WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 8.084
Volume 10, Issue 13, 1005-1016. Review Article ISSN 2277–7105

FILING REQUIREMENTS FOR INVESTIGATIONAL NEW DRUG APPLICATION IN UNITED STATES AND CLINICAL TRAIL AUTHORIZATION IN EUROPE

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Article Received on
09 Sept. 2021,

Revised on 30 Sept. 2021,
Accepted on 21 Oct. 2021

DOI: 10.20959/wjpr202113-22162

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ABSTRACT

Developing a new drug requires great amount of research work in chemistry, manufacturing, controls, preclinical science and clinical trials. Drug reviewers in regulatory agencies around the world bear the responsibility of evaluating whether the research data support the safety, effectiveness and quality control of a new drug product to serve the public health. Every country has its own regulatory authority, which is responsible to enforce the rules and regulations and issue the guidelines to regulate the marketing of the drugs. This article focuses on drug approval process and filing requirements for Investigational New Drug Application (IND) in United States and Clinical Trail Authorization in Europe.

KEYWORDS: Investigational New Drug Application (IND), MAA, USFDA, Drug approval, Clinical trial Authorization.

1. INTRODUCTION

The Drug regulatory affairs is responsible for ensuring the safety, efficacy and quality of medicines in the entire product lifecycle, and is expected to carry out its tasks by applying the best available scentific knowledge and skills without bias. FDA's role in the development of a new drug begins when the drug's sponsor (usually the manufacturer or potential marketer), having screened the new molecule for pharmacological activity and acute toxicity potential in animals, wants to test its diagnstic or therapeutic potential in humans. At that point, the molecule changrs in legal status under the Federal Food, Drug, and Cosmetic Act and

becomes a new drug subject to specific requirements of the drug regulatory system. The IND application is the crucial stepping stone from non-clinical to clincial testing. The IND must contain information on a number of areas including animal pharmacology, drug distribution, toxicology, manufacturing, and the clinical protocol.[1]

The FDA reviews the IND application for safety to assure that research subjects will not be subjects to unreasonable risk. If the application is cleared, the candidate drug usually enters a phase 1 clinical trial. A sponsor wishing to conduct clinical studies with an investigational drug in the European Union must seek and gain approval before each phase of clinical development. This entails submitting a Clinical Trial Authorization (CTA) application to the regulatory competent Authority of each Member state (MS) in which the clinical trial is to be conducted. At the same time, the sponsor must apply for a favourable opinion from the relevant ethics committee (s) in each MS. Only when the authorization and favourable opinion have been obtained can the trail commence. My project provides regulatory professionals with knowledge necessary to enable them to complete and submit applications for CTA and for Ethics Committee (EC) favourable opinion to conduct a clinical trial in EU.[2]

2. DOCUMENTS REQUIRED FOR INVESTIGATIONAL NEW DRUG APPLICATION[4-10](IND)

An IND submission for Phase 1 studies is required by regulation to contain the sections enumerated below. Clarifications are described when appropriate beneath each section heading.

Types of IND[3]

There are three IND types

1. **An Investigator IND** is submitted by a physician who both initiates and conducts an investigation, and under whose immediate direction the investigational drug is administered or dispensed. A physician might submit a research IND to propose studying an unapproved drug, or an approved product for a new indication or in a new patient population.
2. **Emergency Use IND** allows the FDA to authorize use of an experimental drug in an emergency situation that does not allow time for submission of an IND in accordance with 21CFR, Sec. 312.23 or Sec. 312.20. It is also used for patients who do not meet the criteria of an existing study protocol, or if an approved study protocol does not exist.

3. **Treatment IND** is submitted for experimental drugs showing promise in clinical testing for serious or immediately life-threatening conditions while the final clinical work is conducted and the FDA review takes place.

A. Cover Sheet (FDA Form-1571) [21 CFR 312.23(a)(1)]

A cover sheet for the application containing the following.

(i) The name, address, and telephone number of the sponsor, the date of the application, and the name of the investigational new drug.

(ii) Identification of the phase or phases of the clinical investigation to be conducted.

(iii) A commitment not to begin clinical investigations until an IND covering the investigations is in effect.

(iv) A commitment that an Institutional Review Board (IRB) that complies with the requirements set forth in part 56 will be responsible for the initial and continuing review and approval of each of the studies in the proposed clinical investigation and that the investigator will report to the IRB proposed changes in the research activity in accordance with the requirements of part 56.

(v) A commitment to conduct the investigation in accordance with all other applicable regulatory requirements.

(vi) The name and title of the person responsible for monitoring the conduct and progress of the clinical investigations.

