GUIDANCE DOCUMENTS FOR REGULATORY SUBMISSIONS

In an effort to help stakeholders get over the regulatory complexities involved in their interactions with the Health Authorities, ministries or regulators, Indian Society for Clinical Research (ISCR) has attempted to provide a gist of the various process documents that are required for submission in the various categories of trials and what needs to be done / submitted, in a simple, easy to understand format.

DISCLAIMER

For document see below

CLINICAL TRIALS WITH VACCINES

The guidelines to conduct the clinical trial on investigational vaccines are similar to those governing a clinical trial with drugs. The phase of these trials differ from drug trials as given below:

Phase I: This refers to the first introduction of a vaccine into a human population for determination of its safety and biological effects including immunogenicity. This phase includes study of dose and route of administration and should involve low risk subjects. For example, immunogenicity to hepatitis vaccine should not be determined in high-risk subjects.

Phase II: This refers to the initial trials examining effectiveness (immunogenicity) in a limited number of volunteers. Vaccines can be prophylactic and therapeutic in nature. While prophylactic vaccines are given to normal subjects, therapeutic or curative vaccines may be given to patients suffering from particular disease.

Phase III: This focuses on assessments of safety and effectiveness in the prevention of disease, involving controlled study on a larger number of volunteers (in thousands) in multi-centres.

Guidelines:

_ The sponsor and investigator should be aware of the approval process(es) involved in conducting clinical trials of vaccines. They should familiarize themselves with the guidelines provided by Drug Controller General (India), Department of Biotechnology (DBT) and Ministry of Environment and Genetic Engineering Approval Committee (GEAC) in the case of vaccines produced by recombinant DNA technology.

The Ministry of Environment and Forests (MoEF) has adopted the recommendations made by the Mashelkar Committee (Task Force on r-Pharma) to streamline the regulatory process for the approval of all recombinant DNA products. The recommendations have been notified w.e.f from 1st April 2006.

The Task Force Report defines LMOs (Living Modified Organisms) as only those organisms modified by r-DNA techniques through human interventions where the end product is living modified organism. The Report has rationalized the regulatory procedure for five categories of LMOs:

Indigenous product development, manufacture and marketing of pharmaceutical products derived from LMOs but the end product is not a LMO -- This category has been further divided into two parts namely (i) organisms falling under Risk Group I & II and (ii) Risk Group III and above. The approval of the Genetic Engineering Approval Committee (GEAC), which under the MoEF has been acting as the key biotech regulator

providing environmental clearance to all products using genetically modified organisms, is required only for organism falling under Risk Group –III and IV. While no approval of GEAC is required for Phase- III clinical trials under this category, instead the Drug Controller General of India (DCGI) will approve the human clinical trials based on the recommendation of the Review Committee on Genetic Manipulation (RCGM) and product approval based on the results of the clinical studies.

Indigenous product development, manufacture and marketing of pharmaceutical products where the end product is a LMO — In this category, since the end product is a LMO, the probability of risk due to accidental release is higher and therefore GEAC will be responsible to evaluate the environmental impact caused by handling and large-scale use/ release of LMOs. Accordingly, GEAC should consider and approve phase III human clinical trials. The GEAC should approve environmental release based on the environmental risks vs benefits analysis, which takes into consideration the recommendation of RCGM and results of the clinical trials. DCGI should examine the data on the toxicity, allergenicity and QC tests and recommendation of RCGM before approving human clinical trials. The DCGI should also take into consideration the views of GEAC on the safety of the product for conduct of human clinical trials from environmental angle. DCGI should be responsible for evaluation of product efficacy and safety based on the data generated during human clinical studies prior to market authorization.

Import and marketing of *LMOs* as Drugs/ Pharmaceuticals in finished formulations where the end product is a LMO -- Since this scenario pertains to import of LMOs, the only activity envisaged within the country prior to issue of market authorization is the conduct of human clinical trials and therefore the approval of GEAC for conduct of Phase – III clinical trials as outlined in Protocol would be applicable.

