Outlines of pharmaceutical discovery and development

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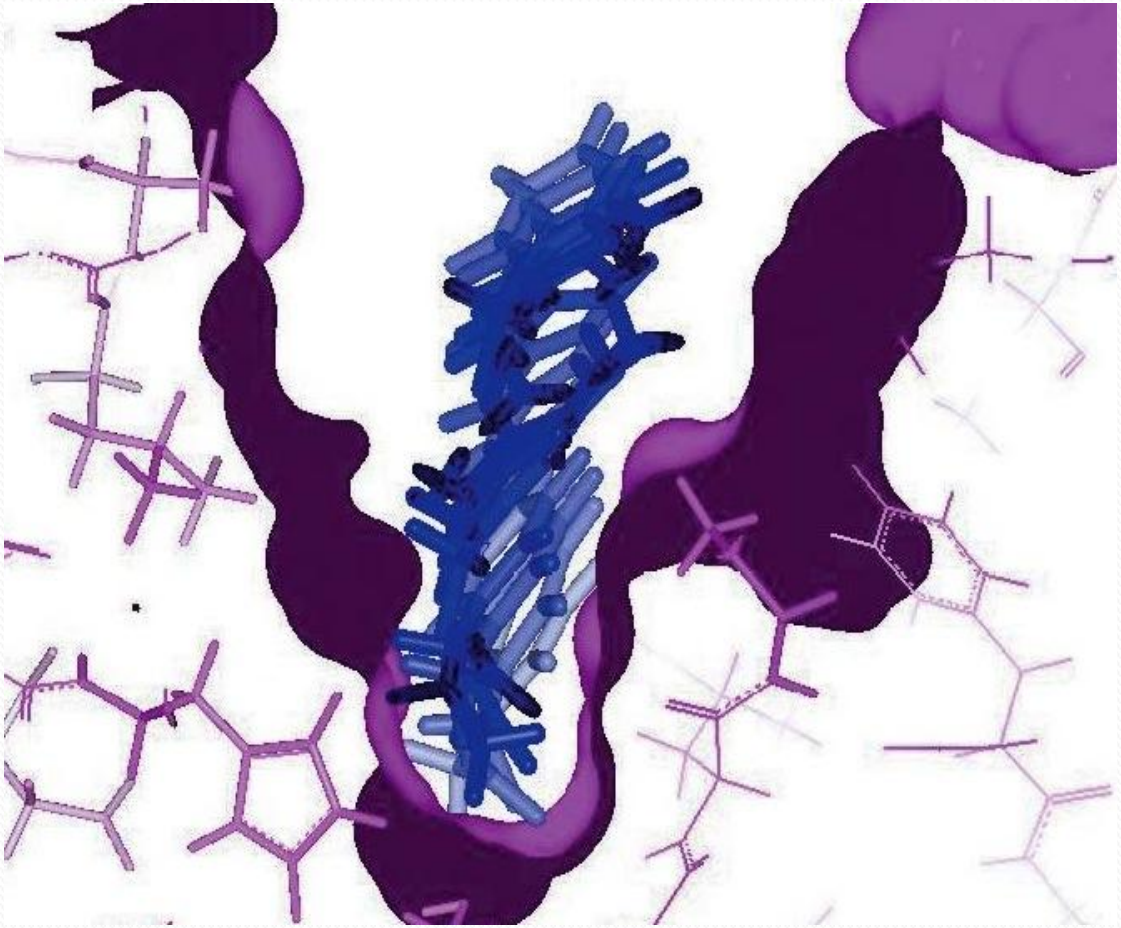
The drug (greek: φάρμακον)

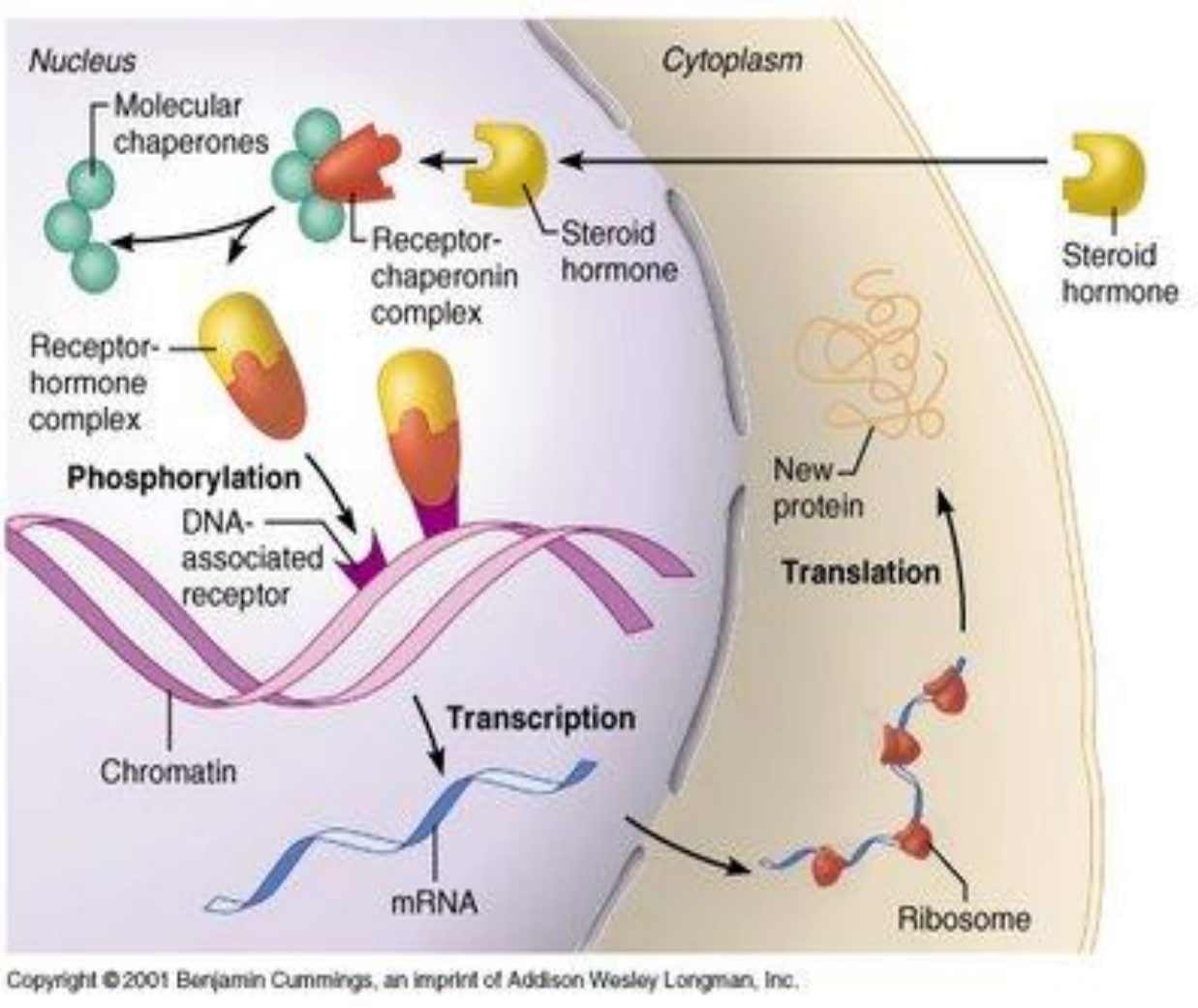
A substance that, by interacting with a biological target, modifies a physiological or pathologic process to produce a therapeutic effect, e.g.:

- bronchodilator: a substance that can expand bronchi by relaxing their smooth muscles, contracted during an asthma attack

The drug links to the substrate…



… and changes the activity of the target



Pharmaceutical R&D

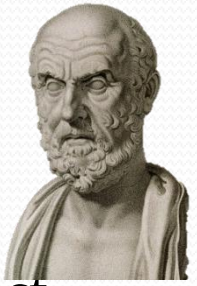
- Our task consits basically of:

«finding the right key for the right keyhole»

- The human body entails billions of keyholes, we have to be specific: interact with the mechanism of action that we want to interact with, interact with as few other targtes as possible (because they could lead to undesired side effects)

The ancient times: how it all begun

The history of pharmacology evolves together with the history of the scientific method. To understand the history of modern pharmacology it is necessary to go back to the ancient ages and to understand the evolution of the scientific doctrine throughout history:



- Hippocrates form Kos (460 - 377 a.C.) was the first to study anatomy and pathology

- Galen (129 – 216) was the first to recognize that there were distinct differences between venous (dark) and arterial (bright) blood.
- Avicenna (980 – 1037): his Canon of Medicine is known for its description of contagious diseases and sexually transmitted diseases, quarantine to limit the spread of infectious diseases, and testing of medicines.

The “middle” ages

Frederick II and the *Schola Medica Salernitana (1200)*

At the court of Frederick II, passionate about medicine, innovative medical treatments and interesting rules for the prevention of epidemics were produced. One of the emperor’s main merit was the establishment of the School of Medicine, through which he funded scientific research and the translation of the treatises of Galen into Latin. Scholars of the University contributed to the "Liber Augustalis", the first constitution-like legislation in many fields, including public health.

The study of anatomy (1400-1500)

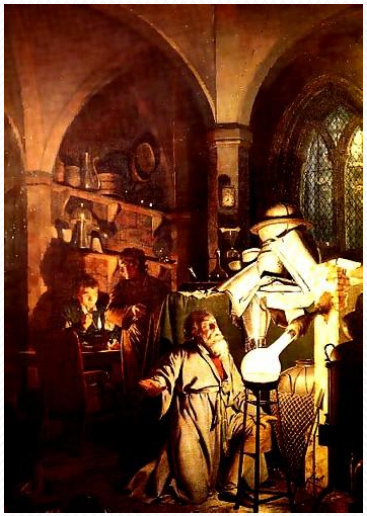
- Antonio Benivieni, a physician at the Hospital of Santa Maria Nuova in Florence, wrote over a hundred clinical observations, the result of Necropsies
- Leonardo da Vinci was the first to represent segments of the human skeleton and to explain how the joints work using the example of the lever
- Andreas Vesalius, with his anatomo-phisiological studies ("De humani corporis fabrica", 1543) showed the importance of surgery in the medical practice and the limits of animal studies
- William Harvey, the father of the first observations on the circulation of the blood
- The microscope observations developed in Tuscany by Marcello Malpighi, demonstrated the existence of blood capillaries.

Thanks to their studies the Renaissance medical science and especially surgery have been able to develop and expand knowledge on the functioning of the human body.

The “middle” ages

Alchemy: the art to separate false from true

The alchemists tried to create the "universal panacea", a remedy that would cure all diseases and prolong life indefinitely. The philosopher's stone was the key to these goals. The third objective was to create life. Alchemy can be regarded as the forerunner of the modern science of chemistry prior to the establishment of the scientific method.



Cosimo I de' Medici

Florence was one of the main centers of the so-called Renaissance alchemy. The reason must be sought in the life and works of Cosimo I de 'Medici (1517-1574), who had it translated and disseminated, first in Latin and then in the vernacular, the "Alchemical Corpus" of Hermes Trismegistus.

The new age (of discretion)

Three scientists lay the foundations of pharmacology

- **Christopher Wren** was among the first scientists to perceive the possibility of experimenting on animals the effects of substances. In 1656 injected various substances and liquids intravenously in animals, especially dogs, recording the reactions and effects
- **James Lind**, a Scottish surgeon, who first achieved a controlled clinical trial. In 1747, working for the British Navy, he provided a dietary integration to sailor suffering from scurvy. The group that had taken citrus showed a definitive improvement and Lind had discovered the virtues of vitamin C
- In 1796, **Edward Jenner**, physician to the County of Gloucester (UK), extracted the serum from the blisters on the hands of a milkmaid who had contracted cowpox, a milder form of the disease, and inoculated in a child of 8 years through two incisions on the arm. As those who worked with cows did not contract the human disease, Jenner supposed that the bovine form could provide protection against lethal infection. Six weeks later, Jenner inoculated the boy with smallpox virus, and discovered that his hypothesis was correct: the child would be unaffected. A few months later Jenner repeated the experiment and got the same result (vaccine)

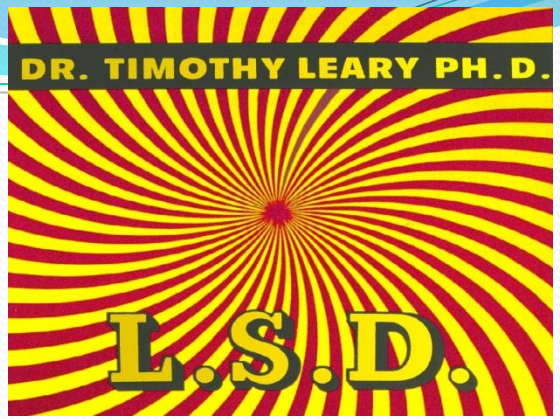
The eighteenth century and the first drug: the anaesthetics

- At the beginning of the nineteen century, **William Thomas Green Morton**, a dentist of Boston, invented the general anesthetic. Morton discovered that ether, a substance known from the '500, drops the patient in a state of deep sleep, allowing the surgeon to operate without inflicting tremendous pain.

