugs and cosmetics. CDSCO is constantly thriving upon to bring out transparency, accountability and uniformity in its services in order to ensure safety, efficacy and quality of the medical product manufactured, imported and distributed in the country.

Under the Drugs and Cosmetics Act CDSCO is responsible for approval of drugs, conduct of clinical trials, laying down the standards for drugs, control over the quality of imported drugs in the country and coordination of the activities of State Drug Control

Organizations by providing expert advice with with a view of bring about the uniformity in the enforcement of the Drugs and Cosmetics Act. Further CDSCO along with state regulators is jointly responsible for grant of licenses of certain specialized categories of clinical drugs such as blood and blood products, IV fluids, vaccines and sera.[2]

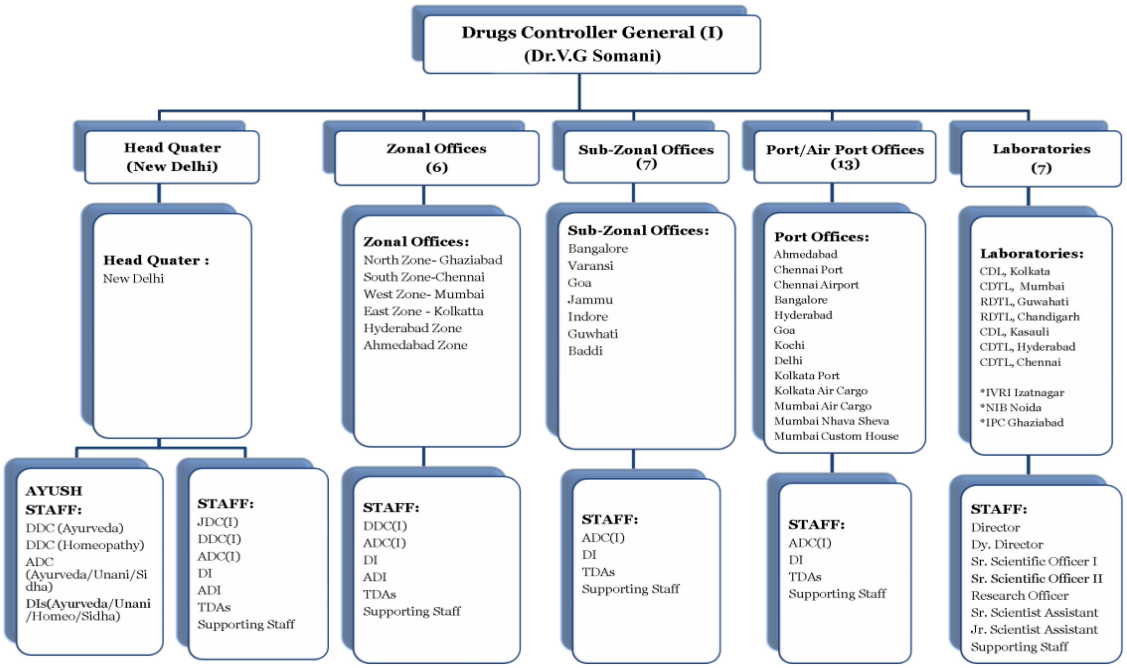
Drug control general of india (DCGI)

- He or she responsible for approval of new drugs, medical devices and clinical trials to be conducted in India
- He is appointed by the central government under the DCGI the state control organization will be functioning.
- The DCGI is advised by the Drug Technical Advisory Board (DTAB) and the Drug Consultative Committee (DCC). [2]

Vision and Mission of cdsco[3]

- To protect and promote the health in India.
- To safeguard and enhance the public health by assuring the safety, efficacy, and quality of drugs, cosmetics and medical devices.

Organization chart



Zonal offices

These are involved in GMP audits and inspection of manufacturing units of large volume parenteral, sera, vaccine and blood products.

- Mumbai
- Kolkata
- Chennai
- Ghaziabad
- Ahmedabad
- Hyderabad

Sub-Zonal offices

These centre co-ordinate with state drug control authorities under their jurisdiction for uniform standard of inspection.

