Managing Multi-Jurisdictional Legal and Regulatory Risks in Clinical Trials, Brussels - C5's Clinical Trials

EMEA Guidelines on Investigational Medicinal Products

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15 April, 2008

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INTRODUCTION

- Guidelines
- Overview of Clinical Trials
- Medicinal Products
- Investigational Medicinal Products
- Safety
- Protocol Design
- Population
- Case Studies
- Legal Issues
- Risk Management Measures

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Guidelines

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GUIDELINES

- **EMEA Guidelines on Investigational Medicinal Products:**
  - Ambiguous
  - Misleading
  - Can lead to misinterpretation and potential litigation
  - Usually must conduct a range of tests. The Guidelines indicate the studies which should be conducted – For example:
    - Full toxicological package;
    - Full pharmacodynamics package; and
    - Full pharmacokinetics package.

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GUIDELINES

"Guidelines on **Strategies to Identify and Mitigate Risks** for **First-in-Human** Clinical Trials with **Investigational Medicinal Products**"

(http://www.emea.europa.eu/pdfs/human/swp/2836707enfin.pdf.)

- Released following the *Northwick* Case, which involved six previously healthy volunteers that took part in a trial for the drug TGN1412. The drug was **being tested in humans for the first time**.

- **Investigational Medicinal Products** – Classification of all Investigational Medicinal Products with a potential for high risk in first-in-man clinical trials.

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GUIDELINES

- **The Guidelines**:
  - Are intended to **assist sponsors** in moving from non clinical to early clinical trials;
  - Provide a new classification of **Investigational Medicinal Products**;
  - Stipulate that **Quality and Safety** are of paramount importance;
  - Outline **non clinical testing strategies and design** for first-in-man clinical trials.

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GUIDELINES

- **The Guidelines:**
  - Cover the **first administration of a single dose** of an Investigational Medicinal Product as well as the initial single ascending dose phase;
  - **Are not binding unless incorporated into a contractual agreement**, such as a Clinical Trials Agreement with the sponsor of the clinical trial;
  - Are intended to allow accurate predictions of any **serious adverse reaction** to the Investigational Medicinal Product being tested;
  - Advise on **special precautions to minimise risks** when making the transition from non clinical to clinical testing;
  - Stipulate that any **risks** should be **thoroughly identified** prior to the clinical trial taking place to avoid a recurrence of the *Northwick* case.

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GUIDELINES

- **The Guidelines:**
  - Are to be read in conjunction with the following:
    - Non Clinical Safety Studies For The Conduct Of Human Clinical Trials For Pharmaceuticals (ICH M3), (CPMP/ICH/286/95);
    - Pre Clinical Safety Evaluation Of Biotechnology-Derived Pharmaceuticals (ICH S6), (CPMP/ICH/302/95);
    - Good Manufacturing Practice: Annexe 13: Manufacture Of Investigational Medicinal Products; and
    - Good Clinical Practice (ICH E6), (CPMP/ICH/135/95).

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Overview of Clinical Testing

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CLINICAL TESTING

- Directive 2001/20/EC concerns clinical trials.

- Clinical testing is the scientific comparison between a new medicinal product and a placebo, or an existing medicinal product traditionally used to treat a particular illness.

- Directive 2001/20/EC defines clinical trials as:

  "*Any investigation in human subjects intended to discover or verify the clinical, pharmacological and/or other pharmacodynamic effects of one or more investigational medicinal product(s), and/or to identify any adverse reactions to one or more investigational medicinal product(s) and/or to study absorption, distribution, metabolism and excretion of one or more investigational medicinal product(s) with the object of ascertaining its (their) safety and/or efficacy*".

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CLINICAL TESTING

- **Clinical Testing Phases**:
  - The **pre-trial study**: Studies involving animal populations.
  - **Phase 0**: Is the first-in-human study which involves a dose too low for any therapeutic effect and is tested on a small number of subjects.
  - **Phase 1**: A larger scale study which seeks to establish any effects of the medicinal product on humans, usually tested on less than 100 healthy individuals.
  - **Phase 2**: If Phase 1 is successful, a larger group, usually less than 300 will be tested to see how well the medicinal product works.
  - **Phase 3**: If Phase 2 is successful, an even larger group 3000+ (Depending on the **medicinal product** being tested) will be tested with the intention of establishing definitively how well the drug works in comparison with placebos and existing medication.

Risks?

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CLINICAL TESTING: RISKS

- **Risks:**
  - The type of medicinal product being tested;
  - The range and severity of likely effects of the medicinal product being tested;
  - The health of the population chosen;
  - The diversity of the population chosen; and
  - Failure to make a full disclosure in the investigative brochure.

