Handbook

for Applicants & Reviewers of Clinical Trials of New Drugs *in India*

JANUARY 2017

Indian Council of Medical Research
P.O. Box No. 4911, Ansari Nagar, New Delhi – 110029, India

Central Drugs Standard Control Organization
Directorate General of Health Services,
Ministry of Health and Family Welfare, Government of India
FDA Bhavan, ITO, Kotla Road, New Delhi -110002, India

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Limit of Liability/Disclaimer of warranty. This handbook is a guidance document for applicants and reviewers of Investigational New Drugs (IND) and New Drugs (ND) applications in India. Readers should refer to the relevant documents, Acts, rules regulations and checklists on relevant websites for updated information. Contributors of this handbook will not be held responsible for any issues arising from use of information in this handbook. The handbook will be updated periodically with changes as applicable.

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FOREWORD

Essentiality of new drugs, devices, diagnostics and their appropriate usage for universal health coverage requires thorough basic, applied and industrial research. Department of Health Research (DHR) & Indian Council of Medical Research (ICMR) provide leadership in biomedical research in the country. DHR focuses on bringing modern health technologies to the people through research and innovations related to diagnosis, treatment methods and vaccines for prevention; to translate them into products and processes and in synergy with concerned organizations introduce these innovations into public health system. The Indian Council of Medical Research (ICMR), New Delhi focuses research on its flagship programmes on communicable (tuberculosis, HIV, malaria, Japanese encephalitis, leprosy, etc) and non communicable diseases like diabetes, cancer, cardiovascular diseases, environmental and occupational health, tribal health, vector borne diseases, mother and child health, malnutrition, etc.

An inter-ministerial meeting involving various stakeholders was organized by ICMR & CDSCO on 3rd and 4rth May 2016 to deliberate on current challenges faced by patients, researchers and industry. There is a general consensus for strengthening capacity for clinical research, reviews and applications for regulatory submissions which are to be of global standard in their practices and processes. These efforts in turn will result in providing better healthcare to the Indian population.

The socio-cultural ethos in India and its varying standards of health care today pose unique challenges in biomedical and health research for which revised 'National Ethical Guidelines for Biomedical and Health Research on Human Participants 2016' is under preparation. In this context, the ICMR has also started online training programs for clinical research and ethics.

Towards capacity building for regulatory submissions and review, the ICMR jointly with CDSCO set up an Expert Group for preparation of a handbook as guidance for applicants and reviewers. Workshops based on this handbook will be conducted for subject experts subsequent to its release.

It is hoped that these activities will provide a major boost to quality and efficiency of clinical research as well as product development in the country.

(Soumya Swaminathan)
Secretary
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Director General
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New Delhi

PREFACE

Make in India, Skill development and Universal health coverage initiatives of Government of India have provided opportunities and incentives for new drug development in India.

The Governing Council of Indian Council of Medical Research (ICMR) in its meeting held on 16th January 2016, emphasized importance of clinical trials in new drug development.

Approval for clinical trials and import, manufacture and sale of new drugs is granted by the CDSCO, assisted by critical appraisal from subject expert committees and evaluation by ICMR.In view of the increase in new drug development there is need to enhance capacity for regulatory review of clinical trials in the country.

This handbook is developed to increase efficiency and quality of review and highlights regulatory, administrative, and scientific review processes that should be followed by applicants and reviewers of new drugs/ clinical trials.

The handbook emphasizes the critical elements of pharmaceutical, preclinical, toxicological, clinical and prescribing information data to be submitted. It focuses on evaluation of the application for risk vis a vis benefit, innovation vis a vis existing therapies, unmet medical need, ethical aspects of patient safety and India specific concerns.

The handbook will be dynamic and will undergo revisions in line with developments and changes in regulations. It will be available on ICMR and CDSCO websites and form the backbone of the capacity building workshops for subject experts who review applications for clinical trials of new drugs.

Contributors

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1.0 Purpose:

The purpose of this handbook is to provide guidance to applicants and reviewers of applications, for approval of Clinical Trials and marketing (import, manufacture, sale) of Investigational New Drugs (IND) and New Drugs (ND) in India.

2.0 Introduction and Background:

The Schedule Y of the Drugs and Cosmetics Act (DCA) and Rules there under specify requirements for clinical trials and market authorization[1].

The reviews of applications for granting authorization to conduct clinical trials or to market a new drug in the country, require a multidisciplinary assessment by regulatory authorities (RAs) and scientific experts, to ensure that the applications meet the necessary regulatory standards and scientific evidence for safety, efficacy and quality.

Good review practices assist the RAs to achieve timely and quality review. A complete application is a prerequisite to ensure an efficient review process.

This handbook is intended to provide clarity, enhance transparency, facilitate understanding of the review process and thereby expedite the review processes of applications for IND and ND in India.

The information in this handbook supplements information stated under good review practices (Appendix 8.1), and does not supersede applicable regulatory laws, rules and regulations.