(vii) The name(s) and title(s) of the person(s) responsible under 312.32 for review and evaluation of information relevant to the safety of the drug.

(viii) If a sponsor has transferred any obligations for the conduct of any clinical study to a contract research organization, a statement containing the name and address of the contract research organization, identification of the clinical study, and a listing of the obligations transferred. If all obligations governing the conduct of the study have been transferred, a general statement of this transfer--in lieu of a listing of the specific obligations transferred--may be submitted.

(ix) The signature of the sponsor or the sponsor's authorized representative. If the person signing the application does not reside or have a place of business within the United States, the IND is required to contain the name and address of, and be countersigned by, an attorney, agent, or other authorized official who resides or maintains a place of business within the United States.

B. Table of Contents [21 CFR 312.23(a)(2)]

This section contains a complete table of contents for the IND, each major section(item number) should also have a table of contents. The tables of contents should be complete and reflect the correct content and page number of each subsection.

C. Introductory Statement and General Investigational Plan [21 CFR 312.23(a)(3)]

Regulations repeatedly describe this section as brief. Ordinarily, two to three pages should suffice. The information requested here is intended to place the developmental plan for the drug into perspective and to help FDA anticipate sponsor needs. Often a sponsor in the first human studies is simply attempting to determine early pharmacokinetic and perhaps early pharmacodynamic properties of the drug. Detailed developmental plans are contingent on the outcomes of such studies. In that case, sponsors should simply state this in this section and not attempt to develop and write detailed developmental plans that will, in all likelihood, change considerably should the product proceed to further development.

D. Investigator's Brochure [21 CFR 312.23(a)(5)]

Under the auspices of the International Conference on Harmonization (ICH), a document that provides general guidance on the Investigator's Brochure has been developed and will soon be published in the Federal Register (Good Clinical Practice: Guideline for the Investigator's Brochure). Sponsors are referred to this document for further information on recommended elements of an Investigator's Brochure. It contains clinical and non-clinical information relevant to the study of the product in humans compiled by the sponsor to provide to the investigator and others involved in the clinical trial. Sponsor-investigators are not required to submit an IB to the IND.

E. Protocols [21 CFR 312.23(a)(6)]

The regulation requires submission of a copy of the protocol for the conduct of each proposed clinical trial. Sponsors are reminded that the regulations were changed in 1987 specifically to allow Phase 1 study protocols to be less detailed and more flexible than protocols for Phase 2 or 3 studies. This change recognized that these protocols are part of an early learning process and should be adaptable as information is obtained, and that the principal concern at this stage of development is that the study be conducted safely. The regulations state that Phase 1 protocols should be directed primarily at providing an outline of the investigation: an estimate of the number of subjects to be included; a description of safety exclusions; and a description of the dosing plan, including duration, dose, or method to be used in determining

dose. In addition, such protocols should specify in detail only those elements of the study that are critical to subject safety, such as

1) necessary monitoring of vital signs and blood chemistries and

2) toxicity-based stopping or dose adjustment rules.

F. Chemistry, Manufacturing, and Control Information [21 CFR 312.23(a)(7)]

The regulations at 312.23(a)(7)(i) emphasize the graded nature of manufacturing and controls information. Although in each phase of the investigation sufficient information should be submitted to assure the proper identification, quality, purity, and strength of the investigational drug, the amount of information needed to make that assurance will vary with the phase of the investigation, the proposed duration of the investigation, the dosage form, and the amount of information otherwise available. For example, although stability data are required in all phases of the IND to demonstrate that the new drug substance and drug product are within acceptable chemical and physical limits for the planned duration of the proposed clinical investigation, if very short-term tests are proposed, the supporting stability data can be correspondingly very limited.

G. Drug Substance [312.23 (a)(7)(iv)(a)]

Sponsors are reminded that, under present regulations, references to the current edition of the USP-NF may be used to satisfy some of the requirements, when applicable.

Information on the drug substance should be submitted in a summary report containing the following items.

a. A description of the drug substance, including its physical, chemical, or biological characteristics

A brief description of the drug substance and some evidence to support its proposed chemical structure should be submitted. It is understood that the amount of structure information will be limited in the early stage of drug development.

b. The name and address of its manufacturer

The full street address of the manufacturer of the clinical trial drug substance should be submitted.

c. The general method of preparation of the drug substance

A brief description of the manufacturing process, including a list of the reagents, solvents, and catalysts used, should be submitted. A detailed flow diagram is suggested as the usual,

most effective, presentation of this information. More information may be needed to assess the safety of biotechnology-derived drugs or drugs extracted from human or animal sources.

d. The acceptable limits and analytical methods used to assure the identity, strength, quality, and purity of the drug substance.