The birth of the organic synthesis

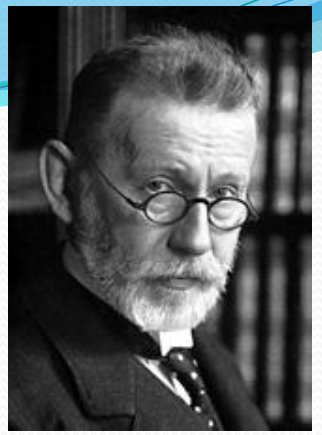
- In 1828, the German chemist **Friedrich Wohler** synthesizes for the first time an organic molecule, urea, by heating an inorganic salt: ammonium cyanate
- In 1869 **Oswald Schmiedeberg** demonstrates that muscarine is able to cause an effect similar to the on that the vagus nerve produces on the heart

The rise of a new era



- The importance of hygiene
  - In 1847 **Ignác Fülöp Semmelweis** realised the importance of disinfection: surgeons must wash hands after dissecting cadavers
- The theory of germs
  - In 1878, in Paris, **Louis Pasteur** presents "The germ theory and its applications to medicine and surgery" at the Academy of Sciences, thus marking the beginning of a conceptual revolution in the history of scientific thought
- The antipyretics
  - The first antipyretic is discovered by accident in 1886. Two doctors, **A. Cahn** and **P. Hepp**, testing the power of a deworming substance, naphthalene, administered by mistake acetanilide to a patient who suffered from various diseases. The administered compound demonstrates properties febrifugal "miraculous"
- The bacteria toxins and the vaccines
  - In 1890 **Emil von Behring** shows that the serum, the liquid part of blood obtained by removing red blood cells, white cells and platelets, taken from animals that had contracted the disease, has the ability to neutralize the harmful effect of tetanus and diphtheria.
- Acetylsalicylic acid: a still up-to-date drug
  - In 1897 **Felix Hoffmann** attached to the hydroxyl group (-OH) to the acetyl salicylic acid, thus forming acetylsalicylic acid. This compound is useful to relieve pain and reduce fever. The first synthetic drug - a new molecule, not a copy of a molecule existing in nature - was born. He is also known for discovery of LSD...

The new Century



The birth of the regulatory authorities

- With the beginning of the twentieth century, it became clear the need to establish monitoring authorities both to fight against dangerous or ineffective substances, and to test all the pharmaceutical specialties the industry is beginning to produce and put into trade. The Food and Drug Administration (FDA, the agency still ruling the sale of drugs and food) was born in the United States in 1906

Problems of toxicity

- In 1910, a bacteriologist, **Paul Ehrlich**, establishes for the first time a synthetic drug (chemotherapy) capable of attacking a germ: the germ of syphilis. When given to patients, however, the drug has a dark side: it is very toxic, produces severe symptoms (pain, liver damage) and can cause death. It will then be replaced, a few years later, by a derivative thereof less toxic and better tolerated. On the basis of his studies of toxicity, Ehrlich develops a theory that the action of a drug is due to its link with a specific receptor that is found in the body [-> the keyhole]

The new Century

The antibiotics: it's all about a mould

- In 1929, an English physician, **Sir Alexander Fleming**, makes a casual remark about changing the course of history: in a capsule where staphylococci are grown, for carelessness, a common mold accessible through an open window settled on the culture medium rich in nutrients and grew more and more. Fleming notes that in areas of the plate where the colony of mold grew bacteria were dead

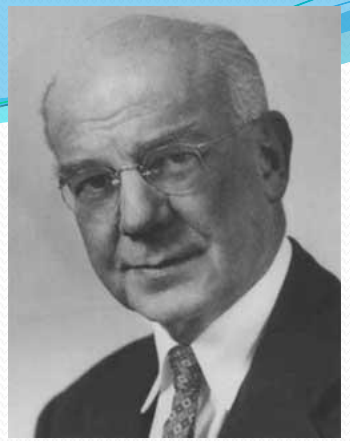
The insulin and the hormones revolution

- In 1921, the Americans **Frederick G. Banting** and **Charles H. Best** discovered that in pancreas there are well detectable areas, a sort of islands of tissue distinct from the rest of the organ, which produce a substance called "insulin". They extracted, not without difficulty, this substance, and showed its physiological effects and the possibility of therapeutic use in diabetes.

1940-50: the decade of the antibiotics

- The industrial fermentation allows the production of penicillin in large quantities. Drug companies start such research to combat organisms with increasingly powerful antibiotics.

The new Century



The defeat of malaria

- In 1800 in France, the chemical **P.J. Pelletier** and **J.B. Caventou** derived from the bark of Cinchona, the active antimalarial in pure form: an alkaloid that will later be called "quinine". In 1971 artemisin is extracted from the plant Artemisia annua, a drug with no resemblance to previous antimalarials, which are then synthesized by the artemether, artesunate and arteetere.

The tuberculosis

- Throughout the twentieth century, the pharmacological commitment to the prevention of TB is enormous:
  - 1927 the BCG vaccine (named after the two discoverers **Charles Albert Calmette** and **Guérin**)
  - 1944 streptomycin, and isoniazid
  - 1965 in Italy, rifampicin, all antibiotics active against the bacillus of Koch

The discovery of cortisone

- **Edward C. Kendall**, a researcher at the Mayo Clinic in Rochester (USA), conducted research on the cortical component of the adrenal glands. Kendall isolated a compound with a high anti-inflammatory power . Later, this compound was developed by another researcher, Lewis H. Sarett, who in 1944, after a complex production process, came to the synthesis of the final product, cortisone.

Fifties to Yesterday

The first pharmacological studies

- In 1955, with the publication of the article by **Henry K. Beecher** called "The Powerful Placebo," the placebo effect is considered a scientific fact. Beecher is the first author that quantifies the effects of placebo in several diseases, thus being able to argue that a placebo can be a medical treatment.

From the sedatives to the antidepressants

- In 1955, **Frank M. Berger** finds meprobamate, a tranquilizer, which seemed at the time could solve the problems of anxiety. The first benzodiazepine was discovered shortly after, in 1957, thanks to research by **Leo Sternbach**: chlordiazepoxide.

The hypertension

- In 1949 the cardiologist **William Schwartz** administered sulphonamide to three patients with severe heart failure and all three are greatly enhanced. Schwartz found, however, that the continuous use of such a drug can be somewhat toxic. The chemist **Karl Beyer** modified the formula to the sulfonamide, creating chlorothiazide. The drug, administered to 10 hypertensive patients, brought their pressure within normal values in a few days.

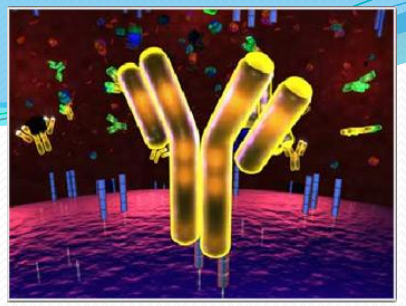
The statins

- In 1976, two pharmaceutical companies, one Japanese and one British, found that mevastatina, selected from over 8,000 compounds capable of inhibiting the synthesis of sterols, blocks the production of cholesterol in the body. Cholesterol, in fact, is not only introduced through the diet: a significant portion is produced by the human body itself and is an important component of cell membranes. The interest in cholesterol in the 50s found, thanks to the **Framingham Study**, the relationship between high blood cholesterol and risk of heart attack and stroke was discovered. The first drug of this class was lovastatin in 1987.