3.0 Submissions:

The Appendix 1 ,and other appendices of the Schedule Y of the Drugs and Cosmetics Act & Rules there under provide detailed guidance on the information and data to be submitted on chemical, pharmaceutical, pre-clinical, toxicological, clinical and regulatory aspects of the new drug and investigational new drug.

The checklists/formats for application are given on CDSCO website. It is to be noted that the nature and extent of information may vary based on type of application, phase of the study, stage in drug development process and objective of the study.

It is important that while at a minimum these are complied with, the submission dossier should present the following in clear and concise manner and provide justification and references where applicable:

1. Regulatory status of the protocol/new drug - any approval/withdrawal/ premature termination of protocol/drug, in other markets or in other countries, safety warnings if any.
2. Conformity to Schedule Y and other rules and regulations, specifically, informed consent, management of AEs, compensation for study related injury among others.
3. Details of all sites selected and assessment for suitability of sites and investigators (with contact details) to conduct the clinical trial as per protocol.
4. Registration status of ethics committees of the selected sites
5. Number of patients and proportion of patients to be enrolled from India.
6. Relevance of the study / investigational drug / any specific aspects of the study to the heath care needs of India.

[1]Ministry of Health and Family Welfare(MOHFW). Drugs and cosmetics Act (DCA) and rules, amended upto 2005. New Delhi and http://cdsco.nic.in/html/D&C_Rules_Schedule_Y.pdf. The DCA and Rules (122 DA) define investigational new drug(IND) as products having therapeutic indication but which have never earlier been tested on human being and new drug(ND) as (122E) which has not been used in the country to any significant extent. It remains a new drug for 4 years from approval for marketing and any new route, dose, formulation, combination is new drug. Applications are required to be made for conduct of clinical trials of IND/ND as per 122 DA, for import (122-A) and manufacture for sale (122-B).In this handbook, the term marketing is used to indicate import, manufacture and sale. Term New Drug Application is used on CDSCO website in draft guidance document for import, manufacture and marketing approved, but is not used in this document to avoid confusion

7. Assessment of risk versus benefit.
8. Innovation *vis-à-vis* existing therapeutic options.
9. Unmet medical need in the country [as applicable].
10. Any India specific safety / dosage concerns / investigational tests to be done.
11. Summary of preclinical and clinical experience thus far with the investigational drug, product insert/ SmPC for marketed drug, published literature.
12. The clinical study reports should be submitted as per Appendix II of schedule Y and ICH CTD
13. Justification and schematic diagram/flow chart of the proposed study and design – relevant references, justification for comparator / placebo / rescue medication / patient population etc.
14. Dosage regimen as justified by pre-clinical, early clinical studies or approved product insert/summary product characteristic (SmPC) for marketed drugs and comparator as justified by the standard treatment guidelines and references.
15. Safety measures built in the protocol based on toxicological studies; early clinical studies, approved product insert for marketed product, and published literature.

4.0 Types of Submissions

Applications could be for

- Investigational New Drug Clinical Trials
- 2-New Drugs Clinical Trials
  (Local bridging clinical trials of drugs already approved outside for obtaining marketing authorization i.e. permission for import/manufacture for sale in India)
- 3-Global Clinical Trials
  (clinical trials in various phases of development as a part of multinational clinical development)
- 4-Post Marketing Studies

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5.0 Reviews:

Reviews
By DCGI
- Regulatory aspects
- Administrative procedures

By Subject Expert
- Preclinical, toxicological, clinical data submitted
- Proposed clinical trial/ marketing approval

5.1 CDSCO Review

On receipt of the application the CDSCO officials must confirm that all information is in compliance with Schedule Y and as per checklist for application (and as specified in section 3 above) with focus on the following:

1. Regulatory status of the study and/or the new drug – any history of approvals/withdrawal/ premature termination for the protocol / drug in other markets or other countries
2. Safety warnings if any
3. Conformity to schedule Y and other rules and regulations specifically informed consent, treatment of AE, compensation for study related injury among others
4. Details of sites selected and assessment for suitability of site and investigator to conduct the clinical trial as per protocol and Ethics committees approvals
5. Registration status of the Ethics Committees for selected sites
6. Number of patients and proportion of patients to be enrolled from India (if drug is to be marketed in India then adequate number of participants must be recruited from India)
7. Chemical and Pharmaceutical information of the drug and dosage form and quality assurance information.

CDSCO officials will provide a summary statement along with protocol highlighting the above, along with the mail or letter statement that application is referred for further review by subject experts, within four weeks of receipt. However, to maintain time schedule of review, CDSCO officials may submit the application to subject experts with CDSCO comments, while awaiting from the applicant, additional information/clarification/ justification which is minor in nature and is expected to be available before /at the Subject Expert Committee (SEC) meeting

CDSCO may conduct a critical in house review so that some of the applications can be addressed at their level without the need for referral to the subject experts/committee

5.2 Subject Expert Committee (SEC) Review

Each application needs to be reviewed for

1. Risk vs. benefit
2. Innovation vs. existing therapy
3. Unmet medical need
4. Ethical aspects for patient safety
5. Study design, protocol, inclusion/exclusion criteria, randomization, blinding, bias, primary- secondary endpoints and standard of care
6. Statistical and medical review of safety and efficacy
7. Level of reliance that can be put on the evaluation of other regulatory agencies that have already approved the said application in their country