- Bangalore
- Varanasi
- Goa
- Jammu
- Indore
- Guwahati
- Baddi

Port/ Airport offices

- Ahmedabad
- Chennai port
- Chennai airport
- Bangalore
- Hyderabad
- Goa
- Kochi
- Delhi
- Kolkata port
- Kolkata Air cargo
- Mumbai Air cargo
- Mumbai Nhava Sheva
- Mumbai Custom House

Laboratories

- CDL, Kolkata

- CDTL, Mumbai
- RDTL, Guwahati
- RDTL, Chandigarh
- CDL, Kasauli
- CDTL, Hyderabad
- CDTL, Chennai
- IVRI, Izatnagar
- NIB, Noida
- IPC, Ghaziabad

Major function of CDSCO

- Regulatory control over the import of drugs, approval of new drug and clinical trial
- It controls meeting of Drug Consultative Committee (DCC).
- It gives certain license as central license and state license approving authority is exercised by the CDSCO headquarters.

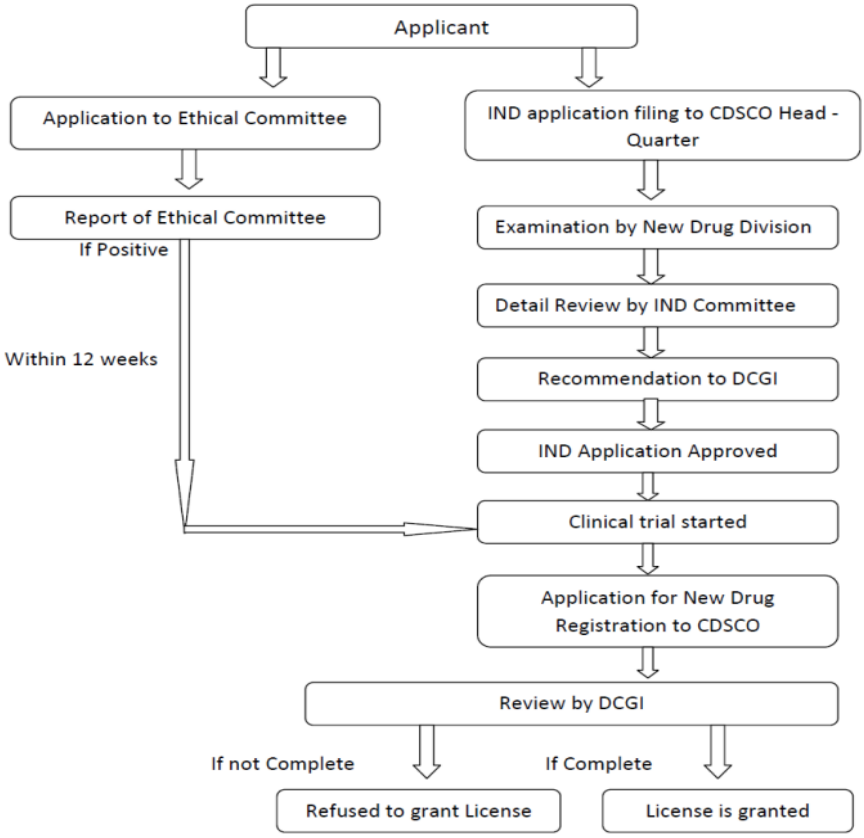
Central licensing authority

- Approval of new drug and clinical trials.
- Banning of drugs and cosmetics.
- Grant of test license, personal license.
- Import registration, licensing and approving of blood banks, vaccines, medical devices.

State licensing authority

- Licensing of manufacturing site for drug including API and finished product.
- It gives approval of drug testing laboratories.
- Monitoring of quality of drug and cosmetics marketed in the country.
- Licensing of establishment for sale or distribution of drug.
- Recall of sub-standard of drug.[3,4]

Drug approval process[6]



Clinical trials process[6]

- Schedule Y of drug and cosmetics act explains the guidelines for grant of permission for conducting clinical trials in India.
- The protocol for such trials is examined by the office of DCGI before the permission are granted.
- Office of DCGI also give grant permission for conducting bioequivalence studies.

1. Registration of clinical trials has been made mandatory with centralised clinical trials.
2. Drugs and cosmetics rule are being amended to make mandatory the registration of clinical research organisation.
3. Drug and cosmetic act id proposed to be amended to include a separate chapter on clinical trials.