Import and marketing of LMOs as Drugs/ Pharmaceuticals in bulk for making finished formulation where the end product is a LMO -- This scenario involves setting up of facilities for formulations and conduct of clinical trials within the country before market authorization. The end product being an LMO approval of RGCM, GEAC and DCGI as outlined for category b would be applicable.

Import and marketing of products derived from LMOs as Drugs/Pharmaceuticals in bulk and/ or finished formulations where the end product is not a LMO -- Approval of GEAC is not required for this category. This scenario in terms of environmental risk falls under the least risk category since there is no exposure to LMOs within the country. Therefore approval under Rules 1989 of EPA would not be required.

- Some vaccines that contain active or live-attenuated microorganisms can possibly possess a small risk of producing that particular infection. The subjects to be vaccinated should be informed of the same.
- The subjects in control groups or when subjected to ineffective vaccines run a risk of contracting the disease.

- The risks associated with vaccines produced by recombinant DNA techniques are not completely known. However, for all the recombinant vaccines/products the guidelines issued by the Department of Biotechnology should be strictly followed.
- Trials should be conducted by investigator with the requisite experience and having necessary infrastructure for the laboratory evaluation of seroconversion.
- Protocols for such trials should include appropriate criteria for selection of subjects, plan of frequency of administration of the test vaccine in comparison with the reference vaccine. It should accompany detailed validation of testing method to detect the antibody titter levels.
- It should specify methodology to be adopted for prevention of centrifuged serum for the purpose of testing.
- The investigator should be provided with Quality Control data of the experimental batch of the vaccine made for the purpose of clinical trials.
- The sponsor should provide the Independent Ethics Committee approval of the nodal body (ies) to carry out clinical trials with the vaccine.
- The generic version of new vaccines already introduced in the other markets after step up clinical trials including extensive Phase III trials should be compared with the reference vaccine with regard to seroconversion in a comparative manner in a significant sample size.
- Post Marketing Surveillance (PMS) should be required following seroconversion studies. PMS data should be generated in a significant sample size sensitive to detect side effects and address other safety issues.
- Protocols for test of new vaccine should contain a section giving details of steps of manufacture, in-process quality control measures, storage conditions, stability data and a flow chart of various steps taken into consideration for manufacture of vaccine. It should also contain detailed method of quality control procedure with the relevant references.

DOCUMENTS REQUIRED FOR CLINICAL TRIAL APPLICATION OF VACCINES IN INDIA

(NOTE: DATA ON ITEM NUMBER 4-9 IS REQUIRED, AS APPLICABLE FOR THE PROPOSED STUDY, IF NOT AVAILABLE IN THE INVESTIGATOR'S BROCHURE)

1. **Delegation of responsibility**

2. **Protocol**

3. **Investigator's brochure**

4. **Vaccine Information:**

   - Introduction
   - Description of vaccine
   - Summary of Pre-clinical studies
   - Summary of Clinical studies

5. **Background and rationale :**

   - Medical need
   - Current status of available vaccine
   - Rationale for improved/new vaccine
   - Vaccine information – Vaccine supplies
     - Preparation and administration
   - Disposal of study material
   - Storage condition and shelf life.

6. **Pre-clinical studies:**

   - Non-clinical pharmacology
   - Pharmacokinetics and product metabolism in animals
   - Pre-clinical toxicology studies
   - Pre-clinical efficacy studies

7. **Clinical studies**

   - Safety
   - Immunogenicity
   - Conclusion

8. **Potential Risks and Mitigating Factors:**

   - Concerns for human use
   - Reactogenicity due to individual susceptibility
   - Allergic reactions and anaphylaxis

- Adverse experiences
- Precautions
- Risk to the community.