Focus of Evaluation

- Risk vs. benefit
- Innovation vs. existing therapy
- Unmet medical need
- Ethical aspects for patient safety
- India specific concerns

5.2.1 Focus of SEC Review:

SECs composed of expert pharmacologists/clinical pharmacologists and leading academicians / clinicians from relevant therapeutic areas (see Appendix 8.2 for SEC Committee composition) are expected to review the application, investigators' brochure and study protocol prior to the meeting[2]. The focus of their review will be:

1. Relevance of the trial/ study/ Investigational drug/ any specific aspect of the study to India vis-a- vis
   a. Assessment of risk vs. benefit to the patient
   b. Innovation vis- a- vis existing therapeutic option
   c. Unmet medical need in the country
   d. Specific concerns on safety/dosage/investigational tests (e.g. pharmacogenetic tests)
   e. Additional information/study needed
   - before marketing approval
   - for inclusion in package insert/ SmPC
   - Post marketing.
2. Information about the development of the IND or ND in the investigators' brochure, especially with reference to the data of the past studies, that have been conducted, summary of preclinical and clinical experience, product insert/ SmPC for marketed drug, published literature.
3. Justification and schematic diagram/ flowchart of the proposed study, design, relevant references.
4. Trial design, inclusion, exclusion criteria, bias minimization techniques used, primary secondary endpoints, standard of care.
5. Patient population, number of patients, type of study population to be recruited, special review is required, should the trials involve vulnerable populations, children, nursing women, geriatric age group or subjects who are unable to give informed consent. Information on the consent procedure, subject recruitment procedure and justification for including such population should be reviewed.
6. Dosage regimen of study drug, route of administration, as justified by preclinical, early clinical studies/ product insert/ SmPC for marketed drugs, published literature and of comparator as justified by standard treatment guidelines and references.
7. Justification for comparator/placebo as appropriate, rescue medication, conformity to standard treatment guidelines.
8. Safety measures/risk minimization strategies/ safety monitoring aspects built within the protocol.

5.2.2 Review Procedure: (Schematic Diagram–Appendix 8.3)

1. Applications, arranged in a systematic manner along with table of contents as specified in Appendix I schedule Y, checklists on CDSCO site and under section 3 of this handbook, duly evaluated by the CDSCO official (as specified in section5.1 of this handbook), with summary of evaluation and a statement that proposal is referred for further review should be sent to subject expert committee members within 4 weeks of receipt of the application.
2. Subject experts after going through the application, including investigators' brochure and clinical trial protocol, will furnish their comments via email to CDSCO. The members as per the Terms of Reference (TOR)by MOHFW, will give their expert comments in writing after evaluating the proposal allocated to

[2]The committees will function as per the terms of reference given by MOHFW

them, within 6 weeks from the receipt of the proposal even if they cannot/ do not wish to attend the meeting.

3. The written comments (if there is a query or some clarification /modification etc needed) compiled by CDSCO should be sent to the applicant within 1 week of receipt. The applicant shall submit written reply to CDSCO within 4 weeks of receiving the comments, which in turn will be sent by CDSCO to subject experts.

4. Meeting will be scheduled between 2-6 weeks after receipt of reply from applicant. Date of meeting will be communicated to the applicant and reviewer, at least two weeks prior to the meeting to allow time for travel bookings particularly for outstation applicants / overseas attendees.

5. Applicant shall make presentation to the committee, summarizing the application, regulatory status, protocol with justifications as relevant and providing explanation to queries sent by experts. The SEC members are expected to come prepared, after having reviewed the application and replies to their queries ahead of the meeting. Experts should ask all their questions and queries during the presentation. Their concerns, if any, should be clearly communicated to the applicant during the presentation. Communication with the applicant should be limited to request for additional information/clarification/ suggestion.

6. The committee shall evaluate the applications keeping in view the requirements as prescribed in the regulatory framework.

7. The committee shall review the application, replies to comments and give their recommendations in a composite manner as far as practical/feasible.

8. In case of query/suggestion for major modification/revision in the protocol, recommended by any SEC after initial review of the proposal, in the subsequent meetings or email communication, for evaluating the compliance or response to said query, the committee shall deliberate the matter keeping in view the earlier decision/suggestion.

9. Minutes of the SEC meeting will be available on the CDSCO website within 3 working days after signing of minutes which is done usually on the same day of the meeting.

10. The applicant shall be given 4 weeks to provide clarification/any additional data requested or request for additional time(with justification) if required. If the applicant's response is delayed, it will be dealt with separately.

11. Once the response is submitted by the applicant, the final decision viz permission /rejection/submission to Technical or Apex Committee by official communication will be provided by CDSCO within 15 days. If it is to be sent again to SEC it will be put up in the immediate next SEC meeting .After the meeting, minutes will be on the website in 3 working days after signing of the minutes which is usually on the same day of the meeting. Final decision by official communication as permission/rejection/submission to Technical or Apex Committee will be sent in 15 days.