Details to be captured in covering letter

- Information of the drugs to be imported.
- Manufacturer information like address and contact details.

- Brief information about the application and list of documents-

1. Original challan and the details of the challan
2. Form 40
3. Schedule D(I) documents as provided by the drugs manufacturer (Module 2 to 5 of CTD format)
4. Schedule D(II) documents as provided by the drugs manufacturer (Module 2 to 5 of CTD format)
5. Power of Attorney issued by the manufacturer
6. Copy of wholesale License of applicant
7. Copy of Authorization letter of applicant
8. An undertaking shall be submitted by the proprietor of the firm in case of Private Limited Company by the board of Directors.[5]

Requirements for common submission format for Import and Registration of bulk Drugs and Finished formulations in India[8]

The following documents are required to be submitted in the following manner and order for the import and registration of the bulk drugs and finished products in India.

Applicants are requested to submit application in 3 or more different files as follows:

1. **Covering letter:** The covering letter is an important part of the application and should clearly specify the intent of the application (whether the application for the registration of manufacturing site is being submitted for the first time, whether the application is for re-registration/ renewal or is for the endorsement of additional products to an existing registration certificate) the list of documents that are being submitted (Index with page numbers) as well as any other important and relevant information may be provided in the covering letter. The covering letter should be duly signed and stamped by the authorised signatory along with the name and address of the firm. Any exemption to the submission requirement to be clearly specified in the covering letter on the firm/company letter head and justified in the submissions.

The resolution shall be submitted by the proprietor of the firm in case of proprietorship firm and by the board of Directors in case of Private Limited Company/firm.

2. **An Authorization letter** in original issued by the Director/ Company secretary/partner of the Indian agent firm revealing the name and designation of the person authorized to sign (along with the name and address of the firm) legal documents such as Form 40, Power of Attorney etc. on behalf of the firm should be submitted at the time of submission of the application for registration (Rule 122 A). It should have validity period as per company's policies. Duly self-attested photocopies of the authorization letter may be submitted at the time of submission of subsequent applications.
3. A duly filled Form 40 as per the proforma prescribed in the Drugs and Cosmetics Rules, signed and stamped by the (Local Authorized Agent / manufacturer) along with the name and designation and date. Form 40 should be signed by the Local Authorized Agent or manufacturer and should have valid sale or manufacturing License in India.
4. **TR 6 challan:** In case of any direct payment of fee by the manufacturer in the country of the origin, the fee shall be paid through Electronic Clearance System (ECS) from any bank in the country of origin to the Bank of Baroda, Kasturba Gandhi Marg, New Delhi, through the electronic code of the bank in the head of Account stated above the original receipt of the said transfer shall be treated as an equivalent to the bank challan.
5. **Power of Attorney:** The authorization by a manufacturer to his agent in India shall be documented by a power of attorney executed and authenticated either in India before a first-class magistrate, or in the country of origin before such an equivalent authority, the certificate of which is attested by the Indian embassy of the said country, and the original of the same shall be furnished along with the application for registration certificate. Apostille power of attorney from Hague convention member countries is also acceptable. The authorized agent will be responsible for manufacturer's business activity, in India. While submitting the power of attorney, the following points should be kept in mind.

- It should be co-jointly signed and stamped by the manufacturer as the Indian agent indicating the name and designation of the authorized signatories (along with name and address of the firm).
- It should clearly list the names of all the proposed drugs, if possible, along with their specific indication and / or intended use. Further, the names of the proposed drug should correlate with those mentioned in the Form 40, Free sale certificate or Certificate of pharmaceutical product (COPP) as per WHO-GMP certification scheme.
- The names and addresses of the manufacturer (contract manufacturer name from different sources) as well as the Indian agent stated in the power of attorney should correlate with the Form 40.
- It should be valid for the period of said Registration Certificate. It implies that a fresh POA is to be submitted at the time of revalidation of RCa.