9. Global Regulatory status:

A. Clinical trial in each participating country:

- Copies of regulatory approval letters, IRB/EC approvals, recruitment figures (Protocol specific) from participating countries (if available)

a) **Regulatory status of vaccine in other countries (if applicable):**

- Approved
- Marketed (if marketed a copy of package insert)
- Withdrawn, if any, with reasons
- Free sale certificate or certificate of analysis, as appropriate

10. Study Status :

A. Status of the proposed study Worldwide:

- Number of countries participating
- Name of countries participating
- Number of study centres per country
- Anticipated recruitment in each country

B. Status of the proposed study in India:

- Number of patients
- Number of study centres

11. Investigator's Undertakings

12. Ethics committee approval letters (in case of studies under category B)

13. Informed consent form and patient information sheets

14. Case record form

15. Relevant published literatures

16. Suspected Unexpected Serious Adverse Reaction (SUSAR) from other participating countries if any reported and summary of any reported problems.

17. Affidavit from the sponsor that the study has not been discontinued in any country and in case of discontinuation the reasons for such a discontinuation and that the applicant would further communicate to DCG(I) about the future discontinuation and Investigator's Brochure containing the summarized information is based on the facts. (on a plain paper duly notarized and apostilled)

DOCUMENTS REQUIRED FOR IMPORT LICENCE APPLICATION:

1. Justification for the quantity of vaccine need to be imported
2. Country from where the vaccine will be imported
3. Packaging information

DOCUMENTS REQUIRED FOR EXPORT LICENCE APPLICATION FOR THE EXPORT OF BLOOD/AND BLOOD PRODUCTS (IF APPLICABLE):

1. Letter from sponsor appointing central laboratory
2. Letter from central laboratory confirming that only protocol specific tests will be done
3. Justification for the quantity of samples to be exported

Form I

APPLICATION FOR ENVIRONMENTAL APPROVAL OF CLINICAL, VETERINARY AND FOOD PRODUCTS BASED ON HAZARDOUS MICRO- ORGANISMS/GMO

PART A

a. Not all the points included will apply to every case. It is to be expected, therefore, that individual applicant will address only the particular parameters that are appropriate to individual situations. In each case where it is not technically possible or it does not appear necessary to give the information, the reasons shall be stated.

b. The details required in response to each parameters is also likely to vary according to the nature and scale of the proposed release.

c. The description of the methods used or the reference to the standardized or internationally recognized methods shall also be mentioned in the form together with the name of the body of bodies responsible for carrying out the studies.

d. A 1-2 page summary of the proposal shall be appended with application.

PART B

1. Name of the Applicant
2. Name of organization/ firm
3. Approval Required
    1. Manufacture
    2. Import
    3. Marketing
4. Quantity per year of the product to be manufactured/ imported/ marketed

PART C

1. Name of the product :
    a. Human Medicine
    b. Veterinary Medicine
    c. Food Product
    d. Others (please specify)
2. Intended use (pathological, Metabolic and Immune Response)
3. SAFETY CONCERN :
    a. Donor (heterologous Nucleic acid segments from sources)
    b. Vector (DNA) molecules to which heterologous nucleic acid segments are joined for transfer to hosts)

c. Hosts (living cells or organisms into which rDNA molecules are introduced)

4. Production Method (the production method should give the details of the cell lines used, the information on the production of the recombinant proteins within or outside the cells, the concentration of the products in units per litre of the fermented broth as well as the concentration in physical weights. The description should also include in brief the methods applied for reducing the genomic particles, proteins and living contaminants including viruses bacteria, fungi, parasites, etc).

    a. Characterization of the system of production used

        i. Details of the expression system

            - Description of the host cell line
            - Identification of the genera and the species.
            - The risks involved in handling the cell line.
            - The classification of the cell line according to the Government of India's Biosafety guidelines or any other accepted Recombinant cell line usage guideline.
            - The method(s) of maintenance and growth of the cell line.
            - The nature and hazards of using substrates, inducing agents, etc.

