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THE SCOPE AND REQUIREMENTS RELATED TO PRECLINICAL AND CLINICAL STUDIES OF A NEW MEDICINAL PRODUCT, INCLUDING BIOTECHNOLOGICAL AND BIOSIMILAR PRODUCTS

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Abstract: The article presents an outline of the requirements concerning the planning of preclinical and clinical studies, necessary for the legal approval of a medicinal product. It describes the clinical research plan of innovative and generic pharmaceutical products, taking into account the specific situations in which the assessment of biological equivalence of a generic product is not possible based on pharmacokinetic parameters. The article also discusses the guidelines which determine the scope of studies which are necessary in the process of registration of biotechnological and biosimilar products.

Keywords: preclinical studies, clinical studies, innovative medicinal product, generic medicinal product, biological products, similar biological products

Introduction and definitions

A number of basic concepts must be defined before we describe the scope and requirements of preclinical and clinical studies which must be carried out in order for the pharmaceutical product to gain a legal approval and the marketing authorization.

Innovative medicinal product – i.e. an original one, is a product whose effects are based on either new, unknown or previously unused active components or on components which, in comparison with the products available on the marked, improve the effectiveness, safety, or comfort of the therapy.

Such a product is registered on the basis of a complete set of registration documents including, in addition to the chemical, biological and pharmaceutical part, the results of original research, as well as pharmacological and clinical assessment. To fulfill these requirements it is necessary to carry out a battery of preclinical studies, as well as studies of phase I, II, III, and IV.

Equivalent medicinal product – i.e. a generic one, is a product therapeutically equivalent to the innovative product. It is assumed that a product is therapeutically equivalent if it is pharmaceutically equivalent and biologically equivalent.

Such a product is registered on the basis of a set of registration documents including, in addition to the chemical, biological and pharmaceutical part, the results of original clinical studies (bioequivalence studies) together with a comparative assessment of the pharmacokinetics or the therapeutic effect, with the aim to prove similarity. No preclinical research is carried out on generic products.

Biopharmaceuticals – are pharmaceuticals produced according to biotechnological methods, although no widely accepted definition exists. This group of products includes:
recombinant proteins, (monoclonal) antibodies, vaccines, blood and plasma-derived products, products obtained from the cells of: bacteria, yeasts, insects, plants, and mammals, as well as of genetically modified plants and animals; products used in gene therapy (vaccines based on DNA, oncological treatment, Parkinson's disease and other neurodegenerative diseases), somatic cell therapy, tissue engineering.
Registration of these medicinal products is based on a complete set of registration documents including preclinical and clinical data.

Medicinal biosimilar products – (terms used: similar biological medicinal product/biosimilar, biotechnological generics, biogenerics, follow-on biologics – the terminology is not synonymous due to a great variety of products) medicinal products of biotechnological origin whose quality, safety and efficacy in relation to the original (referential) product has been proven, and which have obtained market authorization. The concept of biogenerics was introduced by EMEA in 2004 (the review of the European pharmaceutical law – Pharma Review).

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This gives the basis for submitting the so-called simplified registration applications. It is necessary to prove the similarity to biological products registered under the centralized procedure. There is no need to carry out a whole battery of studies as it is in the case of original products.

Europe has worked out a system of recommendations concerning the scope of preclinical and clinical studies (general and detailed, prepared by CHMP – Committee for Medicinal Products for Human Use). The USA has been working on the legalization of this system.

Research and development in the pharmaceutical industry and the risks associated with them

It takes on average 13.4 years from the discovery of a compound to the registration. The process of developing a new medicinal product is very expensive and the risk of failure is very high. The risk for various phases of the research is estimated as follows: preclinical phase – 61%, phase I / II – 78%, phase III—51%.

Preclinical studies of innovative pharmaceutical products

Preclinical studies are conducted only for innovative products. Their aim is to discover the toxic effects, especially their impact on particular organs. Moreover, the studies have to examine the relation between the impact of the toxic effect and the length of the exposure to the tested product, as well as the reversibility of the impact.