6. A duly attested / notarized (India) and valid copy of wholesale license for sale or distribution of drugs under drugs and cosmetics rules in Form 20B and 21B or its renewal in Form 21C issued to the manufacturer (subsidiary office / representative of the parent company) or its agent by the State Licensing Authority in India. If the agent is a manufacturer, a duly attested / notarized (in India) and valid copy of manufacturing License issued by the State Licensing Authority.
7. A) Schedule D(I) undertaking as per the proforma prescribed in the Drugs and Cosmetics Act and Rules, signed and stamped by the manufacturer / authorized signatory is required to be submitted as

per the proforma for Schedule D(I) along with CTD module 1 covering the Schedule D(I) requirement.
B) The requirements for Plant Master File.

8. Module 2-5 covering the Schedule D(II) requirements

Standard of drug: Second Schedule of the Act prescribes standards to be complied with by imported drugs and by drugs manufactured for sale / sold stocked or exhibited for sale or distributed in the country. If the drugs are in IP, it must be meet the standards of identity, purity and strength otherwise USP, BP or EP.

Label submission: True copy of label as per Rule 96 of the Act. If the drugs is in IP label to claim must be as per IP.

Testing of drugs: In case of registration of bulk (Active Pharmaceutical Ingredient) drugs the consecutive three batches are asked to be submitted to the designated laboratory for testing for which fee is to be paid by the applicant to the laboratory as per their norms.

The applicant should enclosed adequate samples for reanalysis purpose from each of the three consecutive batches along with specifications, method of analysis, COA tested in their laboratories, impurity standards, marker compounds, reference standard along with its COA where ever applicable.

9. Duly notarized / apostilled / attested (by Indian Embassy the country of origin) and valid copy of free sale certificate / certificate to foreign government / certificate to marketability / for each drug issued by the National Drug Regulatory Authority of the country of origin. Freely sale certificate should state the proposed drug is freely sold in country of origin and can be legally exported.

10. Duly notarized / Apostilled / Attested (by Indian embassy the country of origin) and valid copy of GMP certificate of WHO guidelines or certificate of pharmaceutical product (COPP) as per WHO GMP certification scheme / product registration certificate issued by NRA and / or CEP (EQDM certificate) for each drug issued by the National Drug Regulatory Authority of the country of origin.

11. Duly notarized / apostilled / attested (by the Indian embassy in the country of origin) and valid copy of Product Registration Certificate wherever applicable in respect of the foreign manufacturing sites).

12. Renewal of registration or re-registration:

At the time of application for renewal of registration or re-registration, the application is to be made 9 months before the expiry of the Registration Certificate. In addition, regulatory documentary compliance like Form 40, POA, GMP / COPP, Registration certificate, DMF (softcopy if no change), License (sale or manufacturing License of drugs of the agent) etc, the following undertaking / information is to be submitted:

1. Undertakings by the manufacturer or his authorized agent in India in respect of any administrative action taken due to adverse reaction, viz., market withdrawal, regulatory restrictions, or cancellations of authorization, and/ or not of standard quality report of any drug pertaining to this registration certificate declared by the regulatory authority of the country of origin or by any regulatory authority of any other country, where the drug is marketed / sold or distributed.
2. Undertaking by the manufacturer or his authorized agent in India in respect of any change in manufacturing process, or in packaging, or in labelling or in testing, or in documentation of any drug pertaining to this Registration Certificate.
3. Undertaking by the manufacturer or his authorized agent in India in respect of any change in the constitution of the firm including name and / or address of the registered office / factory premises operating under this registration certificate.
4. Details of drugs imported in India during last three years.
5. Submission of original RC.

Sugam-Online licensing portal[8]

- An online licensing portal of CDSCO to file application for various services like application submission, processing and grant of permission for quick delivery of services.

Benefits

- Applicant can apply license under import and registration division to CDSCO.
- Track the status of application through online.
- Answer back to raised queries.
- Applicant can also upload essential documents for registration, import license and other related activities.

Types of licenses can apply through SUGAM portal:

- Registration certificate – Form 41 for drug
- Registration certificate – Form 41 for medical device
- Registration certificate – Form 41 for diagnostic kit
- Import license – Form 10 for drug
- Import license – Form 10 for medical device
- Import license – Form 10 for diagnostic kit
- Test license for clinical trials
- Registration certificate for cosmetics

Guidelines on data required to be submitted for approval of clinical trials (Phase I/II/III/IV)[9,10]

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 sizes to be involved in the conduct of clinical trial will depend on 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 centres. 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 centres 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.