        ii. Characteristics of the target gene and vector

            - The full description of the source of the target gene.
            - The composition of the vector used indicating the promoter sequence as well as the regulatory mechanisms utilized in the expression cassette.
            - Schematic diagrams of the expression cassette to describe fully the marker genes used.
            - The restriction sites related to specific endo-nucleases, and the cell lines used for shuttling and amplification of the expression cassette.
            - The method of constructing the target gene along with all the sequences added or deleted.
            - The extent of target gene amplification into the host genome.
            - The target gene should also contain, along with the nucleotide sequence, the description of the amino acids below the codons.

        iii. Approaches adopted for expression of the gene

- The description of the transcripted messenger RNA with its analysis of sequence and identification procedure.
- The translation information indicating whether the protein product is Chimeric, whether the expression is found as inclusion bodies or as intracellular protein or whether the protein is secreted out.
- The extent of the target protein produced as the percentage of the total cell dry mass as well as its percentage compared to the total proteins of the cell
- The quantity of the target protein produced after the cell growth per litre of the fermented broth.
- The full sequence of the recombinant gene along with the promoters the marker genes and the terminator sequence.

b. Description of the production process

i. Production setup

- The handling of the stock cell lines.
- The evaluation and uses of the cell lines in pre-fermentor processes
- The preparation of the seed vessel
- The main production fermentation conditions need to be described in brief.

ii. Growth Kinetics

- Graphical plots of the versus substrate usage, optical density change, biomass formation, protein products formation, inducing agents used and their effects on the target protein formation.
- The effects of change of standard parameters like pH, dissolved oxygen, temperature, etc. in the main production fermentor.
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iii. Fermentation parameters

- The pH, temperature, aeration, and rpm of the shaft.
- Volume of seed to the volume of main fermentor.
- Main substrates used inducing agents used if any.
- The fermentation time and the concentration of the target protein in the fermented broth.

c. In-process control methods

i. All the .analytical methods used for this in-process control must be described to ensure the regulatory authorities that the chances of entry of unwanted products have been minimised.

d. Description of the raw and processing materials used
    i. Description of all the raw materials and processing materials used starting from the stock cells handling to the finished dosage form must be in a tabular form.
    ii. Grades of materials used and their usual sourcing.

e. Description of the Plant and Machinery used
    i. List of all the equipment along with the indicative capacity.
    ii. Names of the manufacturers.
    iii. List of Main production equipment and the quality control equipment.

f. Description of the building and facilities created for the manufacture
    i. The manufacturing area.
    ii. The flow of the process/ operation starting from the stock culture area to the finishing area.
    iii. The plot plan of various floors used in the manufacture and processing.
    iv. The building diagram in the plan and/ or elevation in the outline indicating the cleanliness maintained in different sections such as class 10,000, class 1000 and class 100 areas etc.
    v. Description of the air handling system which is very important.
    vi. A separate writeup indicating the movement of operating personnel in the area.

5. Approaches for the extraction and purification of the product. The purification methods should particularly indicate the modes of elimination of viruses, bacteria, fungi, parasites etc., if the cell lines are mammalian origin. It should also include methods for the removal of genomic particles, and proteins irrespective of cell lines/hosts used for production, removal of adjuvants, reagents, chemicals including vectors, donor and recipient organisms foreign DNA and adventitious materials associated with production methods.
    a. The methods of handling the cells.
    b. The methods of isolating the cell soup containing the target protein the methods of enzyme treatment if any.

c. The methods of concentration, precipitation (if applied) reconstitution, salt separation (if applicable), absorption and desorption methods, chromatographic methods used if any, ultracentrifugation methods if used.

d. Sterilization and final dosage formulation.

e. Processes to obtain the product in the finished dosage form.

6. Quality Control and Quality Assurance

a. Bulk material :

i. Test relating to the identification of the stock cells.

ii. The plasmid construct retention, in the cells during cell growth.

iii. The media used

iv. The procedures adopted for testing and the percentage retention of the target plasmid.

v. Description of the contamination test of the stock culture to assess and monitor the microbial contamination including the media used and the procedures adopted.

vi. The criteria of acceptance of contamination free culture

vii. Characterization of the bio-active molecule produced by monitoring physical & chemical properties of the molecules by the following or more authentic method should be provided.