Pharmacological studies of safety

These studies assess the impact of the product on the functions of, for example, the cardiovascular system, the central nervous system, and the respiratory system.

Toxicokinetic and pharmacokinetic studies

These studies help to obtain information on absorption, distribution, metabolism, and excretion. The results of these studies are analyzed before the start of phase I studies.

Toxicity tests

The first step are studies of acute toxicity after the administration of a single dose or increasing doses to two species of mammals. In the next step there are the so-called chronic toxicity tests, which must be adequate to the planned manner of administration to humans. The product is given to two species of mammals, of which only one may be a rodent. A part of the study must be completed before the first in men administration, another part is continued parallelly with the studies of subsequent phases.

The set of toxicity tests includes a test for local tolerance, in which the way the product is administered must be identical to the one in the planned study involving human subjects. Another type of study is genotoxicity testing, whose purpose is to detect any potential mutations or chromosomal damage by means of tests performed on cells. The results must be known before the start of phase II studies. Similarly, before the start of phase II studies, an assessment of the effects of the product on the male and female reproductive systems must be carried out. In some cases, an additional study on the potential carcinogenic effects is performed. This study may be conducted after the registration of the product. If there are doubts concerning the safety of the product, the scope of the study shall be appropriately extended (1).

Clinical studies of medicinal innovative pharmaceutical products

Phase I

The aim of phase I of clinical studies is solely a research (exploratory) one, rather than therapeutic. The participants of the study are essentially healthy volunteers (10 – 20 persons), unless administration of the medicinal product to healthy people would be unethical, regarding its profile.

The aim is to make initial estimates as to the safety after a single and repeated administrations, discovering the pharmacokinetics of the product (absorption, distribution, metabolism, and excretion), and discovering the pharmacodynamic effect (i.e. the effects of the product on the organisms of healthy or sick people). Sometimes it is possible to plan the study in such a way as to preliminarily estimate the potential therapeutic effect.

Phase II

The aim of phase II clinical studies is to discover the therapeutic properties of the product. The study is carried out on a selected group of patients. A typical participants' group in this study phase is small and very homogeneous, (typically up to 100 participants in 1 – 3 research centres). During the study, the size of the doses (through an increase in dosage) which will be used in phase III is determined. An important aim of phase II is to verify the end points that will be used in phase III.

Phase III

The aim of phase III studies is to prove the expected therapeutic benefits. The selection of par-

ticipants is not as strict as in phase II, although certain criteria for acceptance or exclusion apply. Studies of this phase are usually multi-centre, there may be even a few thousand participants. During the study, a further assessment of the relation between the size of the dose and the therapeutic effect is performed, moreover, the effects of the medicine applied together with other medicinal products is assessed. The results of phase III studies will serve as the basis for the registration of the product.

Phase IV

During this postregistration phase further studies on the administration safety and the relation between the administration and the effects of the product are carried out. The participating patients do not undergo any selection; the only criteria are the indications / contraindications written on the product's information leaflet. This phase of the study involves thousands of participants.

Preclinical studies of generic pharmaceutical products

In the case of generic products, in principle, no preclinical studies are carried out.

Clinical studies of biological equivalence of generic pharmaceutical products

The aim of the study of biological equivalence, preceded by studies designed to demonstrate the pharmaceutical equivalence, is to demonstrate pharmacological equivalence, and thus therapeutic equivalence – and hence also therapeutic interchangeability which provides the basis for the registration of the generic product.

In other words, biological equivalence indicates pharmacological equivalence, and thus, on this basis conclusions about biological equivalence can be drawn.

An evaluation of the biological equivalence is carried out according to an analysis of the following parameters: pharmacokinetic, pharmacological, the results of comparative therapeutic studies

Analyzed parameters

Parameters of primary importance: AUC – area under the curve; C_{max} – maximum concentration. Secondary parameters: T_{max} – the time of maximum concentration from the administration; $T_{1/2}$ – the time of achieving half of the maximum concentration of the active component; MTR – mean residence time; % of extrapolated AUC value.