Fifties to Yesterday

- Transplant and reject
  - The first drug to be used as an immunosuppressant was azathioprine, administered in combination with cortisone: was 1962. A cornerstone of immunosuppressive therapy is cyclosporin A, discovered by **Jean Francois Borel**. The advantage, compared to the previously used drugs, consists in the fact that weakens the immune response against the transplanted organ, but does not alter the force to the immune system when this comes into contact with viruses and bacteria.
- The discovery of the DNA
  - On April 25, 1953 **James Watson** and **Francis Crick** describe in a short letter in the journal Nature their discovery: the molecular structure of DNA, preserved in the nucleus of all living organisms. The identification of its structure has revolutionized the scientific world. The discovery of DNA has overstepped the boundaries of biology and inspired the most diverse sectors of society in the century just ended.
- From incurable disease to the cancer therapy
  - In the '40s and then the researchers develop drugs based on the principles of nitrogen mustard (the so-called alkylating agents)
  - A few years after the American pediatrician **Sidney Farber**, Boston University, shows that aminopterin, a folic acid vitamin derivative, is able to induce remission in children suffering from acute leukemia
  - The first therapy for metastatic cancer is administered in 1956
  - According to a recent study, only one patient out of ten had to leave work in the four years after diagnosis. Four out of ten have discontinued activities during the treatment, but they resumed soon after.

Fifties to Yesterday



Genetic engineering

- In 1972 **Paul Berg** (Stanford University) created the first DNA molecule reconstructed by combining the DNA of two different organisms. Berg understood the dangers of his experiment and temporarily suspended it. Therefore he proposed a moratorium on studies of reassembled DNA. Then, he resumed his studies on the technique of the reassembled DNA (or recombinant) and, in 1980, he was awarded the Nobel Prize for chemistry

The Eighties: the AIDS emergency

- In 1984 in France, the Pasteur Institute identified a virus that seems related to acquired immunodeficiency syndrome (AIDS).
- In 1987 AZT (azidothymidine), the first anti-AIDS molecule is approved. A year later, on 1 December, the first World Day against AIDS is celebrated. In 1991, new anti-AIDS: the DDI (didanosine) is approved; like AZT, it inhibits an enzyme necessary for viral replication, reverse transcriptase.
- The real breakthrough in the treatment of AIDS was the appearance, in the early '90s, of the protease inhibitors, a class of drugs that can eradicate the virus from the blood, though it does not cure the disease

The development of immunology

- During the '80s immunology, i.e. the branch of biomedical science that deals with the immune system, has had an extraordinary development. Today the bio-medical community knows in detail several mechanisms of the immune system: a unique and complex set of chemical and cellular systems potentially active against everything the body recognizes as something different from itself.
- The discovery of monoclonal antibodies has led to important innovations in the diagnostic industry. These highly specific antibodies, which bind only to a single antigen, have found significant use in oncology, because they allow to distinguish specifically the structures produced by tumor cells.

R&D: a complicated business

"Here's how it works. First we discover the drug and identify the market, then we invent the disease."

Four possible paths to develop a drug

1. Natural drugs: pharmacologically active ingredients already available in nature, such as: acetylsalicylic acid, quinine-based antimalarial, many antibiotics and even some antitumor drugs (taxanes).
2. Chemical synthesis: based upon the computer-aided screening (HTS or High Throughput Screening) of a large number of molecules that can interact with the biological mechanism in scope.
3. Recombinant DNA techniques: the most recent way uses the biological systems (usually bacteria, yeasts or mammal cells) to produce active substances, e.g antibodies.
4. Advanced therapies: cells, tissues, genes.

The research & development process

1) Research:

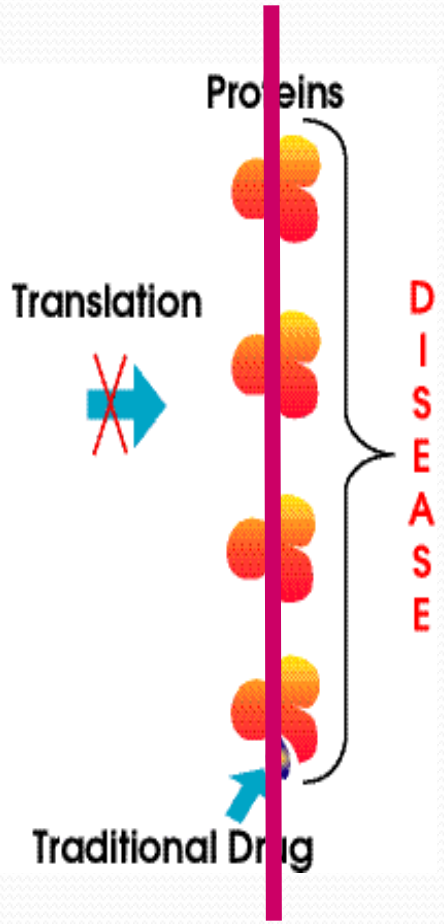
- Basic: study of the human biological functions at a molecular / cellular level, to identify new therapeutical targets [-> the keyhole]
- Applied: identification of new chemical entities with pharmacological activities on the established targets [-> the key]

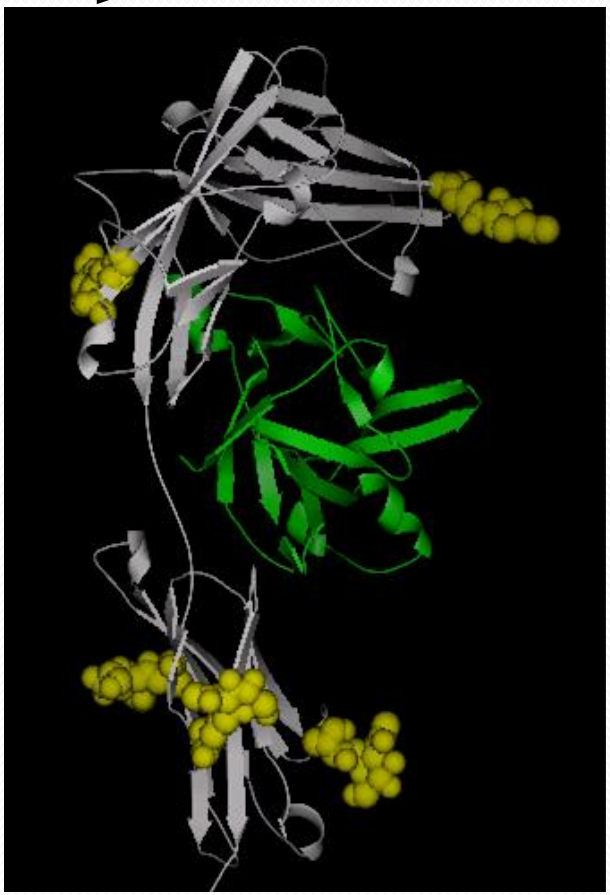
2) Development:

- All the activities needed to demonstrate the pharmacological and therapeutical efficacy of the new molecules
- Study of the new molecole in animal models and in men

