PRECLINICAL RESEARCH IN HUMAN DRUG DEVELOPMENT

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Abstract: The paper presents the preclinical research requirements according to the legislation in force and its implementing guidelines in European Union (EU); tracking down its origins to ICH when appropriate. The development of any medicinal product requires its research in terms of quality; safety and efficacy. The new codification system for ICH guidelines adopted by ICH Steering Committee is presented in detail. The five categories of CHMP guidelines are explained. The non-clinical research represents a critical stage for the transition to studies in humans. The paper supports the researchers in their efforts to assess the needs and the timelines in the preclinical research field.

INTRODUCTION

The development of a medicine before marketing authorization requires its research in terms of quality; safety and efficacy; so that only those medicines which are of good quality; safe and effective will be available to the general public.

The provisions for authorizing medicines for marketing purposes through different procedures (national; decentralized; mutual recognition and centralized) is contained in Law 95/2006 Title XVII - Medicine; which is a implementation of the European Directive 2001/83/EC amended by Directive 2004/27/EC.

In order to clarify and detail the provisions specified in the legislation; the Committee for Medicinal Products for Human Use (CHMP) and the International Conference on Harmonization (ICH) have adopted scientific guidelines which provide a basis for drug research as well as for the practical harmonization of the Member States in interpreting and applying those provisions.

MATERIAL AND METHOD

We reviewed the legislation in force and its’ implementing guidelines in European Union (EU); tracking down its’ origins to ICH when appropriate.

In the EU; the rules governing medicinal products are contained in scientific guidelines prepared by the CHMP; which is the scientific body of the European Medicines Agency (EMEA);

The need for standardization of the requirements to prove that a medicine is suitable for marketing authorization leads to the standardization of the research for drug development.

This standardization; which was referred to as harmonization of regulatory requirements was pioneered by the European Community; in the 1980s; followed by the set up of ICH at a meeting in Brussels in April 1990. The ICH regions are EU; Japan and USA. The main purpose of ICH was to implement a common format for all regions. At the first meeting of ICH the topics adopted by the ICH Steering Committee in order to achieve
harmonization have been divided into Safety; Quality and Efficacy to reflect the three criteria which are the basis for authorizing any medicinal product.

In November 2005; the ICH Steering Committee adopted a new codification system for ICH Guidelines; divided into four major categories:

Q - "Quality" Topics: i.e. those related to chemical and pharmaceutical Quality Assurance (ex: Q1 Stability Testing; Q3 Impurity Testing).

S - "Safety" Topics: i.e. those related to in vitro and in vivo pre-clinical studies (ex: S1 Carcinogenicity Testing; S2 Genotoxicity Testing).

E - "Efficacy" Topics: i.e. those related to clinical studies in human subject (ex: E4 Dose Response Studies; Carcinogenicity Testing; E6 Good Clinical Practices)

M - "Multidisciplinary" Topics: i.e. cross-cutting topics which do not fit uniquely into one of the above categories:
  - M1: Medical Terminology (MedDRA)
  - M2: Electronic Standards for Transmission of Regulatory Information (ESTRI)
  - M3: Timing of Pre-clinical Studies in Relation to Clinical Trials
  - M4: The Common Technical Document (CTD)
  - M5: Data Elements and Standards for Drug Dictionaries [1].

The first ICH Guideline which dealt with harmonizing of the format of reporting data was E3; Content and Format of Clinical Study Reports. This Guideline describes a single format for reporting the core clinical studies that make up the clinical section of a registration dossier.

A target for the first phase of ICH activities was to adopt a single format of submitted documentation necessary to demonstrate the quality; safety and efficacy of a new medicinal product; which has led to creation of the ICH Guideline M4; The Common Technical Document (CTD); adopted in final form in November 2000. The date agreed upon implementation for the CTD; in all three regions; was July 2003.

Thus; information and documents accompanying an application for approval of marketing authorization in any of these regions mentioned above must be submitted in accordance with the requirements set out in the form of 5 modules:
Module 1 - Administrative information and prescribing information;
Module 2 - Common technical document summaries;
Module 3 - Information on chemical; pharmaceutical and biological features of the product;
Module 4 – Non-clinical study reports;
Module 5 - Clinical study reports.

The ICH guidelines are submitted to the CHMP for endorsement. Initially EMEA publishes these guidelines for comments (up to 6 months); and then the final form is subsequently published by the European Commission in the Rules Governing Medicinal Products in the European Union [1].

