Xplore Health

DISCOVER THE LATEST ON HEALTH RESEARCH

Educator's guide on Drug development

(Background information)

AUTHORS

Parc Científic Barcelona

B:KC Barcelona Knowledge Campus

European Schoolnet

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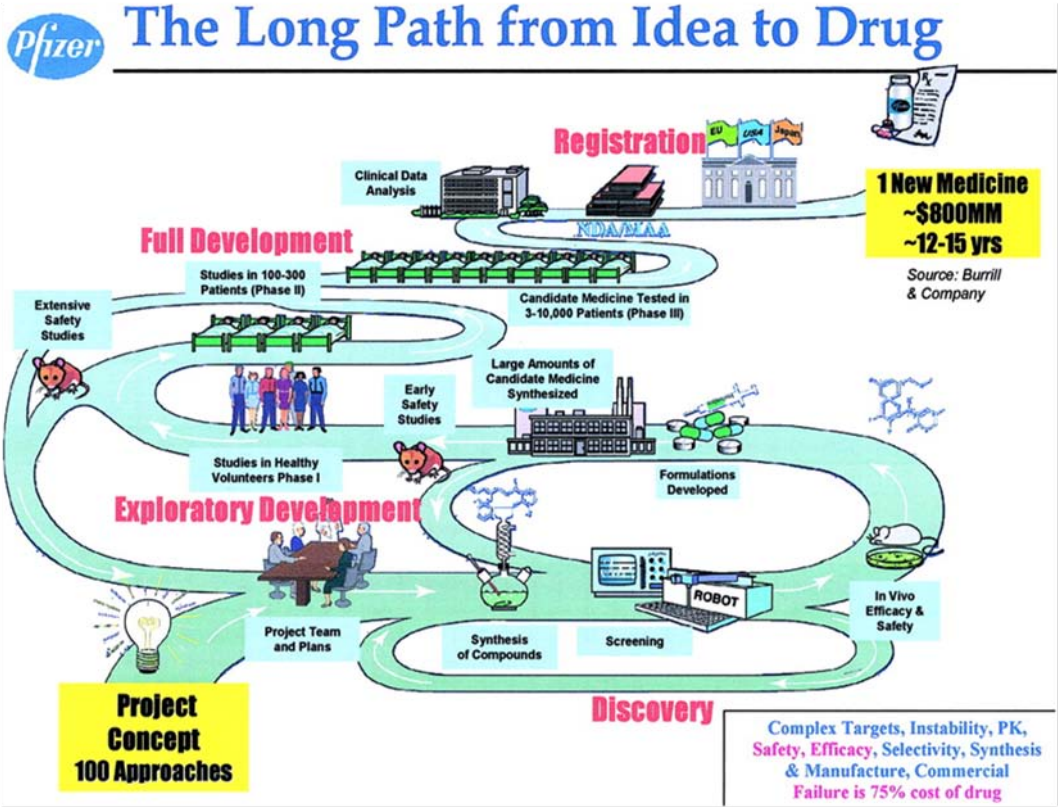
I. Introduction

These teacher guidelines will give you information on the first module of Xplore Health: How are drugs developed? It will first introduce the topic to enable you to prepare your lesson and gives you the necessary information to provide your students with the pre-knowledge they should have and to organise introductory activities. The guidelines provide information on the state of the art in this research field and on the ethical, legal and social aspect of this topic.

II. State of the art

The first module of Xplore Health tackles the topic “drug discovery” and explores the development phases of a drug from a scientific and technical point of view. It describes the long discovery and development processes from the scientific research to the collaboration between pharma and biotech industries and academic researchers, the expenses behind the development of a drug to the final testing and registration stage. This long cycle, that can take several years, can be seen in the following image.



From: Scott P. Kennedy and B. J. Bormann, *Experimental Biology and Medicine* 231:1690-1694 (2006)

The following are points that should be discussed with the students in the course of teaching this module:

1. Where do ideas for new drugs come from

The process of development of a new drug, from the idea to the market is different for each case. In the past, many drugs were found by serendipity. In the last part of the 20th Century, rational drug design started to contribute to the drug discovery and development process, and new technologies started to be important elements for new drugs development. Drugs discovered in the 21st Century may be generated from a better knowledge of the functioning of our cells and bodies, and from the analysis of the human and other genomes.