Biological targets

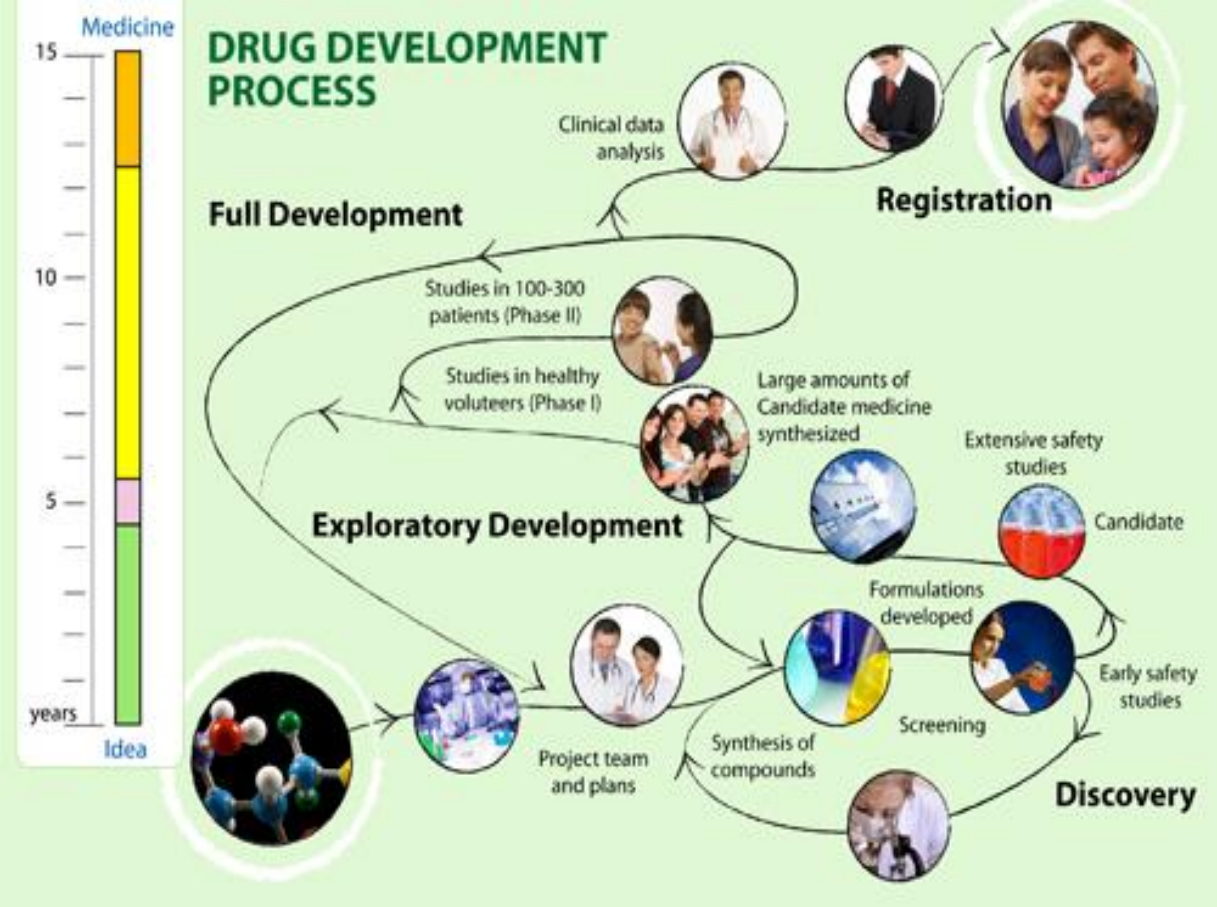
Genomics ← → **Pharmacology**



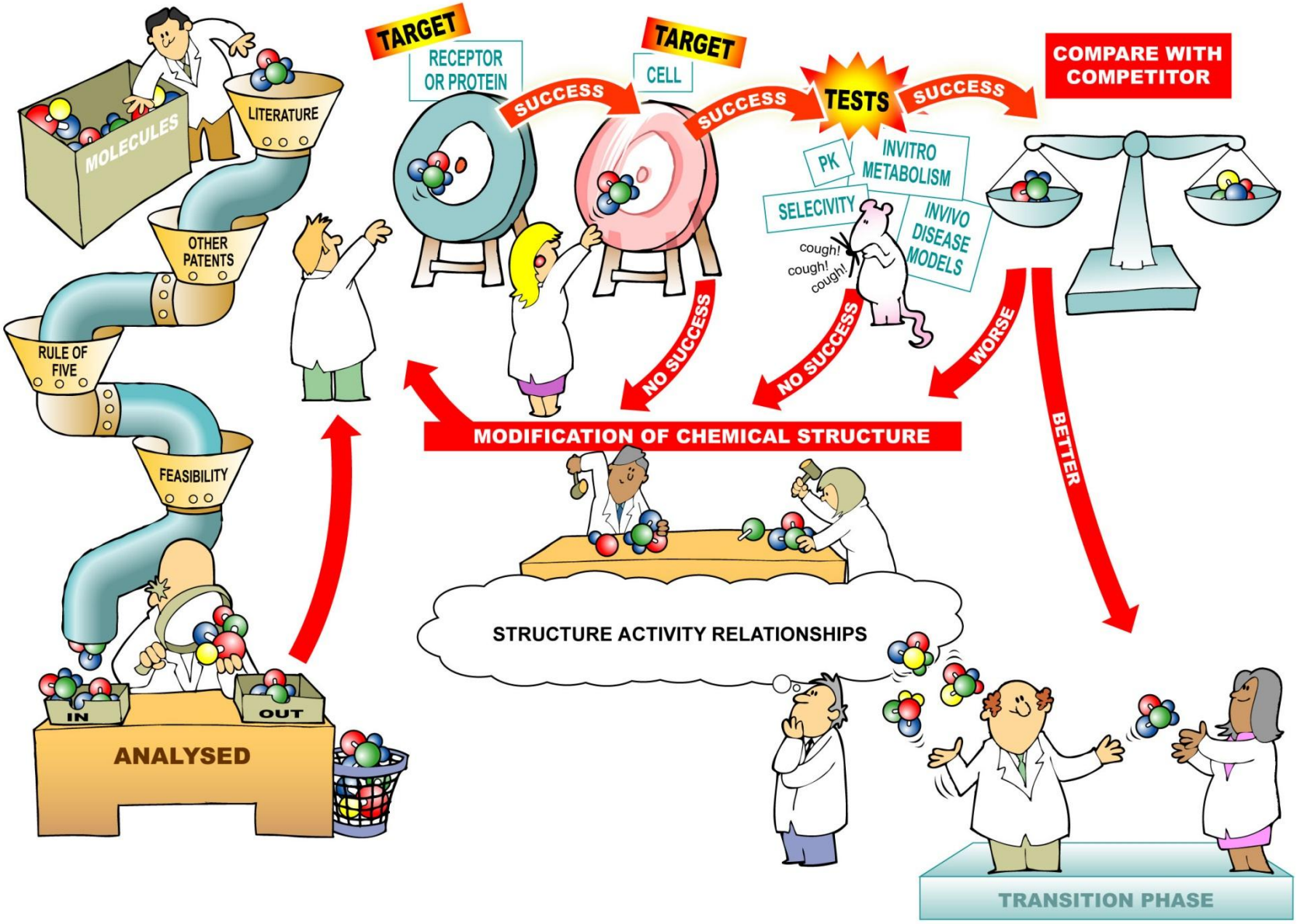


The complex path of a new drug

The phases of development of a new drug are partially overlapped and iterative

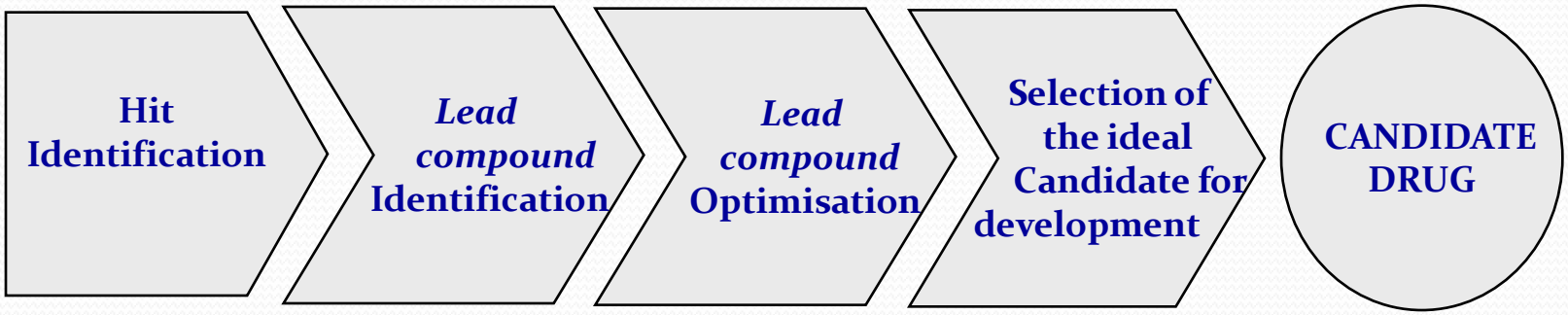


What we do in “Research”



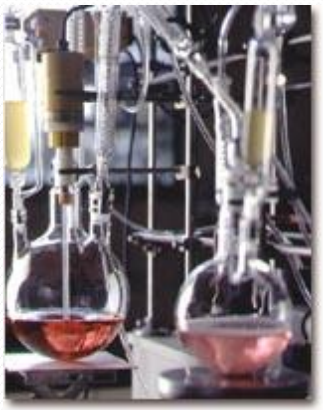
The “Research” phase

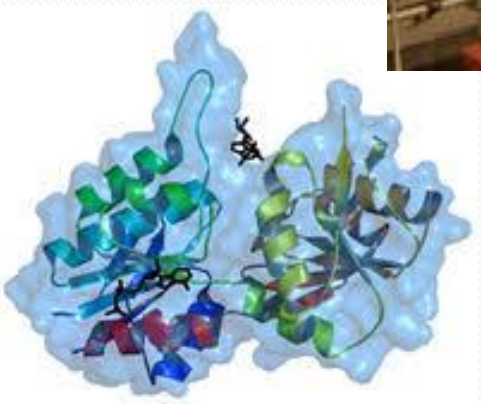
