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

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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.*

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INTRODUCTION:

Current Federal law requires that a drug be the subject of an approved marketing application before it is transported or distributed across state lines. Because a sponsor will probably want to ship the investigational drug to clinical investigators in many states, it must seek an exemption from that legal requirement. The IND is the means through which the sponsor technically obtains this exemption from the FDA.

During a new drug's early preclinical development, the sponsor's primary goal is to determine if the product is reasonably safe for initial use in humans, and if the compound exhibits pharmacological activity that justifies commercial development. When a product is identified as a viable candidate for further development, the sponsor then focuses on collecting the data and information necessary to establish that the product will not expose humans to unreasonable risks when used in limited, early-stage clinical studies.

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 diagnostic or therapeutic potential in humans. At that point, the molecule changes 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.

There are three IND types:

- **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.
- **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.
- **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.

There are two IND categories [3-5]:

- Commercial
- Research (non-commercial)

The IND application must contain information in three broad areas:

- Animal Pharmacology and Toxicology Studies - Preclinical data to permit an assessment as to whether the product is reasonably safe for initial testing in humans. Also included are any previous experience with the drug in humans (often foreign use).
- Manufacturing Information - Information pertaining to the composition, manufacturer, stability, and controls used for manufacturing the drug substance and the drug product. This information is assessed to ensure that the company can adequately produce and supply consistent batches of the drug.
- Clinical Protocols and Investigator Information - Detailed protocols for proposed clinical studies to assess whether the initial-phase trials will expose subjects to unnecessary risks. Also, information on the qualifications of clinical investigators--professionals (generally physicians) who oversee the administration of the experimental compound--to assess whether they are qualified to fulfill their clinical trial duties. Finally, commitments to obtain informed consent from the research subjects, to obtain review of the study by an institutional review board (IRB), and to adhere to the investigational new drug regulations.

Once the IND is submitted, the sponsor must wait 30 calendar days before initiating any clinical trials. During this time, FDA has an opportunity to review the IND for safety to assure that research subjects will not be subjected to unreasonable risk.

Resources for IND Applications:

The following resources include the legal requirements of an IND application, assistance from CDER to help you meet those requirements, and internal IND review principles, policies and procedures.

Pre-IND Consultation Program:

CDER's Pre-Investigational New Drug Application (IND) Consultation Program fosters early communications between sponsors and new drug

review divisions to provide guidance on the data necessary to warrant IND submission. The review divisions are organized generally along therapeutic class.

GUIDANCE DOCUMENTS FOR INDs [5-7]:

Guidance documents represent the Agency's current thinking on a particular subject. These documents provide FDA review staff and applicants/sponsors with guidelines to the processing, content, and evaluation/approval of applications and also to the design, production, manufacturing, and testing of regulated products. They also establish policies intended to achieve consistency in the Agency's regulatory approach and establish inspection and enforcement procedures.

Because guidances are not regulations or laws, they are not enforceable, either through administrative actions or through the courts. An alternative approach may be used if it satisfies the requirements of the applicable statute, regulations, or both. For information on a specific guidance document, please contact the originating office. To find guidance documents to help prepare INDs, go to Guidances (Drugs) and use "investigational" in the search box.

LAWS, REGULATIONS, POLICIES AND PROCEDURES IN INDs [7-9]:

The mission of FDA is to enforce laws enacted by the U.S. Congress and regulations established by the Agency to protect the consumer's health, safety, and pocketbook. The Federal Food, Drug, and Cosmetic Act is the basic food and drug law of the U.S. The law is intended to assure consumers that foods are pure and wholesome, safe to eat, and produced under sanitary conditions; that drugs and devices are safe and effective for their intended uses; that cosmetics are safe and made from appropriate ingredients; and that all labeling and packaging is truthful, informative, and not deceptive. While advanced GPS systems and the advent of Big Data analytics are negating some of their advantages, early birds are still capturing worms at a good clip. We've heard this slogan since childhood. For those of you planning to implement eCTD, the early bird's experience rings true.

Many people erroneously believe that your first eCTD submission is restricted to a major milestone application – Investigational New Drug (IND) application, Biologics License Application (BLA) or New Drug Application (NDA). That's simply not the case. It's 100% possible to file pre-NDA meeting requests, meeting packages and meeting minutes via eCTD in advance of the original NDA submission.

The first step in the process is asking the FDA to assign an application number. It's a straightforward process that only requires an exchange of emails. Typically sponsors hear back in less than a week. Complete instructions for Requesting a Pre-Assigned Application Number are available online at the FDA.