2. Interdisciplinary research: chemistry / biology / computation

The first steps in Drug Discovery research are in many cases carried out by interdisciplinary teams of people, usually coming from scientific areas like chemistry, biology, and computation (both to predict the chemical-biological interactions, and to analyze the large number of data generated in the assays).
The fields of research are:

- **Genomics and bioinformatics**

The availability of the genomic sequence of humans and other species allows scientists to analyse the position of genes in the species' chromosomes and, from there, to decipher the proteins that constitute each species' proteome. All these analyses require expertise in the area of bioinformatics, the results being the availability of targets, mainly proteins, which may be associated with particular diseases (drug targets).

- **Structural biology and drug design**

Protein drug targets are three dimensional entities whose structures may be determined by techniques like X-ray Crystallography or Nuclear Magnetic Resonance. Using computers, the interaction of chemical or biological entities with these drug targets may be analysed, future drugs may be designed and, when synthesised, the structure of their complex with the drug target may be determined to confirm these interactions. This cycle is known as Structure-Based Drug Design (SBDD).

- **Medicinal chemistry**

Chemical compounds that may become drugs need to be synthesized in the laboratory to test their possible interaction with drug targets that may be associated with a disease, because they are over-expressed, or they are not expressed, or they do not work properly, in the cells. Medicinal Chemistry allows to optimise the compounds found with some initial activity (named “hits”), so that they may become compounds with better activity and better drug properties (named “leads”).

- **Screening and pharmacology**

“Hits” and “Leads” compounds are usually tested in screening assays against proteins (biochemical assays), cells (cellular assays) and organisms (phenotypic assays). Once compounds have been identified with interesting activities in these assays, their activity is analysed through additional in vitro and in vivo pharmacological assays.

- **Animal research in drug discovery**

Before lead compounds can be used as drugs to cure disease of human beings, it is necessary to analyse their effects in animal species. Animal in vivo pharmacology assays are highly regulated to limit the number of animals treated, and to carry out such tests under ethical codes. All animal research experiments in the pharmaceutical and biotechnological industries need to be approved by ethical committees. However, drug approval agencies require tests carried out in animals (like rodents, dogs or non-human primates) to be included in each drug dossier.

- **Metabolism, toxicology and drug safety**

Lead compounds are usually tested for their bioavailability. A compound is approved for human tests, if a detailed knowledge of its ADMET (absorption, distribution, metabolism, elimination and toxicology), properties in animals and in human beings is available. Drug safety profiles are carried out in cells or in animals, so that possible adverse interactions may be found and compounds are selected with the best properties and no toxicity.

Compounds that are selected for preclinical safety tests need to be produced in large amounts, and the possible impurities that result from these synthetic procedures are identified and separated from the active compound in regulated environments (Good Laboratory Practices, GLPs).

An active principle may be approved for human testing only when the impurities are below a certain safety level, and once the toxicity of these impurities has been tested as well.

Preclinical candidates (active principles) selected for human tests are prepared in forms that are bioavailable, depending on the way of administration (i.e. oral, intravenous, etc).

This drug formulation development usually requires testing the combination (active principle + excipients) in terms of stability, absorption, release, etc.

3. Clinical phases

- **Clinical phase I**

The first phase consists in testing healthy volunteers to confirm the safety of the compound previously observed in animal tests, in escalating doses in the human species. Possible side-effects of the compounds are tested, as well as levels of compounds in human samples (blood, urine). ADMET properties of clinical candidates in several human volunteers are also statistically analysed.