- Devoted to pharmacological innovation:
  - We define the target we want to hit (-> the keyhole)
  - We synthetise/identify molecules able to interact with the target (-> the keys)
  - We evaluate therapeutic efficacy in in vitro and in vivo experimental models (-> we try the keys to find the most suitable one)



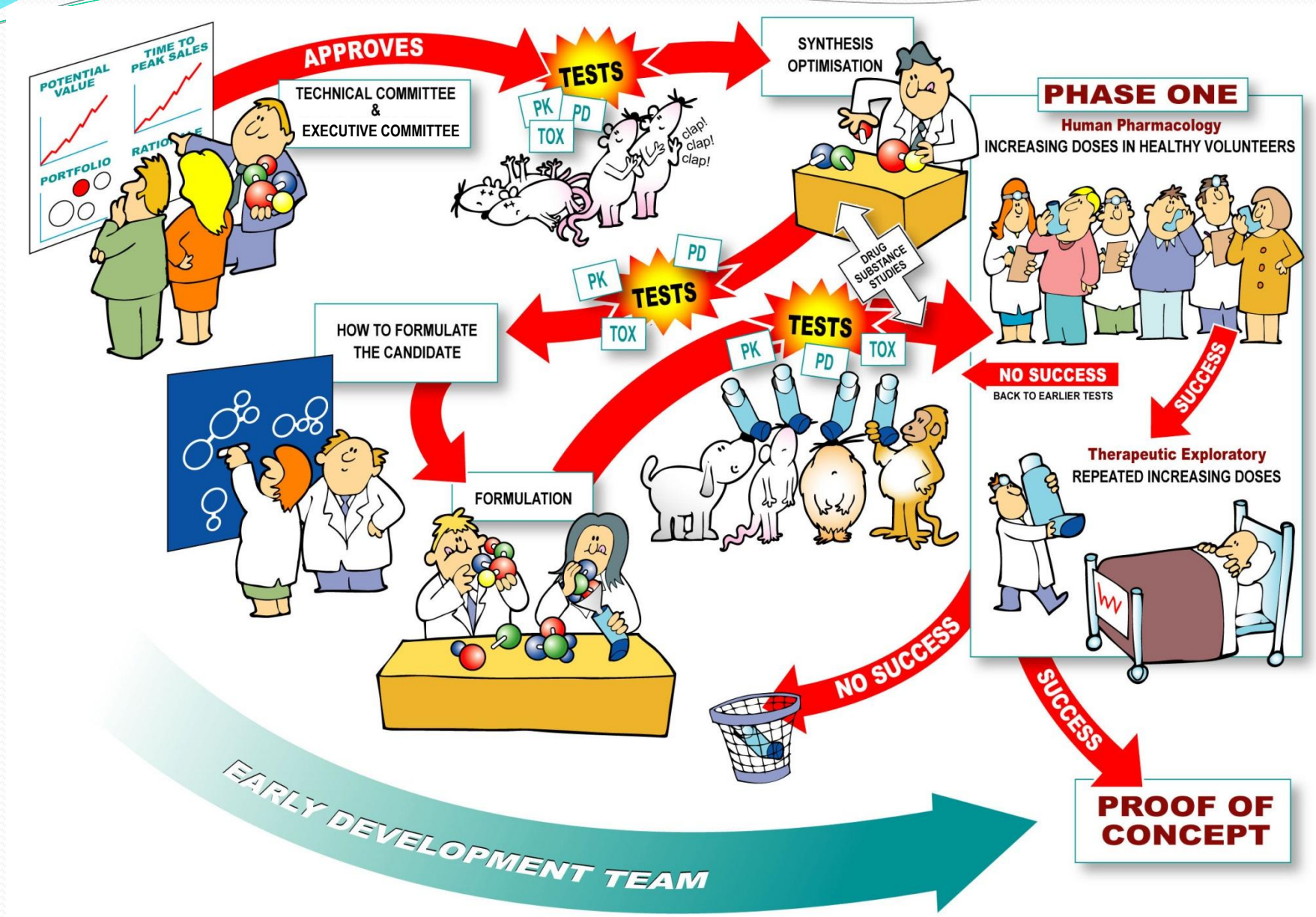
Medicinal chemistry

- Finding the «key»:



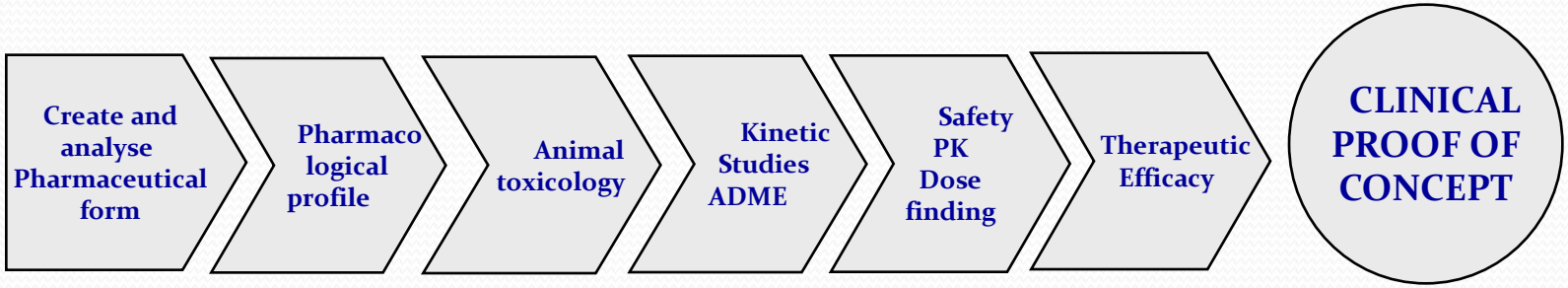


What we do in the "Learn" Phase



The "Learn" Phase

- The "Learn" establishes the so called "proof of concept"
  - We identify an appropriate formulation
  - We conduct toxicology studies in various animal species
  - We study the drug metabolism in the human body
  - We establish safety and active doses
  - We identify a maximum of two effective doses in the desired indication to progress into full development (pivotal studies)

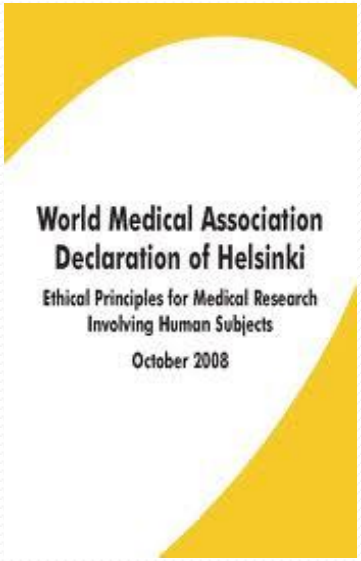


Animal welfare

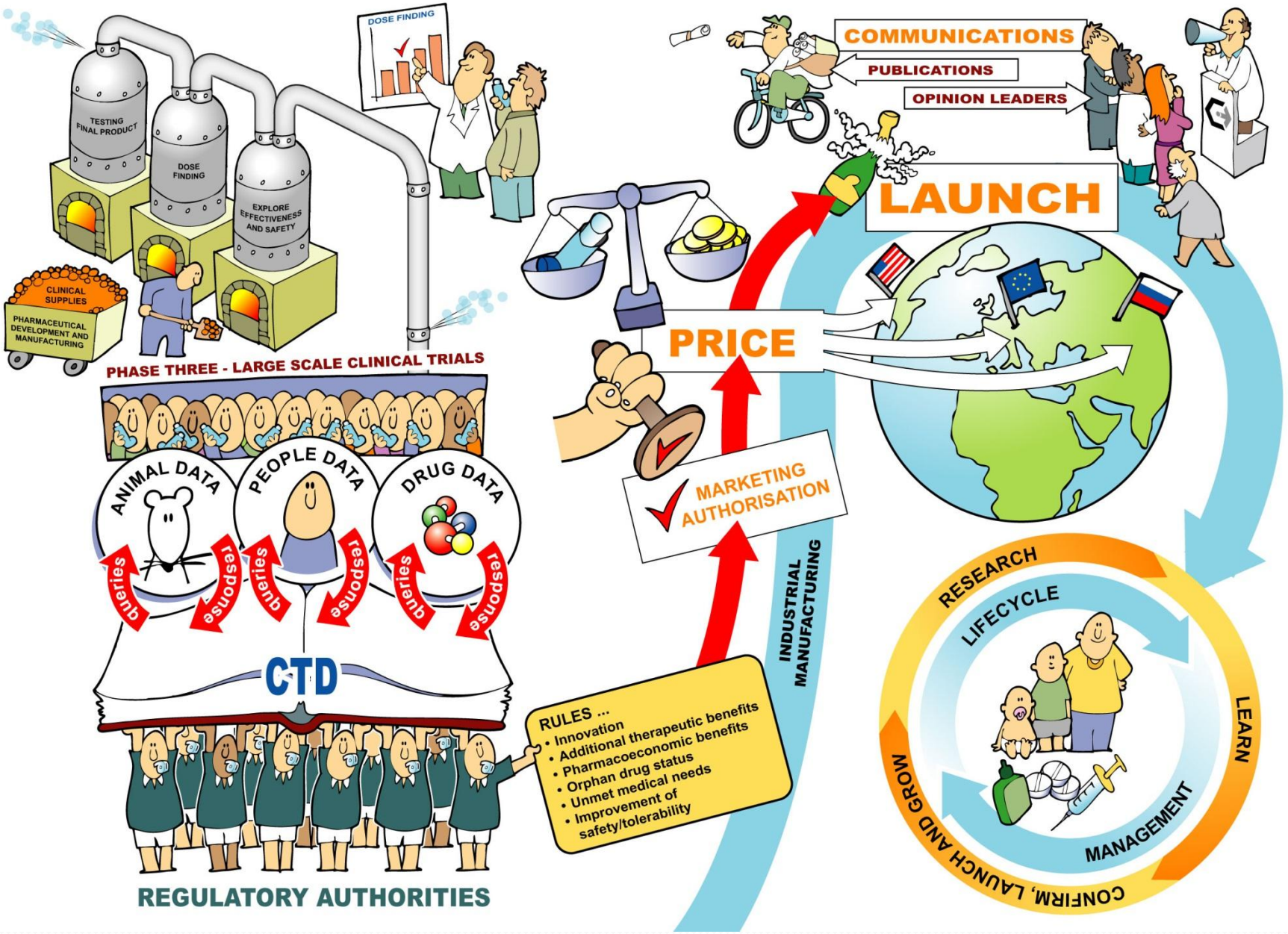
- Is regulated by;
  - rules [i.e. laws]
  - praxis
  - scientific know how
- Good «Animal» practices have been issued since the '90s
- The «3R» initiative helps create the balance between animal welfare and medical research by:
  - Replacing animal testing with non-animal methods whenever scientifically possible
  - Reducing the number of animals required
  - Refinement of techniques so that the distress or pain of animals is avoided or minimised and that animals are always treated with care