RESULTS AND DISCUSSIONS

The CHMP guidelines are divided into five categories [2]:
  - Quality Guidelines – include a total number of 61 guidelines; divided in the following categories: Active substance; Manufacture of the medicinal product; Impurities; Specifications; analytical procedure and analytical validation; Excipients; Packaging; Stability; Pharmaceutical development; Specific types of products; Herbal medicinal products.
- Biotechnology Guidelines - include a total number of 93 guidelines; divided in guidelines related to a drug substance (Manufacture; Characterization and Control of the Drug Substance; Specifications; Comparability / Biosimilarity; Plasma-Derived Medicinal Products; Vaccines; Stability) and guidelines related to a drug product (Pharmaceutical Development; Product Information; Adventitious Agents Safety Evaluation; Viral Safety; Transmissible Spongiform Encephalopathies (TSE) (Animal and Human); Creutzfeldt-Jakob Disease CJD related; Investigational Medicinal Products; Genetically Modified Organisms (GMOs).

- Non-Clinical Guidelines - include a total number of 66 guidelines; divided in the following categories: Pharmacology; Pharmacokinetics; Toxicology (Single-Dose Toxicity; Repeat-Dose Toxicity; Genotoxicity; Carcinogenicity; Reproductive and Developmental Toxicity; Local Tolerance; Other Toxicity Guidelines); General guidelines and Herbal medicinal products.

- Clinical Efficacy and Safety - include a total number of 359 guidelines; divided in the following categories: Clinical Pharmacology and Pharmacokinetics; Alimentary tract and metabolism; Blood and blood forming organs; Blood products (including biotech alternatives); Cardiovascular system; Dermatological; Genito-urinary system and sex hormones; Anti-infectives for systemic use; Anti-neoplastic and immunomodulating agents; Musculoskeletal system; Nervous system; Respiratory system; General Guidelines; Herbal Medicinal Products.

- Multidisciplinary Guidelines - include a total number of 71 guidelines; divided in the following categories: Pediatrics; Cell therapy and tissue engineering; Vaccines; Biosimilar; Gene Therapy; Pharmacogenomics; Miscellaneous.

During the development of a new medicinal product; evaluation of non-clinical safety represents a critical step needed to support the clinical development. From all the non-clinical guidelines there is one; CHMP 285/95 that summarize the requirements for non-clinical safety studies necessary to perform clinical trials for evaluation of medicinal products. Due to the importance of this guideline it was implemented as National Medicine Agency’s Scientific Council Decision.

This guideline contains international standards for evaluation the non-clinical safety studies with a given scope and duration; it facilitates the timely conduct of clinical trials and reduces the unnecessary use of animals and other resources.

The goals of the non-clinical safety evaluation include a characterization of toxic effects with respect to target organs; dose dependence; relationship to exposure; and potential reversibility.

This information is important for the estimation of an initial safe starting dose for the human trials; the therapeutic index and the identification of parameters for clinical monitoring of potential adverse effects.

The non-clinical safety evaluation in order to grant marketing authorization to a new investigational medicinal product contains the following types of studies [3]:

1) Pharmacological studies
Primary and secondary pharmacological studies that investigate primary pharmacodynamic effects related to proposed indications and the general pharmacological effects.

2) Toxicokinetic and pharmacokinetic studies
The pharmacokinetic studies investigate absorption; tissue distribution; metabolism; profile of metabolites; routes of excretion of the active substance and metabolites.

The toxicokinetic studies investigate the systemic exposure and calculate the safety ratio of AUC in animals and humans.
3) **Toxicological studies**

The goals of the toxicological evaluation include detection of potential toxicity of the pharmaceuticals with special emphasis on the possible relevance to the proposed indication.

The toxicology studies usually include: single dose toxicity studies; repeated dose toxicity studies; reproduction toxicity studies; genotoxicity studies; local tolerance studies and for medicinal products which are intended for long time use or if there is a suspicion of carcinogenic potential; carcinogenicity studies.

**a) Single dose toxicity studies (Acute toxicity)**

The single dose (acute) toxicity for a pharmaceutical should be evaluated in two mammalian species prior to the first human exposure. A dose escalation study is considered an acceptable alternative to the single dose design.

**b) Repeated dose toxicity studies** should be conducted in two mammalian species (one non-rodent); the recommended duration of this being usually related to the duration of the therapeutic indication and scale of the proposed clinical trial; as follows:

Conduct of longer duration toxicity studies is recommended as given in Table 1.

** In the US; as an alternative to the 2-week studies; single dose toxicity studies with extended examinations can support single-dose human trials.

*** See. Data from 6 months of administration in non-rodents should be available before the initiation of the clinical trials longer than 3 months. Alternatively; if applicable; data from a 9-month non-rodent study should be available before the treatment duration exceeds that; which is supported by the available toxicity studies.

Table 1

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<th>Minimum Duration of Repeated Dose Toxicity Studies</th>
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<tr>
<td><strong>Rodents</strong></td>
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<tr>
<td>Single Dose</td>
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<tr>
<td>Up to 2 Weeks</td>
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<tr>
<td>Up to 1 Month</td>
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<td>Up to 3 Months</td>
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<td>Up to 6 Months</td>
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* In Japan; if there are no Phase II clinical trials of equivalent duration to the planned Phase III trials; conduct of longer duration toxicity studies is recommended as given in Table 2.