12. Request for reconsideration by the applicant giving reasons, will be reviewed by CDSCO and if accepted it will be sent to SEC once again(or to the Technical Committee as per the request of the applicant. If reconsideration request is rejected by CDSCO, such letter will be sent by CDSCO). After the SEC meeting, minutes will be on the website in 3 working days after signing of the minutes which is usually on the same day of the meeting. Final decision by official communication after SEC review, in the form of permission/rejection/query/ or requirement for further submission to Technical or Apex Committee will be sent in 15 days.

6.0 Guidance for Submission and Review:

The background information and Clinical trial protocol will vary depending on the phase of drug development, regulatory status of study drug in India and other countries, objectives of the application. This is elaborated

in checklists on CDSCO website and in section 3 above and should be noted by the applicant and reviewer. Applicant shall submit the application accordingly.

Following points should be noted while submitting and evaluating the application. For marketed drugs information on chemistry, pharmaceutics, preclinical and clinical data will be as per approved product insert/ SmPC, published literature.

1. Introduction:

   This section should state investigational product name, a brief description, the therapeutic class to which it belongs and proposed indications.

2. Chemical and Pharmaceutical information:

   This information will be seen in detail by the Pharmacy/pharmaceutics experts from CDSCO who will certify its appropriateness, in their report

3. Animal Pharmacology:

   This section should provide information as per schedule Y and ICH CTD. It will be reviewed more particularly by pharmacology experts. Application must include comparative data with suitable (preferably standard treatment) control, information on conversion of animal/ in-vitro efficacy safety data, dose, to human, using standard methods with justification and references. This should be stated also in the dose selection section in clinical trials.

4. Animal Toxicology:

   - Application must state schedule Y requirement as per proposed route and duration in humans, the toxicology studies done by applicant and conformity to schedule Y, and comparison with control (Preferably standard treatment).
   - In case of deviation from schedule Y, suitable justification for deviation with suitable references and documents, must be provided.
   - Conversion of in vitro and animal toxicity data and dose, to human using standard methods with justification and references should be provided. This should be also stated in the dose selection in clinical trials.
   - Information should be provided as per schedule Y requirement and as per ICH CTD.

   Interpretation:

   - Interpretation of each in-vitro and animal toxicity observed should be stated in terms of possibility of occurrence in humans, likely dose, duration, route, frequency with which it can occur. This information should be also stated in the clinical trial protocol to justify dose proposed, safety precaution taken in the design and details of the clinical trial.
   - In case the observed animal toxicity is a naturally occurring frequent phenomenon in animal and hence not relevant to human safety, it should be explicitly stated and appropriate suitable references for such statement must be provided.

5. Human/Clinical Pharmacology Phase I:

Phase I study: Specify

a. How first in human dose was calculated, rationale, justification

b. Extrapolated effective dose

c. Extrapolated no adverse event dose

d. Expected ADRs (on the basis of chemical structure, class effect, observed preclinical effects)

e. How ADRs were / are being monitored

f. How expected efficacy is being monitored

6. Therapeutic exploratory trials Phase II

7. Therapeutic confirmatory trials Phase III

8. Special studies

Study protocols should be as per Appendix X of schedule Y(see appendix 8.4 of this handbook for additional guidance)

Report of each of the Clinical trials for Phase I, II, III and special studies should be provided as per Appendix II schedule Y and as per ICH CTD.

9. Regulatory status of the investigational drug and comparator in India and other countries

State regulatory status of the investigational drug and comparator in India and other countries, whether

a. Marketed

b. Approved

c. Approved as IND

d. Withdrawn, if any, with reasons

e. Restriction on use if any in countries where marketed/approved,

If approved and marketed, copy of approved package insert/ SmPC in those countries, free sale certificate, certificate of analysis as appropriate should be provided.

10. Prescribing information

Provide approved/ proposed full prescribing information, approved/proposed drafts of labels and cartons.

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 be provided if required.

7.0 References:

7.1 The Drugs and Cosmetics Act 1940 and Rules, 1945,

http://www.mohfw.nic.in/43503435431421382269.pdf

7.2 Norms and standards. Good review practices: guidelines for national and regional regulatory authorities. WHO Drug Information,2015;29:7-12

http://apps.who.int/medicinedocs/documents/s21799en/s21799en.pdf

7.3 Guidance for Review Staff and Industry for good Review Management Principles and Practices for PDUFA products , U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER), Center for Biologics Evaluation and Research (CBER) April 2005 procedural.

http://www.fda.gov/downloads/Drugs/.../Guidances/ucm079748.pdf

8.0 Appendices:

Good Review Management: Fundamental Values

- Quality
- Efficiency and timeliness
- Clarity
- Transparency
- Consistency

8.1 Good Review Management Practices

1. Fundamental Values:

The fundamental values on which good review management is based include quality, efficiency, clarity, transparency, and consistency.