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CLINICAL TESTING: RISKS

- **Risks Management:**
  - **Research** into the medicinal product being tested should be carried out (Including, where necessary, appropriate cross species toxicology testing).
  - **Screening** of the chosen population will identify subjects which may pose a greater risk during the clinical trial.
  - Risks can be further **minimised** during the **calculation of the first dose** to be given (s 4.3.6).
  - Usually the first dose is calculated using the **No Observed Adverse Effect Level** (**NOAEL**) system. This system is based on safety studies carried out in the relevant animal species.

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CLINICAL TESTING: RISKS

- The **Minimal Anticipated Biological Effect Level** (**MABEL**) is the anticipated dose level leading to a minimal biological effect in humans and should take into account the following safety factors:
  - The novelty of the active substance in the medicinal product being tested;
  - The biological potency of the active substance; and
  - The mode of action of the active substance.
- Drugs should be **administered slowly** (Even perhaps over several hours).
- Volunteers in the clinical trial should be very **carefully observed**.

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What are Medicinal Products?

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MEDICINAL PRODUCTS

- Article 1 of Directive 2001/83/EC *as amended* defines a "**Medicinal Product**" as:
  - "Any substance or combination of substances presented **as having properties** for treating or preventing disease in human beings; or
  - Any substance or combination of substances which may be **used in or** administered to human beings **either** with a view to restoring, correcting or modifying physiological functions **by exerting a pharmacological, immunological or metabolic action, or to making a medical diagnosis.**"

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MEDICINAL PRODUCTS

- A product is medicinal if it falls within **either of those definitions** (European Court of Justice *Upjohn* 1989 C-1 12/897).
- European Community legislation is **not fully harmonised** and a medicinal product in one EU country maybe a classified as a food in another state.

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INVESTIGATIONAL MEDICINAL PRODUCTS

- Definition:
  - Investigational medicinal products are products which have a **potential high risk of adverse reaction in first-in-man administration**.

- **Clinical Requirements**: (See s.4.1 of the Guidelines)
  - **Investigational** Medicinal Products are medicinal products about which concerns may arise (from knowledge or lack thereof) regarding the following:
    - The **mode of action** of the drug in question
    - The **nature of the target**
    - The **relevance of suitable animal models**

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INVESTIGATIONAL MEDICINAL PRODUCTS

- **The Mode of Action**:
  - Novelty, plausibility and extent of current knowledge in the relevant area needs to be considered.
  - Nature and intensity of the effect of the **active substance** of the **target** needs to be assessed.
  - **Type of dose response** should be evaluated (for example: linear, non-linear, u-shaped, bell shaped etc).
  - Any compounds with **related biological effect**?

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INVESTIGATIONAL MEDICINAL PRODUCTS

- **The Nature of the Target**:
  - The nature of the target itself might impact on the risk, irrespective of the mode of action.
  - If there is limited knowledge on the target, such as information relating to structure, tissue distribution, cell specificity etc, then there is an inherent higher risk which will need to be assessed before the trials commence.

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INVESTIGATIONAL MEDICINAL PRODUCTS

- **Relevance of Animal Models**:
  - The reliability of the target species used for **non-clinical toxicology** testing should be assessed.
  - It is important that the comparison includes functional data.
  - If there is only limited relevance relating to the animal models, there is a greater chance that the medicinal product will be classified as an investigational medicinal product.

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INVESTIGATIONAL MEDICINAL PRODUCTS

- **Quality**
  - **Characterisation**: The active substance and the drug itself needs to be sufficiently characterised.
    - **Determination of safe starting dose**: The strength and potency of the product (For example in *in vivo* activity) has to be considered when determining the safe starting dose.
    - Extensive validation of **non clinical data** should be carried out.
    - Correct **doses** are paramount.

