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REGULATORY REQUIREMENTS FOR FILING AN INVESTIGATIONAL NEW DRUG APPLICATION WITH FDA

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ABSTRACT

Prior to conduct of any clinical trial on human volunteers for any new investigational product (IP), there are specific regulatory requirements which are required to be fulfilled by the investigator and sponsor. An investigational new drug (IND) application should be filed with the Food and Drug Administration (FDA). It can be exempted, if it meets specific criteria of exemtion from IND. The filing of an IND mainly involves 3 parts viz., FDA form 1571, FDA form 1572, and FDA form 3674. After getting approval from FDA, the clinical study may be proceeded after 30 days. The study may not be started if it is on "clinical hold" or any further information is required by the FDA. This review article addresses briefly the process of filing an IND application.

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INTRODUCTION

Before the testing of any new drug especially on human volunteers it is mandatory to file in for permission from the FDA by filling an IND application. Various regulatory requirements are to be followed inorder to protect the human subject undergoing clinical trials. The investigation conducted is mandatory as it helps by informing about the safety and efficacy of that particular drug and also about its toxicity level in the human body, with reference from the USP. The US FDA is mainly responsible for the regulatory affairs of most of drugs and other products which is to undergo clinical trials or clinical study. Until the FDA approves for any particular clinical trial it is important to leave the work on hold till futher instructed, for legal and safety aspects. Also the clinical study must meet the requirements of the FDA, failing which there might be legal and financial implications on the research person and the institute supporting the research activity [1].

Initally, as a part of the regulatory process, it is necessary to notify the FDA that a particular drug reagent would be used for experimental basis. This notification is called an Investigational New Drug (IND) application. Filing of an IND application involves three important parts viz., FDA Form 1571, FDA Form 1572, and FDA Form 3674. Once it is approved by FDA, the study is initiated after 30 days. Any investigator, belonging from a pharmaceutical industry or other commercial sponsor, appointed for the clinical trial of a new drug must be a well trained and highly skilled medical person. If not then the investigator is considered to be a misfit for the addressing of the regulatory requirements of an IND application and is barred from performing the drug studies. Many of the IND applications submitted are noncommercial because of which many investigators considers the investigation mandatory and continues to perform the drug study by following the required regulatory rules. Here, the correct regulatory process and the steps involved in filing an IND application with FDA in an organised manner have been addressed for simplifying the drug study [1, 2].