- Quality: The CDSCO seeks the highest levels of quality in the submission, reviews, review processes, management, and outcomes.
- Efficiency and timeliness: Efficiency is critical to the review process. Process efficiency, however, must not be achieved at the expense of quality. Good review practices will improve both the efficiency of the review process and the quality of the review and outcomes.
- Clarity: throughout the submission, review and approval process communications are expected to consistently achieve the highest possible degree of clarity.
- Transparency: Transparency ensures that review staff and applicants are kept informed of how the review is progressing. Both parties can then anticipate and plan the next steps and respond to potential problems as they are identified.
- Consistency: Achieving consistent processes across review committees and offices is an important goal of good review management.

Good review with public health context should have critical integrated analysis, be balanced, thorough, evidence based, identify, investigate, solve problem and be well documented.

Operational Principles- Responsibilities

- Good R and D and submission- sponsor
- Review process- CDSCO
- Quality, timely review- expert
- Effective, appropriate communication and code of conduct –all

2. Operational principles:

- The foundation for good review management is created during product development.

  Product development phase is under the primary management of the applicant. It can achieve efficiency by attending to adequate evidence of efficacy (e.g., endpoints, study design, patient populations), safety (e.g., sample size, dose response, assessment of drug-drug interactions, demographic differences), and quality (e.g., manufacturing procedures, facility compliance with good manufacturing practices).
- The applicant is responsible for submission of a complete application to maximize the efficiency of the review process and reduce the need for multiple cycle reviews.

Central to this document is the concept that industry will submit a complete application that will receive a comprehensive and complete review within a specified time. A complete application contains all required and expected information as per Schedule Y, checklist given on CDSCO website and additional guidance in this handbook. A complete application should be in a readable, well-organized, electronic and hardcopy format. CDSCO guidance is available on the format and content. It is important for the applicant to provide a complete application at the time of initial submission to limit the need for amendments during the review process. Significant omissions lead to requests for amendments or more data (i.e., not a first cycle approval). An application is not considered complete if it meets the regulatory criteria for filing, but lacks important information needed for approval. The focus on initial submission of a complete application does not preclude post submission amendment, but it is expected that such will be needed only in exceptional situations.

- Effective and efficient management of the review process is CDSCO responsibility.
  - CDSCOs' and Reviewers' adherence to review timelines is critical for optimal review performance.
  - CDSCO will establish and observe review timelines to help ensure efficiency and consistency in the review process. A well-managed review process helps staff to allocate the time and resources necessary to complete reviews soon enough to accommodate and adequately consider unanticipated events or findings that may develop during the course of the review. Adherence to these timelines with key internal milestones helps avoid the potential errors associated with crisis-style management dealing with unresolved issues at the end of the review cycle.
  - Review divisions are expected to inform applicants about major elements of the review timeline for each application, anticipating some flexibility for resolution of unanticipated review findings that require adaptation of the review plan. Changes to the review plan can stem from additional team interactions, interactions with senior management, need for consult input, problems identified during facilities inspections, and requests for additional data or analysis from the applicant. Staff should communicate any significant changes in the review timeline to the applicant.
- Good review management requires targeted input from the entire review team.

  Given the multilevel nature of the review and decision-making process, it is important that the review team, supervisory staff, and reviewers adhere to the agreed-upon timelines.
- Good review management increases first time approvals.

  A complete and well-formatted application that meets the standards for approval will be approved on the first cycle. Good review management allows sufficient time for careful regulatory decision making and, if needed, time for the applicant to resolve minor and readily correctable deficiencies in the application.
- Effective and timely communication between the CDSCO and applicants enhances the review process.

  Timely notification of correctable deficiencies allows the applicant to begin corrective actions, maximizes the chance for a first cycle approval, and shortens the overall time to approval. Timely notification of significant and potentially uncorrectable deficiencies in the application may also influence product development decisions.
- CDSCO should not communicate to applicants the proposed or planned regulatory action before issuance of the official written regulatory action.
  - It is important that communication with the applicant during the review of an application be generally limited to requests for additional information/clarification, conveyance of identified deficiencies that need to be corrected before the application can be approved. CDSCO should make clear to the applicant that such communications are preliminary and that the official regulatory action for the application has not yet been taken. Once the person responsible for making a decision on this

application has made a decision on the official regulatory action, it is important to communicate this decision in writing to the applicant in the form of an official written regulatory action.

- The review division should confirm by telephone that the applicant has received the communication of information/deficiency, official written regulatory action and document the call in the application file. This approach provides a clear record of the timing of communication of the official action to the applicant and provides the applicant with the full text of the official regulatory action and time to respond. This assists the applicant in understanding the terms of an approval or the deficiencies identified, and what additional information is required to support approval.
- The standard processes are subject to change as the CDSCO continues to identify and implement new best practices as part of developing a quality systems approach to the new drugs and biologics review and approval process.

3. Review personnel:

Quality, timeliness and success of medical product reviews are dependent on sufficient number of competent reviewers. Reviewers may be RA staff and/or external experts. They should be free of actual or perceived conflicts of interest, sign a conflict of interest statement, should keep their scientific expertise up-to-date, should have critical, analytical thinking to make decisions that are reproducible and clearly understood by others which is strengthened by learning from others and discussion.