- **Clinical phase II**

The second phase aims at finding the right dose. Once compounds tested in Clinical Phase I have been shown to be safe at different doses, the first efficacy tests of the clinical candidate compounds in human patients with the disease to be treated are carried out under conditions approved by drug regulatory agencies. The goal of these Clinical Phase II tests is to determine the best dose to observe a therapeutic effect, and the therapeutic margin between the effect obtained and possible minor side effects observed. In most cases, these Clinical Phase II tests are carried out in double-blind mode: some patients receive the compound analyzed, while others receive a placebo (with no effect expected), and neither the people carrying out the tests or the analyses of data, nor the patients, know in which group (drug or placebo) they are.

- **Clinical phase III**

This phase tests the efficacy of drug vs. disease validated in human patients. For compounds that were tested as statistically effective in several patients treated in Clinical Phase II, an effective safe dose is selected for extensive Clinical Phase III studies, usually carried out in a larger number of patients in different countries. A double blind system is applied here as well and, in addition, the efficiency and safety of the compound under study is compared in a blind manner with compounds that may have been previously approved for the same disease. After Clinical Phase III, a compound effect to treat a disease in human patients is validated.

4. Registration / Approval / Marketing process

A drug can be introduces on the market, after being approved by regulatory agencies in each country or geographical area (e.g. the European Medical Evaluation Agency, EMEA,

the Food and Drug Administration Agency, FDA). These agencies carefully analyse the documentation to approve the new drug to enter the market or request additional tests, or deny approval of the drug, because of a lack of efficacy or possible side-effects associated with drugs administered to humans.

Once a drug enters the market, administration to patients is carried out only through authorisation of medical doctors that determine if a patient should benefit from the treatment with the new drug, at a certain dose. The medical doctors analyse the possible side effects associated with the use of a new drug, and report possible adverse side effects to pharmacovigilance agencies in the different countries. If a new drug is taken by a large number of patients, and some unexpected side effects occur that are statistically significant, the drug can be withdrawn from the market

III. Ethical, Legal and Social Aspects (ELSA) of drug development

Here are number of opinions and incentives for discussions in class on ethical, legal and social aspects (ELSA) of the development of drugs process:

1. Drug consumption: scarce, adequate or excessive?

- **An overmedicalised world**

A growing number of experts seem to think that we live in an overmedicalised world. There is no doubt that drugs are absolutely necessary when individuals suffer from disease or serious conditions that can seriously compromise their health and well-being. However, we should ask ourselves: do we really agree with the fact that everything can be cured or treated with drugs? Do we give enough importance to things such as a varied diet and proper nutrition, avoiding a sedentary life style by exercising regularly or playing some sort of sport, spending less time sitting in front of our TV set or computer, decreasing our consumption of toxic substances, sharing more time with the people we love or with whom we feel close to, or reducing as much as possible our consumption of drugs?

- **Responsibility over your own health**

Our body is a wonderful machine, the result of millions of years of evolution, but we also need to help it, considering the well being of our mind by helping it to develop and make much more informed decisions in accordance with what makes us feel the happiest.

- **Drugs consumption**

The growing life expectancy is directly proportional to the rational use of drugs, in all societies. Antibiotics save lives, and their appropriate use is directly correlated with the growing life expectancy.

There are really no innocuous drugs (not even the highly consumed aspirin) and it must be considered very seriously, as all drugs, to a larger or lesser extent, have unwanted and impossible to avoid side effects. But we are still unable to avoid side effects. Moreover, the higher consumption, the higher the risks are. The sentence “the dose makes the venom” is attributable to the physician, alchemist and astronomer Paracels (1493-1541); which wanted to deliver the message that any product administered in sufficiently high quantities or in a continuous or repeated dose can eventually become toxic (leads to toxicity). Prolonged drug consumption may lead to toxicity. It is so important to make the least possible use of drugs and only over the strictly necessary period.

The massive consumption (and often abusive use) of antibiotics has already alerted health authorities because it appears these drugs are causing microorganisms to develop significant resistance to the same antibiotics people are taking or to other similar ones. We must not forget that microorganisms are living creatures. If they adapt to a hostile environment they will survive in it; and bacteria are particularly good at this. There are scientists who believe that currently available antibiotics will soon stop being effective in populations that routinely take large amounts because of this resistance.

