RAREDUCANDO EDUCAZIONE DIGITALE

Lesson 10

ORPHAN DRUGS

What is an orphan drug?

The medicines called 'orphans' are intended for the treatment of diseases so rare that they do not allow pharmaceutical companies to realise revenues that will make it possible to recover the costs of their development.
The process from the discovery of a new molecule to its marketing is long (on average 10 years), expensive (several tens of millions of euros) and very random (between ten molecules tested, only one can have a therapeutic effect). The marketing of a drug intended for the treatment of a rare disease does not make it possible to recover the capital invested in its research.

Orphan drugs can be defined as:

Medicines are not distributed by the pharmaceutical industry for economic reasons but respond to a need for public health.
In fact, a substance that is used to treat a frequent disease may also have an orphan indication that has not yet been developed.

In practice, three cases may arise:
Products intended for the treatment of rare diseases:
They are designed for the treatment of patients with very serious diseases for whom there is still no satisfactory treatment. These diseases affect a limited part of the population (less than one in 2000 people in Europe), very often from birth or childhood. To date, in the world, the number of rare diseases for which there is no cure is estimated at around 4000 to 5000; and 25 to 30 million would be affected by these diseases in Europe.

Products are withdrawn from the market for economic and therapeutic reasons:
For example, thalidomide was widely used as a hypnotic a few years ago, then withdrawn from the market for the discovery of a powerful teratogenic effect (capable of causing foetal malformations). In any case, this drug has shown very interesting antalgic properties in diseases such as leprosy and lupus erythematosus, diseases for which there is no satisfactory cure.

Products that have not been developed:
either because they are derived from a non-patentable search process;
both because they relate to important but not solvent markets.
Patients with rare diseases cannot be excluded from advances in science and therapy, as they have the same health rights as all other patients. In order to stimulate research and development in the orphan medicines sector, the authorities have adopted incentives for industries, health and biotechnology. All this began in the United States, in 1983, with the adoption of the Orphan Drug

Act, then in Japan and Australia in 1993 and 1997; Europe followed in 1999 by establishing a unified policy for orphan drugs for all countries.

The European Regulation for Orphan Drugs

A combined effort has been undertaken both at the national and European levels, by industries and health authorities (EMEA — European Agency for the Evaluation of Medicinal Products), to provide the necessary incentives to stimulate the development of orphan drugs.

Europe has delayed the process of adopting a single policy on orphan drugs, compared to the United States, mainly due to the splitting of its territory and the dispersion of competencies in health matters.

After 1 January 1995, with the new system of Community marketing authorisation, valid throughout the territory, and the resulting freedom of movement, Europe can now be regarded as a territory with a population of 377 million inhabitants, higher than that of the United States where unified regulations are applied.

On 16 December 1999, the European Parliament and the Council adopted Regulation (EC) No 141/2000 on orphan medicinal products.

Inspired by U.S. regulation, its objectives were:

encourage pharmaceutical and biotechnology industries to develop and market orphan drugs; set up a Committee for Orphan Medicines (COMP) within the European Agency for the Evaluation of Medicinal Products (EMEA) to examine applications for designation and to advise and assist the Commission in discussions on orphan drugs.

The Commission also adopted Regulation (EC) No 847/2000 of 27 April 2000 laying down provisions for the application of the criteria for orphan designation, defining the concepts of ‘similar medicinal product’ and ‘clinical superiority.

According to European Regulation No 141/2000, only medicinal products intended for human use may be designated as ‘orphan drugs. Veterinary medicines, medical devices, food additives and dietary products are excluded from this Regulation.

Medicines that have the designation of orphans are entered in the Community Register of Orphan Drugs (COMP).

The objectives currently pursued by the European authorities are:

encourage the pharmaceutical and biotechnology industry to devote itself to research and development of orphan drugs;

encourage the competent small and medium-sized enterprises to participate in this development in specialised sectors;

at the same time promote the development of knowledge of these diseases, and their environment; improve communication and exchanges between different research centres, institutions, patients, etc...