** In the US; as an alternative to 2 week studies; single dose toxicity studies with extended examinations can support single-dose human trials.

*** See. Data from 6 months of administration in non-rodents should be available before the initiation of clinical trials longer than 3 months. Alternatively; if applicable; data from a 9 month non-rodent study should be available before the treatment duration exceeds that which is supported by the available toxicity studies.

Table 2

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* The above Table also reflects the Marketing recommendations in the 3 Regions except that a chronic nonrodent study is recommended for clinical use > 1 month.

**c) Local tolerance studies**
Local tolerance should be studied in animals using routes relevant to the proposed clinical administration. The evaluation of local tolerance should be performed prior to human exposure. The assessment of local tolerance may be part of other toxicity studies.

d) Genotoxicity studies include in vitro and in vivo tests in order to evaluate the mutations and chromosomal damage and are necessary; usually prior to first human exposure; if an equivocal or positive finding is obtained; additional testing should be performed.

The standard battery of tests for genotoxicity (6) should be completed prior to the initiation of Phase II studies.

e) Carcinogenicity studies

Completed carcinogenicity studies are not usually needed in advance of the conduct of clinical trials unless there is a cause for concern.

f) Reproduction toxicity studies

Reproduction toxicity studies should be conducted as is appropriate for the population that is to be exposed.

In Pregnant women; prior to the inclusion in clinical trials; all the reproduction toxicity studies and the standard battery of genotoxicity tests should be conducted. In addition; safety data from previous human exposure are generally needed.

4) Supplementary studies

Additional non-clinical studies may be needed if previous non-clinical or clinical findings with the product or related products have indicated special safety concerns.

First dose in humans’ clinical trials; conducted in order to demonstrate the efficacy and safety of a pharmaceutical; will be performed starting with a relatively low exposure in a small number of subjects; followed by clinical trials in which exposure usually increases by dose; duration and/or size of the exposed patient population.

For some new investigational medicinal products; the non-clinical safety pharmacology and toxicological programs can provide sufficient safety data for estimating risk prior to first administration in humans. However; for some novel medicinal products this non-clinical safety program might not be sufficiently predictive of serious adverse reactions in man and the non-clinical testing and the design of the first-in-human study requires special consideration; which involves the identification of the risk factors; derived from particular knowledge or lack of regarding; the mode of the action; the nature of the target and/or the relevance of animal models.

The estimation of the first dose in human is an important element to safeguard the safety of subjects participating in first-in-human studies and all available information has to be taken in consideration. Different methods can be used:

a) In general; the No Observed Adverse Effect Level (NOAEL) determined in non-clinical safety studies performed in the most sensitive and relevant animal species; adjusted with allometric factors or on the basis of pharmacokinetics gives the most important information in estimation of the first dose in human. The relevant dose is then reduced/adjusted by appropriate safety factors according to the particular aspects of the molecule and the design of the clinical trials [4].

b) In exploratory studies (pre-phase I) of an early characterisation of a substance's pharmacokinetic/distribution properties or receptor selectivity profile using sensitive analytical techniques (positron emission tomography- PET; accelerator mass spectrometry – AMS; etc); a microdose is used; defined as less than 1/100th of the dose calculated to yield a
pharmacological effect; based on primary pharmacodynamic data obtained in vitro and in vivo studies and at a maximum dose of 100 micrograms [5].

c) For some investigational medicinal products for which risk factors were identified; an additional approach to dose calculation should be taken. Information about pharmacodynamics can give further guidance for dose selection and the ‘Minimal Anticipated Biological Effect Level’ (MABEL) approach is recommended. The MABEL is the anticipated dose level leading to a minimal biological effect level in humans. When using this approach; potential differences in sensitivity for the mode of action of the investigational medicinal product between humans and animals; need to be taken into consideration all pharmacokinetic and pharmacodynamic data derived from in-vitro studies.

When the methods of calculation (e.g. NOAEL; MABEL) give different estimations for the first dose in humans; the lowest value should be used [4].

CONCLUSIONS

- Various requests lead to specific protocol designs for non-clinical studies.
- Safety is the primary design concern to be taken into consideration and thoroughly assessed.
- From the beginning; it is very important to design and conduct the studies considering the calculation of the first dose in humans; including the analysis of the risk factors for the substances that are developed.
- These recommendations facilitate the timely conduct of clinical trials and reduce the unnecessary use of animals and other resources.
- The rules governing medicinal products in the European Union are specified in scientific guidelines prepared by the Committee for Medicinal Products for Human Use (CHMP) in consultation with the competent authorities of the EU Member States; to help applicants preparing the marketing-authorization applications for medicinal products for human use.

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300