- **Intensive childhood vaccination programmes**

Intensive childhood vaccination programmes and the massive use of certain drugs is associated with, according to some specialists, an increase of allergies, particularly among the youths, due to exaggerated reactions of the immune system that would lower the side effects caused by the excessive use of medication since early in childhood. This can explain the fact that more and more parents refuse to vaccinate their children, except in extreme circumstances, because they understand that in the majority of cases the risks outweigh the potential benefits.

Some scientists don’t agree with this view, according to them, the main reason is that unfortunately some parents don’t fully understand the risks – which can sometimes be blown up out of proportion in the media, and by some doctors misleading the public. Vaccinations are necessary and are recommended by the World Health Organisation and by the health authorities of many countries: they have saved many lives and their benefits exceed significantly the risks derived from not being vaccinated.

- **Recycling expired drugs**

Medicines that we no longer need and have not expired yet, should not be left sitting in our home medicine chest. They should be taken to a pharmacy where they will be given to recycling organisations (who will take these drugs to other areas of the world where there is great need for them). Medicines that have already expired should not be thrown to the garbage or thrown down the drain into residual waters; they should be taken to recycling points where they will be handled and discarded off appropriately.

- **Interaction between different drugs**

Some drugs may interact negatively with other drugs taken by the patient. This should be taken into account very seriously, because this interaction may either reduce the drug´s efficacy or increase its toxicity. This is also explained in drug inserts and adds one more reason to be cautions regarding drug consumption.

- **Role of medical advice and drug inserts**

Medical advices must always be followed when consuming drugs: for prescription drugs this should always be the case, and patients should always inform their doctors, and their pharmacies, if they are consuming other drugs, when asking for a particular non-prescription (over the counter) drug: pharmacies have an information system available that reports the possible interactions of all approved drugs. Have you ever asked yourself why drugs inserts very often warn that if the consumer is pregnant or thinks she might be pregnant, special caution should be taken before taking the medication? This could be an example of the possible toxicity mentioned above, which could negatively affect the foetus.
Drug inserts included in packages contain a very complete description, as mandated by law, of the beneficial effects the drug is expected to provide and on possible unwanted side effects (generally referred to as “adverse reactions”) classified according to a risk scale ranging from rarely or infrequently to very frequently. Reading these inserts more carefully, users are invited to be a cautious when taking drugs. If adverse reactions are reported to the doctors responsible for patients, they report this to a centralized system (pharmacovigilance) in each country.

2. Treating symptoms or treating people?

With some exceptions, most of the drugs produced are intended to alleviate or suppress symptoms, but they do not usually affect the causes of the disease (they do not usually treat the underlying cause of the disease). This is, to a large extent, because the causes of diseases are more related to the overall state of health of the affected individual than to the bad function of a specific body organ, even though at present biomedical research

tends to focus more on the possible molecular origin of disease. More and more citizens seek help for their health problems in alternative types of treatments or “unconventional” therapies, which bear fewer risks and less unwanted side effects. These other treatments, called “alternative” treatments or “complementary” treatments (and particularly homeotherapy, acupuncture and orthomolecular treatments) are based on a conception of disease or health dysfunction that views the person as a whole, including emotional, nutritional and environmental factors.

Using alternative types of treatments may have important risks depending on the disease. If the patient invests some time in an alternative treatment and that time is critical in the disease progression, sometimes it may be too late to administrate conventional drug because the disease has progressed too much. This would make sense for diseases such as genetic disorders, or cancer.

There are alternative treatments that work because they contain an active principle extracted from nature, such as some herbal infusions, which have been demonstrated to be effective. Critics of alternative medicine argue that there is a lack of conclusive clinical evidence from medical trials to show that these treatments are effective. For example, a study published in The Lancet in 2005 looked at more than 100 clinical trials and found no evidence that homeopathy worked any better than a placebo.