4. Quantifying risks and benefits, assessing innovativeness and relevance to meeting unmet needs:

Review team should quantify and qualitatively characterize risk benefit considering product characteristics, indication, context of use, certainty, generalizability, availability of alternatives, public health priorities, country and region specific factors, unmet need, methods of risk mitigation and benefit enhancement.

5. Review report:

Review report should be well documented, with statement of reasons, with details of documents, information, and regulatory requirement taken into account in reaching the decision.

6. Other Aspects:

There should be a procedure for reconsideration of SEC decision

Public communication mechanism should be implemented increasing transparency of regulatory action.

8.2 Subject Expert Committee's (SEC) Composition and Code of Conduct

1. As per the terms of reference, the Subject Expert Committee is expected to advice the CDSCO with an in depth evaluation of non-clinical data including pharmacological and toxicological data and clinical trial data (Phase I, II, III and IV) furnished by the applicant for approval.
2. MOHFW has approved panels of experts of various therapeutic areas for evaluation of various categories of applications of clinical trials for import or manufacture of new drugs and new medical devices for marketing in India. Subject Expert Committee (SEC) usually comprising of 6 medical experts including pharmacologists/clinical pharmacologists, and medical specialists shall be constituted drawing the names of experts from respective panels.
3. SECs should be established for all therapeutic areas, with the number depending on workload.
4. CDSCO as per need may invite suitable additional expert having experience in the particular area of specialization as required by the SEC.
5. CDSCO may add names of experts from Government Medical Colleges/Hospitals or persons of eminence in the panels wherever considered necessary. However, a standard procedure will be followed for induction of experts in the panels.

6. All SEC members should be appropriately oriented on the Good Review Practices, regulatory framework governing clinical research and approval process in the country and familiarized with the basic principles of clinical research including Good Clinical Practices.
7. The expert nominated as a member of the SEC should declare any conflict of interests and sign confidentiality agreement a priori.
8. The members of the expert panel shall hold office for a period of three years but shall be eligible for re-nomination provided that the persons nominated continue to hold their offices in their respective Organization by virtue of which they are nominated. In case any expert from the panel retires from his Institute/Organization, subject expert from the same or similar Institute/Organization or same specialty may be included in the panel.
9. There should be a mechanism in place to periodically review expert panels – ensuring no members have retired/ moved out, etc. The members can be from public or private institutions. Attempts should be made to involve retired academicians well versed in regulatory rules and tenets of clinical research.
10. The committee shall evaluate the proposals keeping in view the requirements as prescribed in the regulatory framework, checklists on website and this handbook.
11. Responsibilities of CDSCO representative in SEC is to conduct of the the SEC and in particular:
    - Propose the agenda of the SEC meetings.
    - Consider 8-10 proposals in one SEC meeting to ensure adequate time for expert review, (However, CDSCO may depending on type of application include more number of applications in a meeting.)
    - Monitor that the mandate and rules of procedure are followed.
    - Ensure that at the beginning of each meeting any potential conflict of interest is declared.
    - Assume responsibility for the conduct and running of the meetings.
    - Ensure that all members have the opportunity to express their views.
    - Before the end of each agenda item, summarize the conclusions.
    - The CDSCO representative should get formal agreement and signature from the members on the key conclusions. This summary will be the content of the communication to the applicant.
    - Ensure that scientific grounds are adequately reflected in conclusions.
    - SEC committee recommendation will be put on CDSCO website and provided to applicant within 3 working days after finalization of the minutes which is usually done on the same day of the meeting.