A brief description of the test methods used should be submitted. Proposed acceptable limits supported by simple analytical data, (e.g., IR spectrum to prove the identity, and HPLC chromatograms to support the purity level and impurities profile) of the clinical trials material should be provided. Submission of a copy of the certificate of analysis is also suggested. The specific methods will depend on the source and type of drug substance (e.g., animal source, plant extract, radiopharmaceutic, other biotechnology-derived products). Validation data and established specifications ordinarily need not be submitted at the initial stage of drug development. However, for some wellcharacterized, therapeutic biotechnology-derived products, preliminary specifications and additional validation data may be needed in certain circumstances to ensure safety in Phase 1.

H. Drug Product [21 CFR 312.23 (a)(7)(iv)(b)]

Sponsors are reminded that, under present regulations, references to the current edition of the USP-NF may be used to satisfy some of these requirements, when applicable.

Information on the drug product should be submitted in a summary report containing the following items.

a. A list of all components, which may include reasonable alternatives for inactive compounds, used in the manufacture of the investigational drug product, including both those components intended to appear in the drug product and those which may not appear, but which are used in the manufacturing process.

A list of usually no more than one or two pages of written information should be submitted. The quality (e.g., NF, ACS) of the inactive ingredients should be cited. For novel excipients, additional manufacturing information may be necessary.

b. Where applicable, the quantitative composition of the investigational new drug product, including any reasonable variations that may be expected during the investigational stage:

A brief summary of the composition of the investigational new drug product should be submitted. In most cases, information on component ranges is not necessary.

c. The name and address of the drug product manufacturer.

The full street address(es) of the manufacturer(s) of the clinical trial drug product should be submitted.

d. A brief, general description of the method of manufacturing and packaging procedures as appropriate for the product.

A diagrammatic presentation and a brief written description of the manufacturing process should be submitted, including sterilization process for sterile products. Flow diagrams are suggested as the usual, most effective, presentations of this information.

