

Clinical trial applications in the EU and US

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Overview of the presentation

- ← This presentation will focus on the US system
- ← Comparison between the EU and the US system

Investigational New Drug Application (IND)

- ← In the US an approved IND is necessary before starting a clinical trial
- ← There are two main types of INDs
 - ▶ Commercial INDs
 - ▶ Non-commercial INDs

Commercial IND

- ← An IND for which the sponsor is usually either a corporate entity or one of the institutes of the National Institutes of Health (NIH)
- ← In addition, the FDA may designate other INDs as *commercial* if it is clear the sponsor intends the product to be commercialized at a later date

Non-Commercial IND

← There are three types of non-commercial INDs

- ▶ Investigator IND
- ▶ Emergency Use IND
- ▶ Treatment IND

Investigator IND

← Submitted by a physician who both initiates and conducts an investigation, and under whose immediate direction the investigational drug is administered or dispensed

← Applies to

- ▶ Unapproved drugs
- ▶ Approved products 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
- ← 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 used to make promising new drugs available to desperately ill patients as early in the drug development process as possible
- ← FDA will permit an investigational drug to be used under a treatment IND if
 - ▶ there is preliminary evidence of drug efficacy
 - ▶ the drug is intended to treat a serious or life-threatening disease, or if there is no comparable alternative drug or therapy available to treat that stage of the disease in the intended patient population
 - ▶ in addition, these patients are not eligible to be in the definitive clinical trials, which must be well underway, if not almost finished

Content of the IND

← The IND application must contain information on:

- ▶ Animal pharmacology and toxicology studies
- ▶ Chemistry, Manufacturing, and Control information
- ▶ Previous clinical experience (if available)
- ▶ Clinical protocols and investigator information

Preclinical and quality data

← Animal pharmacology and toxicology studies

- ▶ Preclinical data to permit an assessment as to whether the product is reasonably safe for initial testing in humans

← Chemistry, Manufacturing, and Control (CMC) information

- ▶ Information pertaining to the composition, manufacturer, stability, and controls used for manufacturing the drug substance and the drug product

Clinical data

← Any previous experience with the drug in humans (often foreign use)

Clinical protocols and investigator information

← Detailed protocols for proposed clinical studies

- ▶ FDA reviewers provide drug sponsors with **greater freedom during Phase I**, as long as the investigations do not expose participants to undue risks
- ▶ In evaluating Phase II and III investigations, however, FDA reviewers also must ensure that these studies are of sufficient **scientific quality** to be capable of yielding data that can support marketing approval

Clinical protocols and investigator information (2)

- ← Information on the qualifications of clinical investigators
- ← 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**

Guidelines for the IND

← Guidance documents to help prepare INDs include

- ▶ Content and Format of IND's for Phase I studies (with separate Q and A document)
- ▶ Immunotoxicology Evaluation of Investigational New Drugs
- ▶ Guideline for Drug Master Files

Source: www.fda.gov

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Content and format of IND's for Phase I studies (1)

← **The amount of CMC information needed will depend on**

- ▶ Phase of the investigation
- ▶ Proposed duration of the investigation
- ▶ Dosage form
- ▶ Amount of information otherwise available

← **The emphasis in an initial Phase 1 CMC submission should generally be placed on providing information that will allow evaluation of the safety of subjects in the proposed study**

Content and format of IND's for Phase I studies (2)

← Reasons for concern may include

- ▶ unknown or impure components
- ▶ chemical structures of known or highly likely toxicity
- ▶ a product that cannot remain chemically stable throughout the testing program proposed
- ▶ impurity profile indicative of a potential health hazard or an impurity profile insufficiently defined
- ▶ a poorly characterized master or working cell bank (biotech products)

Content and format of IND's for Phase I studies (3)

- ← For pre-clinical studies to be useful in assuring the safety of human studies, sponsors should be able to relate the drug product being proposed for use in a clinical study to the drug product used in the animal toxicology studies
- ← The regulations require a full tabulation of data from each non-clinical toxicology study suitable for detailed review
- ← Most sponsors provide detailed reports of each study

Content and format of IND's for Phase I studies (4)

- ← If final individual study reports are not available at the time of IND submission, an integrated summary report based on the unaudited draft toxicological reports may be submitted
- ← Full toxicology individual study reports should be available to FDA, as final, fully quality-assured documents within 120 days after receipt of the final application

Guideline for Drug Master File (DMFs)

← In the US there are five different types of DMF's (not only for drug substance)

- ▶ *Type I:* Manufacturing site, facilities, operating procedures, and personnel
- ▶ *Type II:* Drug substance, drug substance intermediate, and material used in their preparation, or drug product
- ▶ *Type III:* Packaging material
- ▶ *Type IV:* Excipient, colorant, flavor, essence, or material used in their preparation
- ▶ *Type V:* FDA accepted reference information (miscellaneous information, discouraged)

Pre-IND meeting (1)

← Pre-IND meetings are very useful

← Request must be submitted in writing and should include

- ▶ Description of the product
- ▶ Description of clinical indication and approach
- ▶ Identification of purpose, objectives, and draft of specific questions
- ▶ Suggested dates and times for the meeting