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Availability of orphan drugs in Europe

The award of the marketing approval does not imply the immediate availability of the drug in all countries of the European Union. Who owns the marketing approval decides in advance on the state of its marketing in each country and the drug will then pass through several steps in each country, in order to lay down the conditions for its management and usually agree on its cost.

Hospital medicines, after approval by the Commission, are registered on the list of medicinal products admitted to the company.

Despite joint efforts, the heterogeneous approaches of European countries make access to orphan drugs much more difficult for patients.

Early access to medicines in Europe

Early access to a drug for patients may be possible before the marketing authorisation has been granted to the pharmaceutical industry developing it, mainly during the third phase of the clinical trial and when its safety and efficacy are strongly assumed. There may be two cases:

1) the pharmaceutical industry that develops the drug in a European country has submitted or is about to submit a marketing authorisation application. The industry forwards a temporary authorisation to the administrative authority for a group of patients (ATU cohort in France and Italy, or authorisation for compassionate use in other European countries) which is valid for a limited period of time in the country concerned.
2) or the doctor asks the administrative authorities for a temporary, named authorisation valid for a specific patient and for a limited period of time in the country concerned.

What is a clinical trial?

A clinical trial is a medical study carried out to test the effects of a new or existing drug, biological treatment or medical device capable of treating or limiting an already identified disease. The main objective of a clinical trial is to compare 2 or more groups of subjects, using 2 or more treatments to determine the effectiveness of a drug or biological treatment.

Clinical studies should be conducted with accuracy and in accordance with ethical codes, in order to protect patients from unnecessary side effects and to allow accurate analysis of disease information.

Four key points on clinical trials:

The purpose of a clinical trial is, on the one hand, to ensure the safety of the treatment that you wish to test, and, on the other hand, to demonstrate the therapeutic efficacy of a precise indication.

Drugs are tested in humans only after preclinical trials (in vitro and animal models) have been carried out, which are necessary prerequisites for studying pharmacology (study of therapeutic effects) and toxicology of the active substance.

Before choosing to participate in a clinical trial, you should be well informed about the study, including the side effects and benefits that the person can derive from research. The doctor, responsible for research, is responsible for explaining the protocol, meeting all requests, and collecting the ‘informed consent of the participants.

The patient may refuse to participate in the trial or abandon it at any time, without in any way affecting the medical/patient relationship.

What is a protocol?

All clinical trials are based on a precise protocol.

The methodology applied to the study is described carefully. The protocol specifies the different protagonists of the experiment: the sponsor, the first researcher and the people participating in the trial. The different methods used in the study and the same assessment criteria for all subjects of the trial shall also be specified, in accordance with ‘good clinical practice. At each stage, the evaluation should enable researchers to measure the efficacy (and tolerance) of the active substance. Such an assessment shall be easy, reproducible and sufficiently sensitive to detect the slightest variations. The conditions and assessment techniques are standardised, and the time of collection of the criteria(s) is the same for all.

What are the purposes of a clinical trial?

The two main objectives of a clinical trial are to determine the safety, tolerance and then efficacy of a drug.

When a drug is active, this is by definition ‘strongly dangerous’ and its misuse can cause more or less serious problems (dizziness, nausea, dry mouth...) or quite serious accidents (heart disorders, anaemia, haemorrhage...). A new drug is tested in humans only after carrying out toxicological and pharmacological studies in animals in the laboratory.

It is not enough to see the disappearance of a symptom to affirm the efficacy of a drug. Such improvement or healing may in fact be due to other causes: natural evolution, a subaltern pathology, another therapeutic factor or a ‘placebo effect.

What are the different stages of a clinical trial?
Clinical studies on new molecules are generally carried out in three phases, involving a large number of people. When the molecule is already known, for another therapeutic indication, you go directly to Phase II trials.

Phase IV studies are the longest and begin once the drug has been placed on the market (post-marketing studies); in order to assess the side effects or pharmaceutical properties highlighted during the first three steps.