When comparing these parameters a 90% confidence interval is applied for the relation between average AUC and C_{max} parameters. For the tested product and reference product they should fall between 80 – 125%.

Comparative clinical studies of pharmaceutical products based on pharmacokinetic parameters

Comparative clinical studies of pharmaceutical products based on pharmacokinetic parameters are carried out when the concentration of the active component in the body fluids is sufficient. The subjects of such studies are a limited number of healthy (with some precisely described exceptions) participants. This number, depending on the intersubject variability (CV), usually varies between 24 and 110. After the administration of the product under strictly specified conditions, samples of body fluids are taken at set times, and then, the concentration of these products is measured. Obtained pharmacokinetic parameters: the AUC, C_{max} and T_{max} are analyzed, and then, as a result of comparison, a conclusion on the biological equivalence can be drawn.

Comparative clinical studies of pharmaceutical products based on pharmacological parameters

Comparative clinical studies of pharmaceutical products based on pharmacological parameters are carried out when there is insufficient concentration of the tested (active) substance in the body fluids. Typical examples are studies of local effect of dermatological preparations containing corticosteroids. The study avails itself of the fact that the preparation penetrates the epidermis and the stratum corneum, causes vasoconstriction and thus blanching of the skin. The above mentioned pharmacodynamic effect is proportional to the time which has elapsed from the application of the preparation and to the therapeutic effect. The participants of this type of studies also comprise a relatively limited number of healthy volunteers (between 60 and 100). The findings, i.e. AUEC (area under effective curve), C_{max} and T_{max}, are compared using the same principles as in the case of pharmacokinetic studies, and conclusions concerning the biological equivalence are drawn.

Comparative clinical studies of medicinal products based on therapeutic data

Comparative clinical studies of medicinal products based on therapeutic data are carried out when the tested substance is not present in sufficient concentration in the body fluids, and when there is no pharmacodynamic effect which could be easily compared.

An example of such a study may be the study of a pharmaceutical product containing mesalazine which practically does not leave the colon after administration. 280 patients participated in the cited

study. The comparative assessment of AUC, $C_{max,}$ and T_{max} was performed on the parameters of the therapeutic effect. The study lasted longer than 2.5 years.

Preclinical studies of innovative and biosimilar biopharmaceuticals

Preclinical studies of innovative biotechnological products (biopharmaceuticals)

Preclinical studies of innovative biotechnological products have a different scope for products of different origins. The scope of the studies is regulated by EMEA directives.

Products such as cytokines, recombinant coagulation factors, enzymes, hormones, recombinant proteins, and plasma-derived products are tested in a different way than heparins, vitamins, DNA vaccines, or products for cell therapy.

The study begins with tests in the *in vitro* system, during which the presence of receptors on cells and the affinity to them is determined, the rules for pharmacological effects are set, and information useful when selecting species of animals for pharmacological studies is obtained (e.g. the animals used in studies on monoclonal antibodies have an epitope to which the tested monoclonal antibody has an affinity, and a cross-reactivity profile that is similar to that of a human).

The next step is usually the safety test with two species of animals. The choice of animals with an epitope involved in a specific reaction is very important. The way of administering the product is the same as in the planned clinical study, and the size of the dose is a multiplication of the dose administered in the clinical study. The immunogenic profile of the product is analyzed in a particular way. The immunogenic potential is checked by several highly specialized and selective methods.

Preclinical studies of biotechnological generic, i.e. biosimilar products

Preclinical studies of biosimilar products are not as extensive as the studies of innovative products. One can track them by looking at the examples of studies, recommended by the EMEA, of biosimilar erythropoietin and insulin.

In the case of biosimilar erythropoietin *in vitro* tests examining the bonds to receptors and differentiation of cells should be carried out. The *in vivo* studies involve tests with the use of policystemic or normocystemic mice.

Toxicological studies involve a 3-month long administration of the product to animals, and assessment of local tolerance in at least one specie. The evaluation of safety pharmacology, toxicology of the reproductive system, as well as mutagenicity is not a routine requirement.