Pre-IND meeting (2)

- ← FDA will respond to request within 14 days
- ← Pre-IND meetings are scheduled within 60 days from receipt of request
- ← Briefing document must be submitted 4 weeks prior to the meeting
- ← After the meeting the FDA issues official minutes within 30 days

Briefing document

- ← Pre-clinical data
- ← Product manufacturing scheme
- ← Data on product characterization (biotech)
- ← Proposed specifications
- ← Clinical protocol
- ← Specific questions, grouped by discipline

IND process

- ← Once the first IND is submitted, the sponsor must wait **30 calendar days before initiating any clinical trials**
- ← In case the FDA does not believe, or cannot confirm, that the study can be conducted without unreasonable risk to the subjects/patients the study will be subject to a so-called **“clinical hold”**

Clinical hold

- ← The FDA may either delay the start of an early-phase trial on the basis of information submitted in the IND, or stop an ongoing study based on a review of newly submitted clinical protocols, safety reports, protocol amendments, or other information
- ← When a clinical hold is issued, the sponsor must address the issue that is the basis of the hold before the order is removed

Comparison between the EU and the US system (1)

← Ethics Committee submissions

- ▶ Submission to all sites in the US
- ▶ One single Ethics Committee opinion per Member State in the EU on a proposed multi-center trial

← Ethics Committees require similar information in both regions

← Ethics Committee review times

- ▶ For Phase I trials (healthy volunteers) in practice slightly faster in some EU countries (14 -21 days) compared to the US (around 30 days)
- ▶ For all other trials similar in both regions (between 30 and 60 days)
- ▶ Review time depends on each EC procedures with a maximum timing set up to 30 to 60 days depending on national regulation in EU
- ▶ Application occurs usually 1 to 4 weeks before meeting, and written positive opinion within 1 to 7 days in EU

Comparison between the EU and the US system (2)

← Regulatory Authority submissions

▶ US

- Pre-IND meeting possible
- Single submission
- All clinical trials for a specific product filed to the same IND

▶ EU

- No pre-IND meeting foreseen in legislation
- Submission to the Competent Authority of each country involved in the trial
- New Clinical Trial Application needed for each trial and each country in the EU

← Information required

- ▶ In the US extensive non-clinical toxicology data is required with (draft) study reports included in the submission
- ▶ In the EU summaries of the scientific information are required

Comparison between the EU and the US system (3)

←Regulatory Authority review times

- ▶ For the US : 30 days for the first submission, no delay for further submissions and no written approval
- ▶ For the EU for early development
 - UK: 21 days with a written approval
 - France: 15-30 days with or without a written approval
 - Germany: 30 days without a written approval
 - NL: depends on EC timelines
 - Belgium: 15-28 days
 - Sweden: 30 days
 - maximum 60 days in all other countries
- ▶ In the EU extension of the review time to 90 days is possible for gene therapy or somatic cell therapy or medicinal products containing genetically modified organisms
- ▶ **Amendments** are usually reviewed in the US within 30 days, in the EU within 35 days or shorter for early development studies (14 days)

Comparison between the EU and the US system (4)

← Annual safety reports

- ▶ In the US an update of all new information is required on all studies whatever their location
- ▶ In the EU the Annual Report contains details of safety in the specific clinical trial in the EU

← In both regions the sponsor (or legal representative) must be established in the respective region

← Pharmacovigilance reporting requirements are similar

← Manufacturing authorization

- ▶ Required in the EU for manufacture or import of clinical trial supplies, but not in the US

← Batch release by the Qualified Person is only required in the EU

Potential differences in assessment in the EU

- ← So in principle the differences between the systems are not that big
- ← However, the US has clear, detailed guidance documents regarding the content of the application
- ← In the EU this guidance is missing and there is the risk of different interpretations of the requirements by different Competent Authorities
- ← CPMP has issued concept paper on the development of a guideline on the requirements to the quality part of the IMPD (CPMP/QWP/1543/04)

CPMP view (1)

- ← Clinical trials will often be designed as multi-center studies, potentially involving different Member States
- ← To ensure transparency and predictability, it is of great importance to harmonize requirements
- ← Care has to be taken to clearly differentiate between the requirements for a clinical trial and a marketing authorization dossier

CPMP view (2)

← Requirements for investigational medicinal products should focus on the risk aspects and should consider

- ▶ Nature of the product
- ▶ State of development/clinical phase
- ▶ Patient population
- ▶ Nature and severity of the illness
- ▶ Type and duration of the clinical trial

Summary

US

- ▶ Clear, validated and efficient process
- ▶ May be filed for several studies. Then, only updates are needed
- ▶ 30 days delay (whatever the phase) for first application, no delay for further applications

EU

- ▶ Needs for more harmonization and more guidance
- ▶ 1 CTA / study / country
- ▶ 60 days maximum
- ▶ 30 days or less for early studies will still allow competitiveness with the US if effective
- ▶ Experience of the first 9 months seems encouraging and successful as no major delays encountered