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INVESTIGATIONAL MEDICINAL PRODUCTS

- **Non Clinical Requirements** (s.4.3)
  - **Pharmacodynamics**
    - Mode of action
    - Identify most relevant animal model
  - **Pharmacokinetics**
    - Standard absorption, distribution, metabolism and elimination (ADME)
  - **Demonstration of Relevance of the Animal Model**
    - Comparison of pharmacodynamics
    - Comparison of pharmacokinetics
    - Cross reactivity studies using human and animals

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INVESTIGATIONAL MEDICINAL PRODUCTS

- **Non Clinical Requirements** (s.4.3)
  - **Toxicology**
    - Toxicokinetics
    - Pharmacodynamic endpoints
  - **No Observed Adverse Effect Level (NOAEL) system**
    - First dose
    - Safety factors to reduce dosage
  - Investigational Medicinal Products, the **Minimal Anticipated Biological Effect Level (MABEL)** system should be used.
    - Use of all *in vitro* and *in vivo* information from pharmacodynamics and pharmacokinetic data
    - PK/PD modelling approach
    - If different estimation of dosage, the lowest value should be used

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INVESTIGATIONAL MEDICINAL PRODUCTS

- **Non Clinical Requirements** (s 4.3)
  - **Doses with cohorts**
    - Sequential dose administration with each cohort
    - Adequate observation between administrations
  - **Further cohorts**
    - Previous results from first cohort must be considered before administering the first dose
    - Compare data between cohorts
    - Compare observed responses from anticipated responses
    - Only administer after all first cohorts are treated and the data/results have been reviewed
  - **Dose Escalation Scheme**
    - Shape of dose response curve from clinical studies
    - Dose toxicity
    - PK/PD modelling approach
    - If different estimation of dosage, use the lowest value

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INVESTIGATIONAL MEDICINAL PRODUCTS

- Where Investigational Medicinal Products are to be tested the following should be considered:
  - The availability of **emergency medical aid**;
  - The availability of staff with **detailed knowledge** of the medicinal product being tested; and
  - The availability of **suitable medical facilities** (Such facilities should be suitably equipped for studying the effects of the medicinal product being tested).

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Protocol Design

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PROTOCOL DESIGN

- **Protocol Design**
  - The process by which the stages of testing in a trial are established. The following should be considered:
    - **Properties** of the medicinal product being tested
    - **Nature** of the treatment
    - **Comparators or placebos** to be used
    - **Patient population**
    - Setting in which the trial is to take place

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PROTOCOL DESIGN

- **Legal requirements** when designing a protocol for a trial?
  - Research Governance Framework for Health and Social Care
  - The Medicine for Human Use (Clinical Trials) Regulations 2004
  - International Conference on Harmonisation (ICH) / World Health Organisation Good Clinical Practice standards

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PROTOCOL DESIGN

- The following safety considerations should be taken into account:
  - The **safety parameters of the trial should be established** in conjunction with the methods for timing, assessing, recording and analysing those safety parameters.
  - Any potentially serious adverse events expected to be possible outcomes of the trial should be defined (**fatal reactions/cascades**).
  - A procedure that should be followed in the event that a serious adverse event occurs should be drawn up.
  - The **responsibilities of specific team members** should be defined.

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PROTOCOL DESIGN

- **Identifying Risks**
  - In order to identify risks associated with the trial of an Investigational Medicinal Product **several key aspects of the trial design should be evaluated** and guide the choice of:
    - Study population
    - First dose
    - Number of subjects per dose increment (cohort)
    - Interval between dosing subjects within the same cohort
    - Dose escalation increments
    - Transition to next dose cohort
    - Stopping rules
    - Defining responsibilities for decisions with respect to subject dosing and dose escalation

Choice of Population

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CHOICE OF POPULATION

- **Choice of Population for a Clinical Trial** (s**4.4.2.1)**
  - The choice of the study population for Investigational Medicinal Products, namely healthy subjects or patients, should be **fully justified** by the sponsor of the trial on a case-by-case basis. Several factors should be considered:
    - The **risks** inherent in the type of medicinal product
    - Its **molecular target**
    - Immediate and potential **long term toxicity**
    - The presence of the **target** in healthy subjects or in patients only
    - The possible **higher variability** in patients

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CHOICE OF POPULATION

- **Selection of Population**
  - **Source** of subjects (also consider why those subjects are appropriate for the trial)
  - **Expected number of eligible participants** available per year and the proportion expected to agree to participate in the trial
  - **Inclusion criteria** defining who is eligible for the study
  - **Exclusion criteria** (Contra-indications to trial treatments, incompatible concurrent treatments, recent involvement in other research)
  - **Method** by which subjects are to be recruited
  - **Payment** of participants

CHOICE OF POPULATION

- **Risk Assessment**
  - Subject withdrawal criteria and procedures. Identify:
    - When and how subjects should be withdrawn from the trial
    - Type and timing of any data collected for withdrawn subjects
    - Whether the withdrawn subjects should be replaced and if so, how?
    - Necessary follow up procedures for withdrawn subjects should be established

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Safety

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DRUG SAFETY MONITORING

- Although not mentioned in the guidelines, every trial of an Investigational Medicinal Product should have a **drug safety monitoring board**.