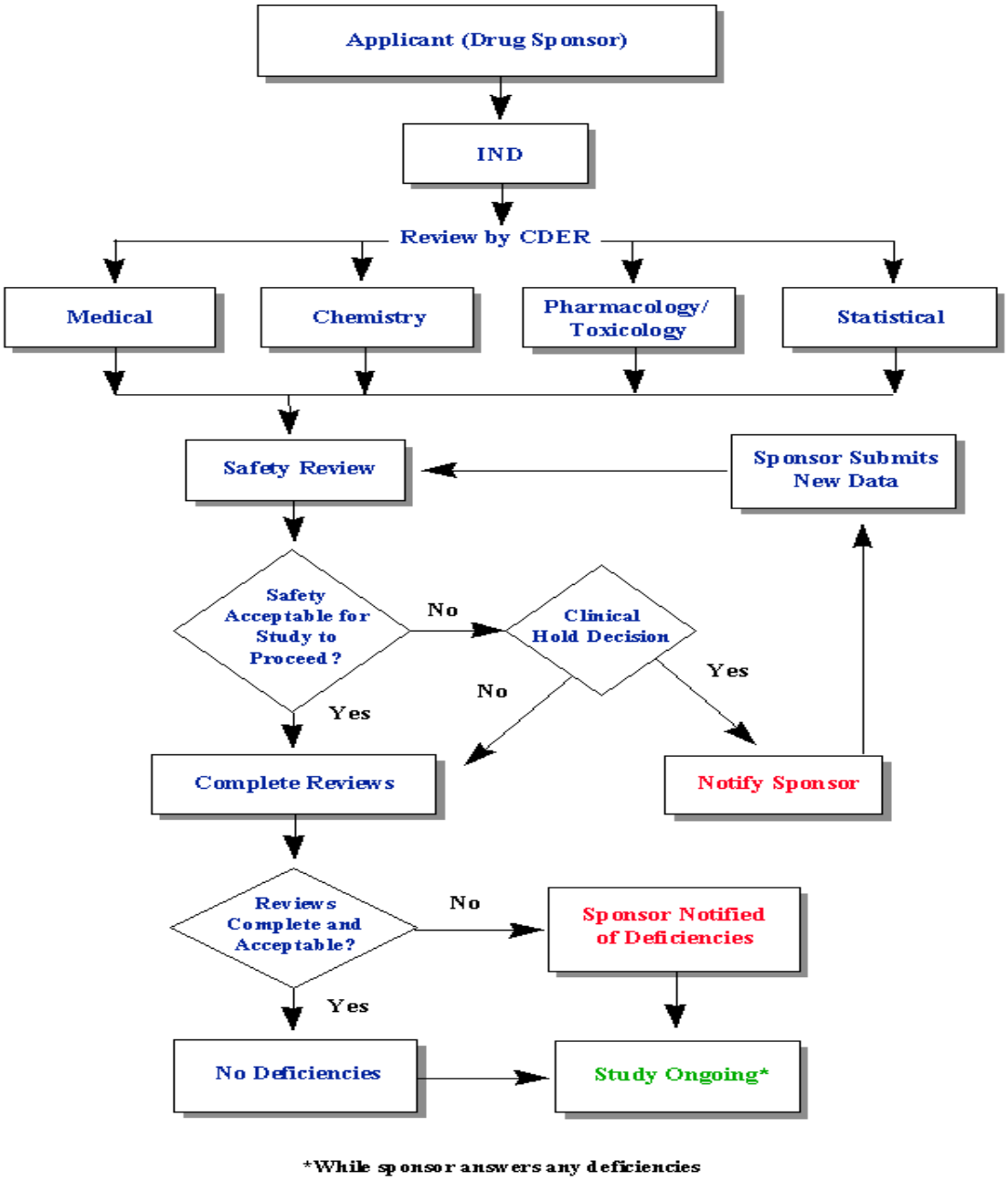


Figure 1: Investigational New Drug (IND) Application Process.

3. CLINICAL TRIAL AUTHORIZATION[11-20] (European countries)

Article 9.8 of the Directive 2001/20/EC requires the commission, in consulation with member states, to draw up and publish detailed guidance on.

(a) The format and contents of the request to conduct a clinical trail on a medicinal product for human use as well as the documentation to be submitted to support that request on the quality and manufacture of the investigational medicinal product, any toxicology and pharmacological tests, the protocol and clinical information on the investigational medicinal product including the investigator's brochure.

(b) The presentation and content of notifications of substantial proposed amendments to the protocol.

(c) The declaration of the end of the clinical trail. The Directive 2001/20/EC, the Directive, should be read in conjunction with this detailed guidance, commission Directive 2005/28/EC and other commission Directives and detailed guidance on the Directive as well as the member states implementing legistration.

Scope

This detailed direction is intended to provide advice on the application format and contents of the request to the competent authority (CA) in any EU Member state for.

- Authorization of a clinical trial on a medicinal product for human use;
- Notification of substantial proposed amendments; and
- Declaration of the end of the clinical trial.

Directive 2001/20/EC applies to all investigational medicinal products, including the following types of product.

- ❖ Chemical entities;
- ❖ Biotechnology products;
- ❖ Cell therapy products;
- ❖ Gene therapy products;
- ❖ Plasma derived products;
- ❖ Other extractive products;
- ❖ Immunological medicinal products (such as: vaccines, allergens,immune sera);
- ❖ Herbal medicinal products;
- ❖ Radio pharmaceutical products; and
- ❖ Homeopathic products.

This detailed guidance should be followed unless it is otherwise justifies in an application to the CA of the Member state in which trial will take place. NOTE:- 2001/20/EC doesn't apply to.