Once the FDA replies with the application number, you're ready to go. Planning to submit a meeting request in eCTD format is an excellent opportunity to establish a line of communication with your assigned FDA Regulatory Project Manager (RPM).

Early birds who take initiative and file pre-milestone submissions in eCTD format have extra time to get acquainted with the intricacies of the standard and an additional opportunity to learn. There is nothing worse than playing "catch up", especially with the eCTD mandate looming.

IND maintenance:

Once an IND is in effect, there are three primary maintenance activities and responsibilities for Sponsors: amendments, safety reporting, and annual reports.

Amendments:

The IND is often amended throughout its lifecycle. There are two types of IND amendments: Protocol Amendments and Information Amendments. Protocol amendments are to ensure that the clinical investigations are conducted according to the protocols included in the application (21 CFR 312.30). Examples of protocol amendments include:

New protocol: As discussed above, an IND may contain multiple studies of the same investigational drug in the same patient population or indication. A protocol for a new clinical trial may be submitted to an IND that has cleared (i.e., an open IND). New studies may begin soon after the protocol has been submitted to the FDA and has been approved by the IRB. The IND submission should include a copy of the new protocol and a brief description of the most clinically significant differences from previous protocols.

Change in existing protocol: Sponsors must submit a protocol amendment to describe any changes in protocols that significantly affect the safety of subjects, the scope of the investigation, or the scientific quality of the study. A protocol change intended to eliminate an apparent safety hazard to subjects may be implemented immediately, provided that the FDA and the IRB are subsequently notified.

The IND submission should include a brief description of the changes and a reference to the submission that contained the original protocol.

New investigator: The FDA should be notified within 30 days of the addition of a new investigator to conduct a study previously submitted to the IND (21 CFR 312.23).[19] The submission should include the investigator's name, qualifications, reference to the previously submitted protocol, and other additional information.

Information amendments are any amendments to information essential to the investigational drug and can be categorized as relating to chemistry/microbiology, pharmacology/toxicology, clinical, statistics, or clinical pharmacology (21 CFR 312.31).[19] These are submitted to the FDA as necessary but generally no more frequently than every 30 days. The submission should include a statement of the nature and purpose of the amendment.

Safety reporting:
Sponsors must notify HAs and all participating investigators of potential serious risks associated with the use of the investigational drug based on prompt review of all relevant safety information (21 CFR 312.32).[19] These include serious and unexpected suspected adverse reactions, findings from other studies, findings from animal or *in vitro* testing, or increased rate of occurrence of serious suspected adverse reactions. Each safety report, in narrative format, should be submitted as soon as possible but no later than 15 calendar days following the Sponsor's initial receipt of the information. Any unexpected fatal or life-threatening suspected adverse reaction reports should be reported as soon as possible but no later than 7 calendar days following the Sponsor's initial receipt of the information. If applicable, relevant follow-up information to an initial safety report must be submitted as a Follow-up Safety Report as well.

Annual reports:
Sponsors are expected to submit a brief report of the progress of the studies conducted under their IND application annually within 60 days of the anniversary date that the IND went into effect (21 CFR 312.33). This annual update and summary is intended to inform HAs of the progress of a drug's development program during the past year and identifies any potential issues or safety concerns in the program (including a summary of any issues beyond routine safety reporting), The Sponsor may report this information as outlined in the inset or use the Development Safety Update Report format as outlined in ICH E2F with prior approval from the FDA.

CLINICAL TRIAL AUTHORIZATION (European countries) [10-15]:

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 being tested or used as a reference in a clinical trial, including products already with a marketing authorization but used or assembled (formulated or packaged) i a way different from the authorised form, or whwn used for an unauthorised indication, or when used to gain further information about the authorized form."

Some clinical trial protocols require the use of non-investigational medicinal products (NIMPS) such as support or escape medication for preventive, diagnostic or thearapeutic reasons and/ or needed to ensure that adequate medical care is provided for the subject. They also be used in accordance with the protocol to induce a physiological response. These products do not fall within the definition of investigational medicinal products in the Directive and may be supplied by the sponsor. The sponsor should provide details of these NIMPs an their proposed use in the trial protocol and ensure that they are of the necessary quality of human use after seeking advice and/or involvement of a qualified person where appropriate.

- EMEA has a limited role in clinical trials.
- EMA doesn't review (or) approve clinical trials.
- Maintains EUDRACT(European clinical trials) data base.
- Co-ordinate pharmacovigilance on behalf of EU (eudravigilance).
- Ensures link between EUDRACT and eudravigilance.

CONCLUSION:

Table 1: Comparison of US-IND and EU-CTA

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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