- Microscopic examination including light, phase contract and electron microscopic studies.
- UV Spectroscopic analysis to show the absorption spectra of the product and comparison of this with authentic material.
- Density gradient centrifugation to show single peak.
- Pattern in High performance liquid chromatography to indicate how many peaks or if only one peak is noticed in the produced and purified bulk.
- Iso-electric focussing analysis to show the pI values.
- Western Blot and SDS-PAGE to map the peptide/ target protein.
- Existence of special bonds like disulfide bonds by breaking the protein and subjecting to SDS-PAGE mapping.

- Immunodiffusion Test to find out the absence of contaminants or the extent of the presence of contaminants.
- Amino acid composition of the purified protein and its comparison with the authentic material.
- N-Terminal Amino Acid Sequence analysis and its comparison with the gene construct used.
- Determination of the biological activity in the animal model.
- Determination of Contaminants per milligram or any convenient unit of the manufacturing bulk purified protein is also to be carried out to indicate the extent of contaminant nucleic acid stretches, proteins, carbohydrates lipids, detergents, salts and other processing chemicals -used in the purification. The impacts of the presence of these contaminants are also to be indicated with authentic references if any to ensure that the risks associated with their presence are minimal. The limits of contaminants and the acceptance criteria need to be quantified for each contaminant.

b. Formulated Materials :

i. The ingredients incorporated subsequently in the manufacture. The specification of the final product.

ii. The Quality Control Department would have to certify that the final product has the results within the specifications prescribed and accepted by the Regulatory Authorities.

iii. The documentation should therefore indicate the following specifically :

- Product presentation.
- Physical appearance
- Product inserts, literature and label claim
- Volume/ Quantity per pack/ dose.
- Potency of the product.
- Particulate matter limits for liquid.
- Preservative usage percentage.
- PH
- Other Extraneous materials used, their extent such as contents of DNA, RNA, Carbohydrates, Lipids, processing materials like detergents, salts, etc.
- Protein content in the product.

- Sterility Status
- Toxicity information
- Pyrogen status

7. Possible Hazards to environment from release of GMO/nucleic acid/micro-organisms or products.
8. Clinical field trials done in India/abroad (whether permission of Institutional Ethics Committee obtained)
9. Stability and Shelf Life of product
10. Method of disposal of vials of syringes/ wastes matter
11. Regulatory status india/ abroad (enclose certificates like free sale certificate/ GMP certificate/ certificates granted by Health & Environment Authorities of the country of origins signed by applicant. In case the certificate is issued by the concerned authority of country of origin, the certificate should be endorsed/ authenticated by Indian Embassy/ High Commission/Consulate in that country.
    i. Every certificate shall be accompanied by other statutory information like manufacturing batch no date of manufacture, date of analysis, date of release of the certificate, signatory to the certificate etc.
    ii. The final formulated product needs to be certified for acceptance by the manufacturer.

Applicants' Signature with Seal

References:

1. NOTIFICATION REGARDING ADOPTION OF THE RECOMMENDATIONS OF THE TASK FORCE ON R-HARMA UNDER THE CHAIRMENSHIP OF DR R A MASHELKAR, DG-CSIR WITH EFFECT FROM 1. 4. 2006
http://envfor.nic.in:80/divisions/csurv/geac/rpharma_tf.pdf

2. Ground Rules for Consideration of Proposals by the GEAC as per the good practices in environmental regulation adopted by MoEF.
http://www.envfor.nic.in/divisions/csurv/geac/groundrules.pdf

3. Good Clinical Practices Guidelines
http://www.cdsco.nic.in/html/GCP1.html

4. ETHICAL GUIDELINES FOR BIOMEDICAL RESEARCH ON HUMAN PARTICIPANTS
http://www.icmr.nic.in/ethical.pdf