In the case of biosimilar insulin, *in vitro* tests are carried out first. Their aim is to detect any differences in the bonding to the receptor. Then a test for cell proliferation is performed. The *in vivo* studies are carried out in rodents (as the model here serve rats deprived of the pituitary gland). They estimate the weight increase or the length of the femur. Toxicological studies involve administration of the product for 4 weeks at least 2 times a week. They assess the local tolerance. The studies that are not required: assessment of safety pharmacology, reproductive toxicology, mutagenicity, and carcinogenicity (2-4).

Clinical studies of innovative biotechnological products

Clinical studies of innovative biotechnological products are planned and carried out in a manner analogous to clinical studies of innovative medicinal pharmaceutical products.

Due to the nature of the products, the safety, and particularly the immunogenic potential of the products of biological origin, is thoroughly analyzed.

Comparative clinical studies of biosimilar products.

When planning clinical studies of biosimilar products, designed to prove the similarities, the following principles must be applied:

- selecting the reference product and its characteristics;
- demonstrating the similarities in the *in vitro* and *in vivo* models in preclinical studies;
- demonstrating the safety and efficacy through limited clinical studies (Phase I and III);
- demonstrating the safety of the product through immunological research.

The rules which apply to the planning of clinical studies of biosimilar products:

- demonstrating the physicochemical and biological similarities to the reference product (preclinically) are as follows:
- demonstrating the relation between the pharmacodynamic and therapeutic effect, and the dose;
- determining the possibility of using surrogate endpoints and their relation to the dose and the concentration of the product in fluids and tissues;
- statistical proof of the efficacy at a 95% level of confidence in relation to the extent to which bioequivalence is accepted, fulfillment of the test sensitivity requirements, taking into account the interchangeability determined by standard deviation, and

meeting the requirement concerning adequate test power;
- an analysis of the potential immunogenicity and the creation of neutralizing antibodies

Examples of biosimilar products with legal approval and those in the course of development: recombinant growth hormone (EMEA recommendations are available); recombinant erythropoietin (EMEA recommendations are available); recombinant insulin (EMEA recommendations are available); recombinant hormone stimulating the growth of granulocytes (EMEA recommendations are available); monoclonal antibodies; genes; cells for cell therapy; vaccines.

Rules for conducting clinical studies of biosimilar products

Phase I. Study showing pharmacokinetic equivalence

The purpose of the study is to demonstrate the pharmacokinetic equivalence, mainly in terms of AUC and C_{max} (80 – 125%) or broader (in justified cases).

An example of applying the analysis of pharmacodynamic parameters (PD) may be a comparison of the well-known PD effect such as measuring the concentrations of glucose for insulin, the measurement of the anti-viral effect for interferon, measuring the IGF -1 for the growth hormone.

Combined PK/PD studies are preferred where one typically plans a double-crossed study for generic products. The studies typically involve about 30 or more participants (healthy or sick).

After carrying out the Phase I study and analyzing the results, further study (or studies) of Phase III is performed. Sometimes, between phase I and III, study of phase II is carried out, although it is not required.

Phase III. Comparative study confirming efficacy and safety

The scope of biological equivalence is relatively narrow and defined *a priori*. It refers to a significant therapeutic effect by setting clinically meaningful endpoints. The power of statistical calculation is usually fixed between 80-90%. The number of patients, often determined on the basis of pilot studies, may even be more than a thousand people. In the case of various indications, separate studies are recommended to prove the therapeutic effects and safety for each indication.

SUMMARY

The nature and origin of a medicinal product determines in advance the scope and requirements concerning the clinical studies necessary to obtain legal approval of the product. In turn, the exactly outlined clinical studies strategy imposes certain aspects of preclinical studies, although, in general, their scope is defined by existing guidelines. The aim of the performed studies is to create a product that is comprehensively tested, maximally safe for the patient, and which has new therapeutic (or generic) possibilities of a medicinal product.

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