- These boards should be independent to the trial and should assess (and implement where necessary) the stopping rules (s.4.4.2.7) for:
  - An individual subject
  - A cohort
  - The trial

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DRUG SAFETY MONITORING

- In addition to the **pharmacodynamic studies**, the following should also be carried out in the non-clinical safety studies:
  - **Pharmacokinetic studies**: To investigate the efficacy of drug and to give an idea of its potency. In addition to ADME requirements, which should be available in all species used for *in vivo* studies, exposures at pharmacological doses in the relevant animal models should be determined.
  - **Safety pharmacology studies**: To investigate the effect of the medicinal product- the effect in other organ systems should be examined, in particular, where the medicinal product targets the immune system potential unintended effects should be investigated.

DRUG SAFETY MONITORING

- With regard to **non-clinical safety** study for Investigational Medicinal Products, it is particularly important to fully characterise the primary and secondary pharmacodynamics, in *in vitro* animal and human systems and *in vivo* in one or more chosen animal models. These studies should include:
  - Receptor binding and occupancy
  - Duration of effect
  - Dose-response
- Long term safety studies

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Legal Issues

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LEGAL ISSUES

- **Legal Issues**
  - **Provide to participants** - Details of procedures, tests and screenings carried out to assess trial suitability
  - **Information sheet** - Participant should be provided with an information sheet concerning the medicinal product being tested
  - **Informed consent** - Very important that the patient's informed consent is obtained:
    - method by which this consent is gained
    - who will gain the consent
    - whether a witness will be present
    - how long the subject will be granted in order to make a decision
    - the arrangements for non-English speakers and those classed in special groups (mentally ill, children, those suffering from dementia) **See Article 3 (2) (d) of Directive 2001/20/EC**.

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LEGAL ISSUES

- **Legal Issues**
- Directive 2001/20/EC Article 3 (2): A clinical trial may be undertaken only if:
  - (a) The **foreseeable risks** and inconveniences have been weighed against the **anticipated benefit** for the individual trial subject and other present and future patients. A clinical trial may be initiated only if the Ethics Committee and/or the competent authority comes to the conclusion that **the anticipated therapeutic and public health benefits justify the risks** and may be continued only if compliance with this requirement is permanently monitored.

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Case Studies

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CASE STUDIES

- **Case Study 1** - Pre-clinical studies show adverse reaction. Clinicians have failed to make a full disclosure of adverse reaction. The adverse reaction is cited in an appendix. The Investigative brochure issued and adverse event takes place. They have also given different pharmacodynamic results to different countries.

- **Case Study 2** - Early stage studies and selected the species to conduct trial for which have large volume of historical data. Conducted pre-clinical testing. Results show genotoxicity.
  - Do we conduct a full pre-clinical package?
  - What are the indications?
  - What is the class of drug?
  - What does the historical data tell us?
  - Did we use the correct dosage?
  - Is it absorbed?
  - Is it absorbed in the gut? If so, how long does it stay in the gut?
  - Does it accumulate?
  - How is it excreted? In the urine? Have we monitored at the kidneys?
  - Is it metabolised?
  - What do the toxicity studies tel us?
  - How long does it take to reach maximum level in plasma?
  - How long does it take to clear? Doe sit clear?
  - If absorbed across the gut – what effect does it have on tissues?
  - Should we repeat the studies?
  - Would we need to consult authorising body?
  - Safe enough to proceed?

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CASE STUDIES

- **Case Study 3** -Conducted protocol, conducted full package of studies, started studies and find adverse events in Phase I or Phase II? Measured blood samples, level of medicinal product in blood, urine samples, functioning of the heart, liver and kidney functions, dosage checks to ensure it does not induce adverse reaction
  - What should we do next?
  - What are the indications?
  - What is the class of drug?
  - What does the historical tell us?
  - Did we use the correct dosage?
  - Safe enough to proceed?
  - Should we conduct another trial?
  - Is the adverse reaction measurable? Can it be controlled? Is it genotoxic – e.g. raised liver enzymes levels?
  - Are they at dangerous levels or slightly raised?

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Risk Management

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RISK MANAGEMENT

- **Liability** of the Investigator and/or sponsor if subject withdraws or is injured.
  - Insurance
  - Indemnity
  - Cannot exclude liability for death or personal injury
- **Data Protection**
  - Compliance with the Data Protection Directive as implemented by Member State, for example safeguards for protection of personal data
  - Transfer of data outside the European Economic Area

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Conclusion

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CONCLUSION

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