Step I:
The purpose of the studies is to determine the safety of a drug and to know its pharmacokinetics (i.e. what happens to the drug in the human body: absorption, metabolism, elimination and excretion).
These studies are generally short-lived (during a few days to a few months) and involve a small number of healthy volunteers without the diagnosed disease who wish to participate in a clinical trial) who are hospitalised, during the trial, to be followed more closely. Attempts are made to determine the maximum dose of the drug tolerated, as well as the side effects that may occur at different concentrations.
About 70 % of the tested drugs pass the initial trial phase.
Once the safety of the drug has been proven, its effectiveness is tested.

Phase II:
These studies have a duration ranging from a few months to 2 years and are conducted in a small homogeneous group of patients (10 to 40 patients).
These allow you to study the effectiveness of the product and determine the smallest effective dose and the best dose for phase III.
Only one-third of the drugs tested successfully completed phase I and II studies.

Phase III:
These are comparative studies carried out on several hundred patients. This comparison is based on the randomisation of treatments. These are double-blind studies.
Treatment under assessment is compared with a placebo, or a reference drug for the therapeutic indication studied. These phase III studies make it possible to determine the tolerance and efficacy of the product and then evaluate the benefit-risk balance of the drug.
They are large-scale studies carried out almost always over one or more years. Based on the results obtained after Stage III, pharmaceutical companies may send a marketing authorisation application to the competent health authorities.
70 to 90 % of the medicinal products entering the phase III trial are considered candidates for marketing authorisation applications.

Phase IV (post marketing):
These studies allow researchers to refine their knowledge about the drug:

comparing the drug with other products already on the market;
assessing the long-term effects on the patient's quality of life;
determining the cost-benefit ratio of the drug in relation to others.
These studies are unlikely to run out and allow pharmaceutical companies to argue for the revision of the marketing authorisation every 5 years.

What is a placebo?
In a therapeutic trial placebo (from Latin: I will like) is a substance that resembles the drug to be tested, but that does not contain an active ingredient. Its potential effect is therefore independent of the active substance you want to test.
During the trial, the tested drug should be compared with another cure. When there is no reference treatment, effective or available, for the disease considered, compare the drug to be tested with a placebo. One group of subjects receive the drug to be tested while the other group receives a placebo.

What is the placebo effect?
It is the difference between the observed change (overall therapeutic effect, clinically measurable) and that attributable to the pharmacological action of the cure (specific or pharmacodynamic effect in the case of the drug).

What is a controlled or randomised trial?
Controlled experimentation allows scientific objectivity. One of the control methods is randomisation, i.e. the random distribution of patients into different groups. Scientifically speaking, it is referred to as 'randomised comparative experimentation'.

What is blind or double-blind experimentation?
A blind trial is an experiment in which the participants do not know the group to which they belong: both it the group receiving the tested drug, and the control group. No patient knows the nature of the treatment he receives.
During a double-blind trial, neither patients nor the medical team knows the nature of the treatment given; in order to avoid reactions that may influence the results of the trial. In case of need, the composition of the groups and the corresponding care may be revealed.
This type of trial is the only recognised procedure, which makes it possible to discover the efficacy of the product, regardless of the placebo effect. However, its realisation is not always possible (in a complex organisation, the use of a placebo is sometimes impossible).
What is informed consent?
Before starting a clinical trial, the sponsor must obtain informed consent and give all participants. The purpose of this procedure is to ensure a sufficient level of information for all to choose to participate in the clinical trial with complete freedom. In order to give their consent, individuals must have been informed about at least:
the objectives of the research and its methodology;
the expected duration of the study;
the expected benefits, foreseeable risks and side effects that may occur during the study, including premature cessation of the trial;
other treatments available;
the right to refuse to participate or withdraw from the trial at any time without harming any of the participants.
All this information is given orally or in writing on a document given to the person giving his/her consent. In addition, a doctor is always present at meetings to answer all questions.
Useful sites:
https://www.aifa.gov.it/farmaci-orfani

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