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 drug 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 forms, new indication, new route of administration etc. of approved drugs, the application will be examined by CDSCO. Wherever required, such applications may be 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 1 of Schedule Y. however, as per clause 1(3) of Schedule Y to Drugs and Cosmetics Rules. For drugs indicated in life threatening / serious disease or diseases of special relevance to the Indian health scenario, the toxicological and 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 and cosmetics act and 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 or 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 form products that treat life threatening / serious diseases, than their would accept from products that treat less serious illnesses.

All such request for exemption of toxicological and 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 and Animal Toxicology studies required to be carried out will be as per Appendix IV and Appendix III of Schedule Y of Drugs and Cosmetics Rules respectively. Depending upon the nature of new drugs and diseases 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.
4. Chemical and pharmaceutical information including:

- **Information on active ingredients**

Drug information (Generic name, chemical name, or INN) and 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 and 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.

5. Animal pharmacology
i. Summary
ii. Specific pharmacological actions
iii. General pharmacological actions
iv. Follow-up and supplemental safety pharmacological studies
v. Pharmacokinetics: absorption, distribution, metabolism, excretion

6. Animal toxicology
i. General aspects
ii. Systemic Toxicity Studies
iii. Male Fertility Studies
iv. Female Reproduction and developmental toxicity studies
v. Local toxicity
vi. Allergenicity / Hypersensitivity
vii. Genotoxicity
viii. Carcinogenicity

A. For phase I clinical trials
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 to support the duration of proposed human exposure. (As per Clause 1.8 of Appendix III of Schedule Y to Drugs and Cosmetics Rules.
iv. Male fertility studies
v. In-vitro genotoxicity studies with proposed route of clinical application (duration depending on proposed length of clinical exposure).
vi. Allergenicity / Hypersensitivity tests (when there is a cause for concern or for parenteral drugs, including dermal application).
vii. 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. For phase II clinical trials
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 initiating starting a phase II trial - complete details of the non-clinical safety data needed for obtaining the permissions for Phase I and Phase 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.

In-vivo genotoxicity tests.
Segment II reproductive / developmental toxicity study (if female patients of child bearing age are going to be involved)

C. For phase III clinical trials
Provide a summary of all the non-clinical safety data (Listed above) already submitted while obtaining the permissions for phase I and II trial, 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 Phase 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 II (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. For phase IV Clinical Trials
Provide a summary of all the non-clinical safety data (listed data) 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, 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. Pharmacodynamics / early measurement of drug activity

8. Therapeutic explanatory trials (Phase II)
i. Summary
ii. Study reports as given in Appendix II

9. Therapeutic confirmatory trials (Phase III)

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

10. Special studies

i. Summary
ii. Bioavailability / 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. 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 along with T-challan of requisite fees (in case of import of investigational products)

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) Names 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 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, toxicology and other biological properties of the drug, and previous efficacy and safety experience should be described.

iii. Study rationale

The 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 objectives: (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) Flowchart 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 required is also mentioned.

vii. Study 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 functions 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.

x. Discontinued subjects: Described the circumstances for subject withdrawal, dropouts, or the 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 should be identified and the criteria used for specific waivers should be provided. Describe how protocol violations will be treated, including conditions where the study will be terminated for non-compliance with the protocol.

xi. 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 drugs, 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) Binding procedures: A detailed description of the binding procedur if the study employs a blind on the investigator and/or the subject.
(g) Unbinding procedures: If the study is blinded, the circumstances in which unblinding may be done and the mechanism to be used fpr unblinding should be given.

xii. Adverse events

Description of expected adverse events should be given
Procedures used to evaluate an adverse event should be described

xiii. Ethical considerations: give the summary of:

(a) Risk/benefit assessment
(b) Ethics committee review and communications.
(c) Informed consent process.
(d) Statement of subject confidentially including ownership of data and coding procedures.

xiv. 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 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.