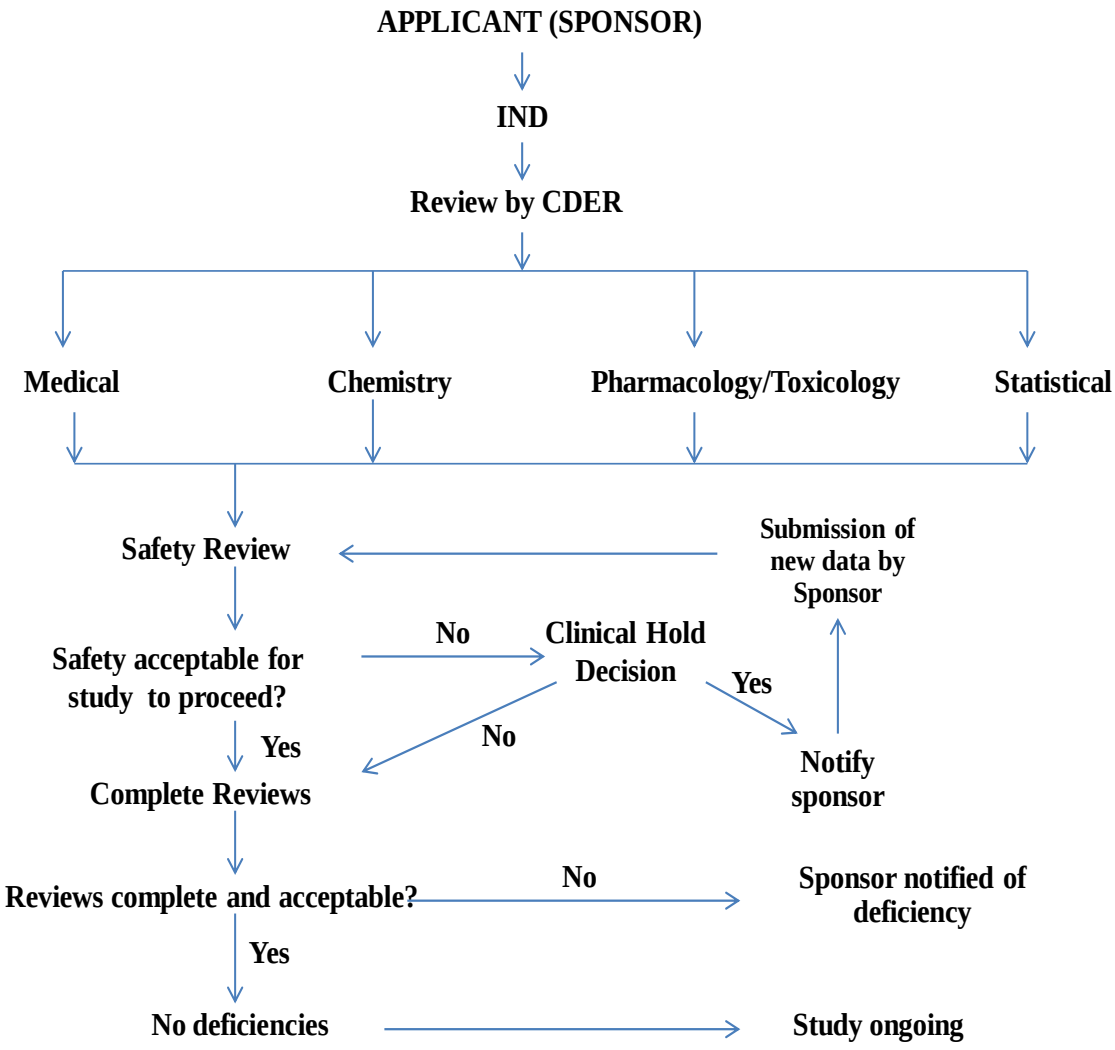

Fig. 1: SCHEMATIC REPRESENTATION OF AN IND REVIEW PROCESS.

Criteria for exemption of IND

FDA has provided three criteria of clinical investigation that are exempt from the IND requirements in part 312, provided the criteria for exemption are met [2]. During the clinical investigation the marketed drug is exempted from IND requirements if all the following criteria for an exemption are met:

- The drug is legally marketed in the United States.
- The marketed product were enquired and not reported to FDA when not required and it as well shows no significant changes in the labelled drug.
- Prescription drugs does not support significant changes for the need of advertising the drug.
- The investigation excludes the route of administration,dose, patient population and other factors that influences the risk factor.
- The investigation is carried out with the review compliance required by an IRB (21CFR part 56) and compliance required for informed consent (21CFR part 50).

Three criteria for exemption [2] of IND application:

- The drug product gets marketed in the United States legally: the investigator uses the drug of same dosage form, patient population as described in the label of the product, but if any changes need to be done for the marketed dosage form it should be done legally.
- The investigational drug's use increases or decreases the risk by approving the uses. FDA issued guidelines for clinical investigators helping them in studying cancer treatment, simulataneously giving the reference for clinical study of marketed drugs.
- A well controlled marketed drug intended to influence the labelling or promotion in significant ways to be conducted under an IND, similarly, studies of marketing drugs are being conducted by an entity.