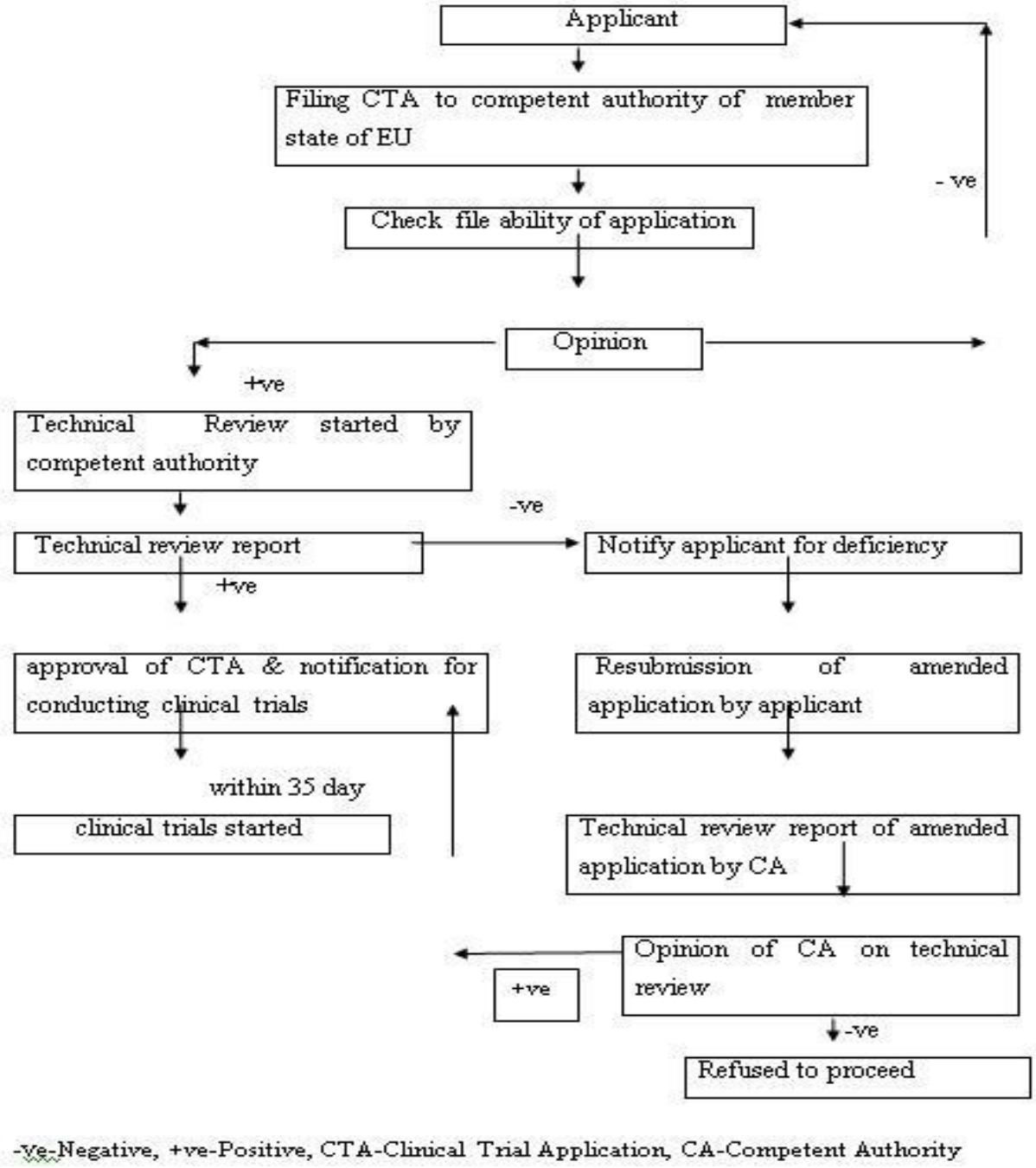
- ✘ Medical devices
- ✘ In vitro diagnostic medical devices
- ✘ Cosmetic product as defined in community legislation.
- ✘ Food as defined in community legistration.

Definition

The definitions of Directive 2001/20/EC are applicable. An authorization of clinical trial by the competent authority of member state will be a **Clinical Trail Authorization (CTA)** and will only valid for a clinical trial conducted in the member state. This authorization does not imply approval of the development programme of the tested IMP. Article 2(d) of the Directive DEFINES AN "Investigational medicinal product" as: " A pharmaceutical form of an active substance or placebo.

FORMAT AND CONTENT OF CLINICAL TRAIL APPLICATIONS

A. Request for a clinical trial authorization
B. Covering letter
C. Allocation of EudraCT number
D. Application form
E. Protocol
F. Investigator's Brochure
G. Investigational medicnal product (IMP) Related Data
H. Investigational Medicinal Product Dossier(IMPD)



-ve-Negative, +ve-Positive, CTA-Clinical Trial Application, CA-Competent Authority

Figure 2: Clinical Trial Authorization Process of EU.

4. SUMMARY AND CONCLUSION

Table 1: Diffrences between Investigational new drug application (IND) & Clinical trial authorization in Europe.

Investigational new drug application (IND)	Clinical trial authorization in Europe
FDA 1571 Table of contents Introductory statement General investigational plan Investigators brochure Protocols: study protocols investigator data facilities data IRB data CMC data Pharmacology and toxicology data Previous human experience Additional information If any part of the trail is to be conducted by a CRO, attach statement Name and title of person responsible for evaluating the safety of the drug	Application form Cover letter NA Investigational brochure Protocol study protocol(signed by sponsor and PI) investigator data(only some MS) facilities data (only some MS) EC data copy of opinion(if available) Investigational medicinal product dossier Quality data Pharamacology and toxicology data Previous human experience data Over all risk and benefit assessment If any part the trial is to be conducted by a CRO, attach statement and mention in cover letter, CRO representatives can sign on behalf of sponsors A simplified IMPD may be submitted in certain instances(eg:when a CTA has been approved by the respective regulartory authority) A number of additional items are required by some but not all of MS: subject related; protocol related; IMP related; facilities and staff related; finance related.

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