Code of Conduct

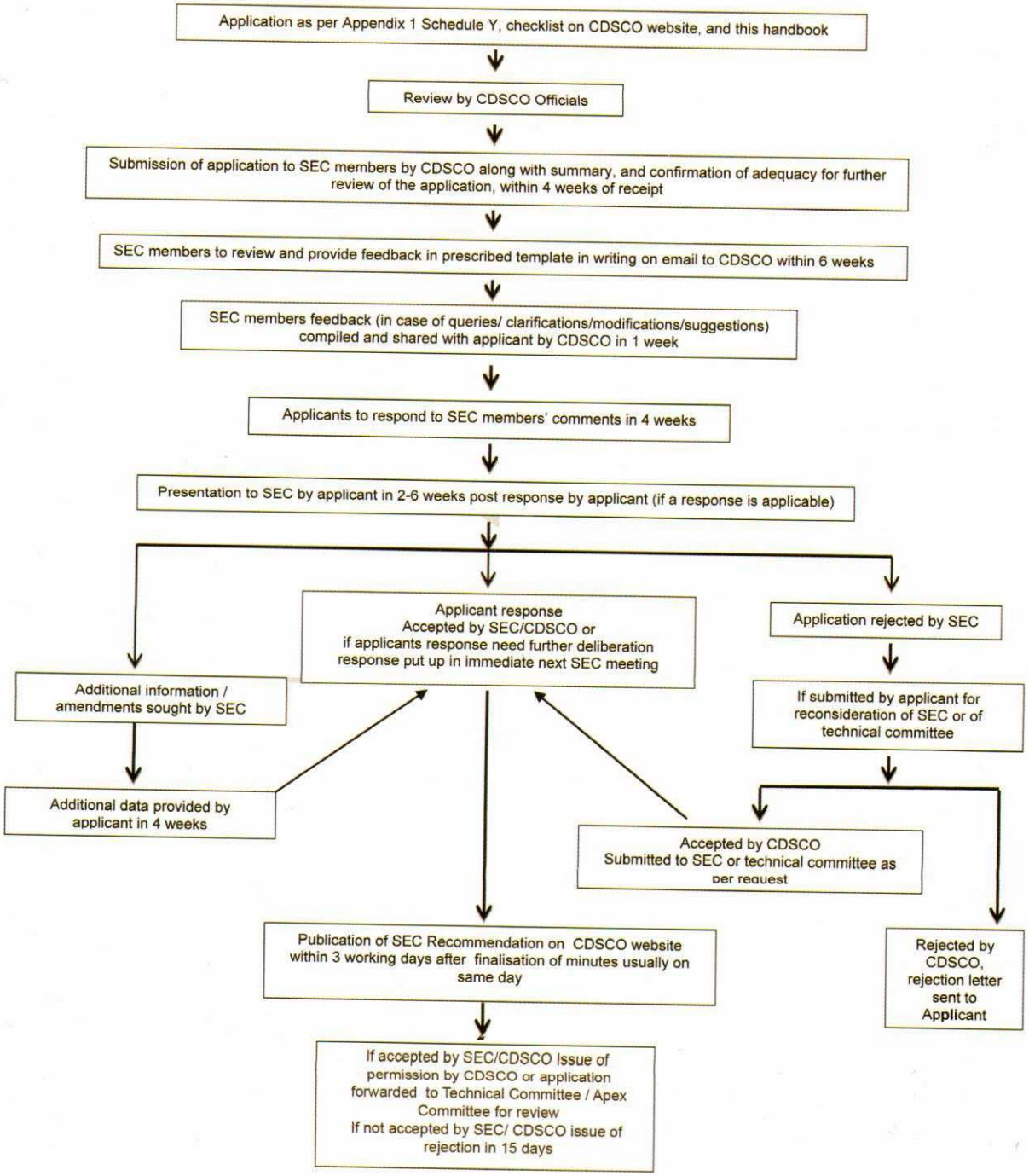
1. Members attending the SEC meeting should review the clinical trial proposal, forwarded well in advance and submit their comments in 6 weeks.
2. Members must have knowledge of current clinical trial regulations and an understanding of Good Clinical Practice (GCP). They must keep abreast of developments.
3. The overall approach of the panel should be scientific, rational, focused, advisory and polite.
4. Recommendations should be governed by valid scientific basis and judgment.
5. Recommendations should be explicit and worded in an easy to understand language.

6. If the proposal does not qualify to receive favorable recommendation from the panel then clear reasons for proposed querry /rejection must be provided to CDSCO.

Members are expected to avoid following:

1. "Conflict of interest" with any of the proposal to be deliberated in the SEC meeting,(and if they do have then they should give this in writing and not participate in the decision making process).
2. Offering the recommendation which are over and above or contrary to the regulatory requirement or which can create a roadblock for reasonable scientific clinical development of new drugs in the country.
3. unprofessional or unscientific conduct and delay in the signing of recommendations at the end of the meeting on the same day.

8.3. Schematic Diagram of SEC Review Process



8.4 Study Protocol Guidance:

There are several books and review articles on protocol design. Here study protocol checklist as per Appendix X of schedule Y, with specific issues which the applicant and reviewer should attend to are given. This guidance is not intended thus to be comprehensive.

1. Title page:

   Ensure that all details are provided in protocol or appendices. While providing site location state if the site, specifically (if relevant) the department, is approved by Medical Council of India(MCI), National Board of Examination(NBE), National Accreditation Board for Hospitals and Healthcare providers(NABH), has ISO certification, Principal Investigator(PI) is approved post graduate teacher. Clinical laboratory has ISO certification, National Accreditation Board for Testing and Calibration Laboratories (NABL) accreditation, Ethics Committee is registered (CDSCO accreditation of site should be specified as and when that assessment system is implemented).

2. Table of contents:

   1. Background and introduction (this information can be provided in Investigator's brochure(IB) and summarized here)

      a. Preclinical experience:

         Provide summary of data, specify the interpretation and extrapolation to human of preclinical, animal pharmacology and toxicology studies done, provide references (refer section 6 of this handbook)

      b. Clinical experience:

Background:

Provide information on benefit and risks of the study drug specifying innovation vis a vis existing options and specific unmet medical need. The Declaration of Helsinki states that biomedical research involving people should be based on a thorough knowledge of literature. It is unethical to expose humans unnecessarily to the risks of research. Need for the study drug, how it fulfils deficiency of standard of care/standard treatment guidelines, incidence/prevalence of disease, disease subtypes, geographical distribution should be specified with a systematic review of International and National published literature.