Form 1571 of FDA

The IND initial application are triplicated (one original copy and two photocopies) and submitted by the form FDA 1571. The form IND 1571 involves all the applications mostly, commercial or research investigator only some excluding application for sponsor-investigator. In the IND form, several responses in the form 1571 are abbreviated, amended, omitted the comparision of the sponsor representing the pharmaceutical industry for the use of the FDA approved drug. The different phases of the study (section 8), IND number (section 6) remains blank for contact information,initial application (section 18 and 19) and section 10. The form 1571 should contain trade name, generic name, strength, dosage form, lot number if the marketed drug used without being modified. Nonapproved product should have pharmacological toxicological data, manufacturing information, human studies information is a must required [3, 4].

From 1572 of FDA

The form 1572 does not need to submit to FDA and FDA also not required the form to submit to the agency, but the information must be submitted to FDA under 21 CFR 312.23 (a) (6) (III) (b). In the form if any changes and updated the information it must be signed by an investigator [3]. This form 1572 consists the "Statement of Investigator". The FDA form 1572 contains the information about the safety requirement for specific sections of the FDA from 1571.

Form 3674 of FDA

Form 3674 involves amendment, supplements, resubmissions under §§ 505, 515, 520 (m), or 510 (k) of the Federal Food, Drug, and Cosmetic Act or § 351 of the Public Health Service Act. FDA Amendment Act of 2007 under the United States Public Law 110-85 Title VIII, Section 801,demands registration of Bapplicable clinical trials.All clinical investigator must get registered with the FDA for phase 1 study,which needs to provide all the trial information, through the US National Library of Medicine at the National Institutes of Health which contain proper clinicaltrail.gov identifiers (NCT number) involved in the registration and with this registration account the sponser-investigator have their entity [3].

Sections in the form are involved are:

1. Sponsor/applicant name.
2. Drug information/product monograph.
3. IND/NDA/ANDA/BLA/PMA/HDE/PDP numbers.
4. Certificate copy.
5. National clinical trial numbers registered with clinical trial.gov.
6. Name, tittle of the person authorized to sign.
7. The authorized persons full name, address, telephone number should be provided.
8. Certification signature and signature of the authorized person/ sponsor.

Submission of an IND

In an IND submission, the contact should be clear and complete as it plays a vital role. It should be taken care of that the address matches exactly with that in FDA form 1571 and FDA form 1572. The sequential identifying serial number should be present in IND which will be "0000" for initial submission. The submission of IND should be done in triplicate (one original and two copies) [4].

IND submission address	
For drug	Center for Drug Evaluation and Research Central Document Room 5901-B Ammendale Rd, Beltsville, MD 20705-1266
For therapeutic biological product	Center for Drug Evaluation and Research Therapeutic Biological Products Document Room 5901-B Ammendale Rd Beltsville, MD 20705-1266
For biological products	Center for Biologics Evaluation and Research for a Biological Product: HFM-99, Room 200N 1401 Rockville Pike, Rockville, MD 20852-1448

Reply of clinical hold

A clinical hold can be differentiate either a complete or partial clinical hold which requires additional reviewed data and after it gets reciewed from the sponsor, then the work is proceeded. If the agency is complied with the clonical hold it does not need to wait for FDA approval. When FDA contacts the sponsor-investigator clinical hold rises and the study continues and describes "clinical hold complete respose" as heading [4].

Amendments to protocol (21 CFR, 312.30)

IND affects the protocol amendment which also ensures about the investigation, maintains according to the protocol in the application and it also needs to be submitted after the amendment and there are certain conditions for filling up the new protocol, change in the protocol [2]. Alteration in the amendment included:

- Any increase or decrease in the exposure of the drug because of the way of the dosing.
- Criteria for inclusion and exclusion.
- Any changes reported during the monitoring the safety.
- The protocol amendment needs to get approval by the IRB. In any case of any elimination of the subject,IRB and FDA should be informed.