xv. Investigational product management

1. Give investigational product description and packaging (stating all ingredients and the formulation of the investigational drug and any placebos used in the study)
2. The precise dosing required during the study
3. Method of packaging, labelling and binding of study substances.
4. Method of assigning treatments to subjects and the subjects identification code numbering system.
5. storage conditions for study substances.

a) Investigational product accountability: Describe instructions for receipt, storage, dispensation, and the return of the investigational products to ensure a complete accounting
b) Describe policy and procedure for handling unused investigational products.

xvi. Data analysis

Provide details of the statistical approach to be followed including sample size, how the 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 along with the description of statistical tests to be used to analyse 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 applicable.

xvii. Undertaking by the investigator (As per Annexure B)

xviii. Appendices

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

Guidelines on data required for approval for marketing of new drug[11,12]

No new drug shall be imported (Rule 122 A) or manufactured (Rule122 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 along with 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).

Annexure A[13]

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[13]

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[13]

Informed consent

1. Checklist for study Subject's informed consent documents

1.1 Essential Elements:
i. Statement that the study involves research and explanation of the purpose of the research
ii. Expected duration of the Subject's participation
iii. Description of the procedures to be followed, including all invasive procedures and
iv. Description of any reasonably foreseeable risks or discomforts to the Subject
v. 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.
vi. Disclosure of specific appropriate alternative procedures or therapies available to the Subject.
vii. 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
viii. Trial treatment schedule(s) and the probability for random assignment to each treatment (for randomized trials)
ix. Compensation and/or treatment(s) available to the Subject in the event of a trial related injury
x. An explanation about whom to contact for trial related queries, rights of Subjects and in the event of any injury
xi. The anticipated prorated payment, if any, to the Subject for participating in the trial
xii. Subject's responsibilities on participation in the trial
xiii. 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
xiv. 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

(a) Study Title:_____
(b) Study Number:_____
(c) Subject's Initials: _____
(d) Subject's Name:_____
(e) Date of Birth / Age: _____

I confirm that I have read and understood the information sheet dated ---------- for the above study and have had the opportunity to ask questions.	[ ]
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.	[ ]
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 it with draw 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.	
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 purposes.	[ ]
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[13]

Structure, Contents and Format for clinical study reports

1. Title page:

The 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 "Guidelines for clinical trials on pharmaceutical products in India:

GCP guidelines issued by the central drug 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 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.

11. 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.

CONCLUSION[14,15]

The goal of clinical supervision is to build and advance the clinical social worker's skills, knowledge and attitudes in order to improve client care and to enhance the professional growth and development of the clinical social worker. A participative system involving the medical community, pharmacists, industry and patients with the help of modern information technology would be beneficial for the Health and Pharmacy stake holders. The latest developments in Indian regulations reflect a concerted effort on the part of the public health community to push clinical trial issues in to a great extent. Here the Indian regulatory plays the desired role which will set the standards for conducting the clinical research in future.

The effort made by the CDSCO towards information technology enabled online process will encourage the sponsors to set their clinical research destination. On the other hand this transparent process will also satisfy the need of entire health care community (patients, researchers and activists) towards trial subject's care and safety.

ACKNOWLEDGEMENT

We heartily thank Dr. B. Venkata Ramana (Principal), and Ms. B. Parameswari (Dept of pharmaceutics), Dr. K.V. Subbareddy college of pharmacy, Kurnool, Andhra Pradesh for providing their immense support throughout our study.

Abbreviations:

1. CDSCO - Central Drug Standard Control Organization
2. FDA - Food and Drug Administration
3. DCGI - Drug Control General of India
4. DTAB - Drug Technical Advisory Board
5. DCC - Drug consultative Committee
6. GMP - Good Manufacturing Practices
7. ECS - Electronic Clearance System
8. COPP - Certificate of Pharmaceutical Product
9. WHO - World Health Organization
10. NDAC - National Drug Advisory Committee
11. IND - Investigative New Drug
12. CRF - Case Record Form
13. FDC - Fixed Dose Combination
14. ADC - Assistant Drug Controller
15. CDL - Central Drug Laboratories
16. CDTL - Central Drug Testing Laboratories
17. DI - Drug Inspector
18. TDA - Technical Data Association
19. NIB - National Institute of Biologicals
20. IPC - Indian Pharmacopoeial Commission

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