Preclinical experience and clinical experience from previous work with the study drug should be reviewed and how the current protocol extends existing data should be provided. For an entirely new indication, how this drug was considered for this indication should be discussed.

This section should provide summary of previous clinical trials (details be given in appendices) as per Appendix II of schedule Y and ICH CTD, specifically highlighting information relevant to dosing, subpopulations studied, limitations, primary, secondary endpoints, efficacy, safety, AEs.

Relevant information regarding pharmacological, toxicological, biological properties of the drug/biological/ medical device and previous efficacy, safety experience should be described, extrapolating, giving reasons from previous data, justifying, efficacy safety evaluation in this protocol.

2. Study rationale:

This section should describe clearly with data/information, justification and refs the rationale for study as part of investigational new drug/new drug development process, post-marketing studies/surveillance, for studying/ improving benefit risk, new indication etc. 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.

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

Primary outcome measure is the pre-specified outcome- considered to be of greatest importance to relevant stakeholders (patients, policy makers, clinicians, funders) and is usually used in sample size calculation. Other outcomes of interest are secondary outcomes, there may be several.

4. Study Design

a. Overview of the Study Design: Include description of the type of study (i.e., double-blind, multicentre, placebo controlled, etc.), details 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. Describe if it is superiority or non inferiority or equivalence study.

b. Schematic diagram/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: Provide details of the rationale for the design chosen for this study.

5. Study Population: The number of subjects required to be enrolled in the study with a brief description of the nature of the subject population required is to be mentioned. Information on the settings and locations is crucial to judge the applicability and generalizability of the trial.

In case of global clinical trial specify total number of patients planned to be enrolled globally and number proposed to be enrolled in India as part of the application.

Rationale for number of subjects to be enrolled should be provided. It will depend on study objective, expected difference between study drug and comparator, variation and statistical significance sought. Clear self-explanatory simple language statement must be provided.

6. Subject Eligibility:

a. Inclusion Criteria: Provide justification and references

b. Exclusion Criteria: Provide justification and references

7. Study Assessments: Plan, procedures and methods to be described in detail providing justification and references.

8. Study Conduct: 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., during visits.,

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 drop outs 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.

Describe how protocol violations will be treated, including conditions where the study will be terminated for non-compliance with the protocol.

9. Study Treatment:

Description of the intervention should be given in detail (e.g. as per TIDieR guidelines)

Provide details of dose adjustments. Treatment given to control arm which will receive standard of care including description of combinations like diet, exercise, drugs, conditions under which interventions are withheld, titration regimen if applicable, should be also described in detail.

a. **Provide justification, specifying efficacy, safety, with preclinical, clinical data, appropriate references** for dosing schedule (dose, frequency, route and duration of the experimental treatment) describe the administration of placebos and/or dummy medications if they are part of the treatment plan. **If standard treatment is being withheld and /or placebo is being given, justify with safety, efficacy issues involved, provide relevant references and review of literature.**

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. **Provide justification; specifically refer to prior preclinical and clinical data and experience.**

Rescue Medication: In case of lack of effect, details of rescue treatment, when to initiate it, should be described in detail, so that patients health is not jeopardized.

d. Possible drug interactions - specify likely drug interactions and methods to ensure patient safety, efficacy.

e. Concomitant therapy: The drugs that are permitted during the study, their dose, frequency and the conditions under which they may be used are to be 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 study, these should be described here.

f. If any concomitant medication is prohibited, specify if treatment is required, how patients should be treated and/or should be withdrawn.

g. Blinding and randomization procedures: A detailed description of the blinding procedure if the study employs a blind on the investigator and/or the subject and of randomization should be provided

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

10. Adverse Events (See Appendix XI of schedule Y): Description of expected adverse events should be given.

This section should specify extrapolation of data from preclinical pharmacology, toxicology, previous clinical experience, expected adverse drug reactions, dose at which it is expected, monitoring, precautions, safety checks, stopping guidelines. Procedures used to evaluate adverse events and compensation to be given as per regulation, should be described.

11. 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.

12. 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, persons who have authorized access, make corrections, take decisions on queries and errors should be stated.

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

13. Investigational Product Management: Describe here

    a. 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, labeling, 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. Policy and procedure for handling unused investigational products.

14. Data Analysis:

    Table for result section, comparison with standard treatment, number of subjects, variables, expected difference, statistical tests to be used and justification should be provided.

    Provide details of the statistical approach followed for sample size calculation, in simple language, determination, assumptions made, with 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

15. Undertaking by the investigator (see Appendix VII of schedule Y) should be provided as part of the application.

16. Appendices: Provide a study synopsis, copies of the informed consent documents (patient information sheet, informed consent form etc. **as per Appendix V with compensation clause as per GSR 53(E) dated Jan 30, 2013);** CRF and other data collection forms; a summary of relevant pre-clinical safety information and any other documents referenced in the clinical protocol.

    It is to be noted that for marketed drug information from approved package insert SmPC, published literature may be provided.

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Ministry of Health and Family Welfare, Government of India
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