Amendment to information (21 CFR, 312.31)

In the amendment, the sponsor should report since it is an important information for IND but these amendment, safety reports are not included as the part of essentialites, the required important details are the :

- Toxicological and chemical information.
- Report of the irregular or failed clnical investigation.

Safety report (21CFR 31.32)

Safety report condition includes:

- Adverse event which is considered as life threatening.
- A serious occurrence of adverse event.
- Reaction suspected to be adverse event.
- An unexpected toward adverse reaction.

The sponsor-investigator are responsible to be inform FDA about the safety report, prepared via FDA form 3500A in described format named as "IND Safety Report". If any life-threatening or death event occur, the sponsor-investigator should report to FDA within 7 calendar days [2].

Annual report (21CFR 31.33)

The progressive report involving the investigational drug, which should be filled and submitted within 60 days of the annual report of IND by the sponsor-investigator. The investigator should submit all the past and present progress report which will include the total number of subject participated or dropped out of the study, date, work completion details and the result, also any significant changes in the pharmacology, toxicology, coming year plan should also be submitted [3].

Withdrawal of IND

A sponsor/s has in his/their right to initiate withdrawal of an IND, if the studies are complete or it is not showing any effectiveness. If any animal studies suggest potential and life threatening adverse drug reactions to human subjects, it should be reported quickly. When an IND is withdrawn because of safety issues, the FDA, all the investigators, reviewing IRB and also all drug stocks accounted for should be notified by the sponsor-investigator, and the notification must be provided with a report of the reasons. Serious and bizarre adverse reactions must be reported as quickly as possible. The safety issues for which an IND can be withdrawn include death, birth defect, life threatening adverse drug reactions, persistent disability [2, 3].

Inactivation of IND

A clinical study may be placed on an "inactive status" by the FDA or the sponsor when sufficient subjects have not been enrolled for more than 2 years, or it has been kept on hold for more than a year. But it is not considered as "discontinued" or "terminated", as it is not the final status of the IND. Delays in the implementation of clinical studies, or failure in responding to FDA inquires may also result in the inactivation of the IND. Submission of annual reports on an inactive IND is not required. But at the request of the sponsor, the inactive status of an IND can be rendered active by submission of a protocol amendment. If an IND remains inactivated for more than 5 years, it is terminated [2, 4].

Termination of IND

Termination of an IND is initiated by the FDA. This is generally done in cooperation with the sponsors, but it is not necessary, i.e. it is unilateral. But the most important thing is an IND cannot be terminated without sending a pre-termination letter. The sponsor is allowed a response to FDA-initiated termination, but the time given is usually very limited. In case of "Terminated-EUAs (Emergency Use Authorizations)", it means that the emergency has been terminated, but not EUA, i.e., if necessary conditions arise again, an experimental drug can be used in emergency conditions. If an IND has been terminated because of potential immediate danger to human subjects, FDA can reinstate the IND, and this is the only circumstance where IND can be reinstated[5-7].

CONCLUSION

Following the regulatory requirements is considerd an essential part of clinical research. The process may seem hectic but by filling an IND the sponsor-investigator, working with the FDA, tends to meet with the regulatory obligations and by following all the requirements, the research work becomes easy to continue without any delays. The FDA can also contact the sponsor-investigator who is responsible of filling the IND. All necessary guidance of filling an IND application are given in the Web. There should not be any hesitation while filing the IND application as it tends to simplifies the clinical drug research. In the days to come, the whole process can be implemented online so as to ease the IND filing process. This will also reduce the workload and will enhance the efficiency and reduce the time.

Abbreviations

ANDA: Abbreviated New Drug Application
BLA: Biologic License Application
CFR: Code of Federal Regulations
FDA: Food and Drug Administration
HDE: Humanitarian Device Exemption
IND: Investigational New Drug
IP: Investigational Product
NDA: New Drug Application
NCT: National Clinical Trial
PMA: Premarket Approval
PDP: Plasma Display Panel
USP: United States Pharmacopoeia

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