3. The economic costs of drugs

The economic cost of drugs is the high cost of research, development and production of the molecules. Pharmaceutical companies tend to stress that, in their opinion, it is the high production cost of the molecules that constitute the active ingredients of the drug that causes their overall cost, a cost that might globally increase from 900 to 1000 million dollars. This figure covers the entire research process, which includes innovation, development, conduct of clinical trials, registry and patents, and stages to be undertaken before a drug obtains approval for marketing or consumption. It is also unclear what the real costs of this whole process are in comparison with the product market price.

The cost to develop drugs is very high, and there is a large uncertainty associated to the whole process. In addition, the prices for pharmaceutical / biotech drugs are strictly regulated by authorities in many countries in the world, and there is not a large margin for the pharmaceutical companies to balance their investments and expenses with income received from the sales of their products.

On the other hand, given that the time a company can sell its product exclusively is limited (what is referred to as patent validity time), it is to be expected that it would want to

amortize the claimed or “supposed” production costs to their maximum. Another option for these companies is to present drugs with a patent that is about to expire as “new” products in which only the presentation form, the pharmaceutical formula or the release forms have been modified, but without any modification having been made to the original active ingredient. In truth, these so called new drugs would in fact be old drugs disguised as novel drugs.

Example: Another way around it is to add other components to the old drugs (e.g. aspirin with vitamin C) that permit to increase the market quote and that are normally sold at a higher price simply because they are considered “new drugs”.

It is also common for the pharmaceutical industry to promote and finance the research and development of drugs that might have competitive power against similar products from the competition to have an increasingly important market. These drugs are the so called me-too drugs that are from the same family with very similar benefits and risks to existing drugs.

In addition, there also exist the so-called “rare” diseases, called that way because a very small number of people suffer from these conditions, and, therefore, it is very unlikely that manufacturing companies would ever recover not even the investment they would have had to make to introduce the new drug in the market. This circumstance gives rise to the issue of “orphan drugs”, referred to with this name, because they are developed for the treatment of diseases with no previous drug available.

Once the validity period of a drug patent is finished, this same drug can be manufactured by other companies, normally at a much lower price. This is what is known as generic drugs (drugs that contain the same active ingredient as the “brand” drug but at a much lower sales price). This encourages health authorities around the world to incentivise the dispensation of generic drugs because by doing so important savings in the health care expenses of the countries and their citizens are materialised.

A report from Médecins Sans Frontières (also known as Doctors without Borders), very explicitly titled Fatal Imbalance, showed that even back in 2001 there were and still there are no effective therapeutic options or ongoing research for the diseases that affect particularly poor countries and their citizens, probably because the investment that would be needed to conduct research in these cases would not be sufficiently profitable for the large companies that develop and market these drugs.

4. Clinical trials with drugs for human use

Before a drug is granted approval for sale, it must go through and successfully pass a long approval process on its claimed efficacy and possible toxicity first in laboratory animals and then in humans, and finally in subjects affected with the disease or healthy volunteers. This process is known as “clinical trials”. The organisation that grants approval for sale is known as the “regulatory agency”. Drug companies must send the regulatory body all the information pertaining to the manufacturing process of the drug, possible indications for its toxicity and possible unwanted side effects, as well as the results from mandatory clinical trials, among other requirements.

An important question is: Do manufacturers really report to the regulatory agency all the results yielded by the clinical trials that have been conducted regardless of whether the results obtained demonstrate the greater efficacy of the drug or vice versa?

When clinical trials are performed on healthy volunteers, the study population that is included in clinical trials with drugs is usually composed of a sample of the population considered to be the “ideal population”: subjects aged 20 to 45 years and in good health. But, is this sample really representative of the population that will really be using the drug once it is launched into the market? Probably not. Elderly people are often excluded, and in many instances, it is precisely these people that will be the greatest consumers of the newly developed drug.

For some time now, some countries of the Developing countries (Brazil, India, South Africa, among others) have decided to bypass the rules of international trade (that is, those proclaimed by the richest countries of the planet) with regard to drug patenting and have started to produce generic drugs (of very low cost and therefore quite accessible) for serious diseases that are widespread in these populations.

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