Clinical sperimentation

- All humans treated with a drug in sponsored clinical trials are informed volunteers
  - Phase I: healthy (with some exceptions, e.g. cancer)
  - Phase II-II-IV: patients
- The World Medical Association (WMA) has developed the Declaration of Helsinki as a statement of ethical principles for medical research involving human subjects
- Ethical committees (Institutional Review Board) are formally designated to approve, monitor, and review biomedical and behavioural research involving humans



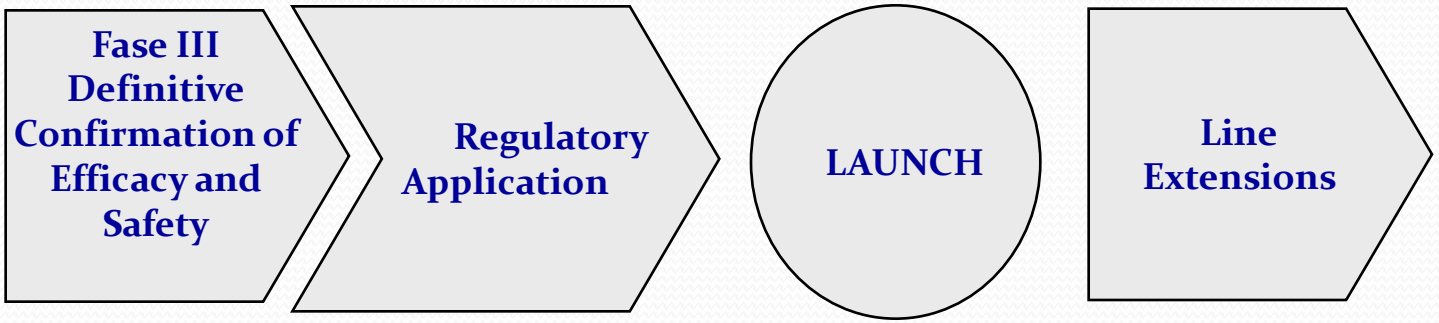
What we do in Confirm, Launch & Grow



The "Confirm Launch & Grow" Phase

- We complete clinical development
  - We demonstrate efficacy and safety in patients with a rigorous comparison with "standard of care" in a larger number of patients (health economics)
  - We expand the the use with studies in all indications and patients populations of interest

Request for Marketing Authorisation (*regulatory dossier*) submitted to the competent Regulatory Authorities (EMA, FDA et al.)



The Regulatory dossier

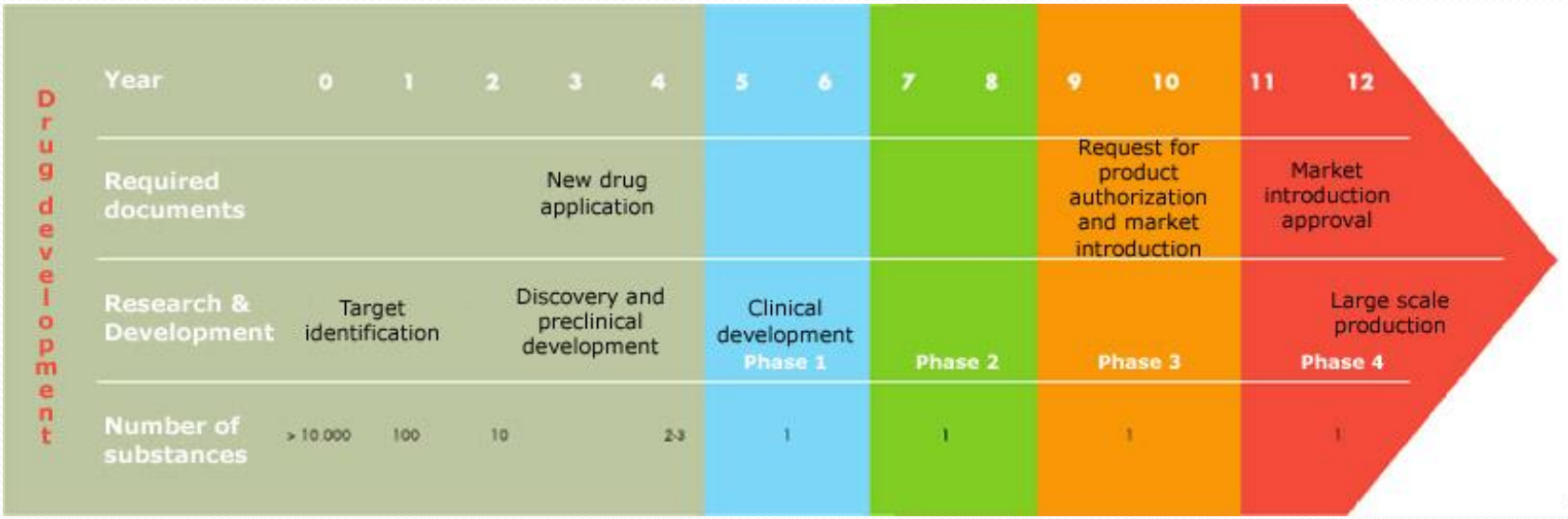
- From paper producers… to CD producers

Pharmacovigilance

- It is the pharmacological science relating to the detection, assessment, understanding and prevention of adverse effects, i.e. long term and short term side effects of medicines [-> undesired locks that are opened by our key]
- It starts from the clinical stage and continues throughout the product life cycle of the drug (pharmacovigilance during pre-marketing and post-marketing)
- Post-marketing surveillance uses different tools that can lead to withdrawal of the Marketing Authorisation of a drug:
  - data mining of spontaneous reporting systems and patient registries
  - investigation of case reports to identify the relationships between drugs and ADRs [-> statistics]
- Recent examples: Cerivastatin, Rofecoxib

How a drug is born

- A drug takes from 12 to 13 years to reach the shelves of a pharmacy: it must successfully overcome many trials and tests before being approved for the market



Tools and organizations of control

1. Guidelines
2. Regulations
3. Convention and biomedical community consensus (praxis)
4. Opinion and evaluation and approval procedures
   - Local authorities (in Italy AIFA, ISS, MINSAL)
   - European authorities (EMA, 1995)
   - American authorities (FDA, 1906)
   - International authorities (ICH, 1990)

The market introduction approval

- All data generated during the development of a drug are collected in a *dossier,* now called Common Technical Document, that is sent to Regulatory bodies around the World for them to evaluate and eventually approve, thus granting a Marketing Authorisation
- The criteria used to develop drugs are regulated to protect patients
  - ⇨ This is why the logic is to test drugs:
    1. first *in vitro*,
    2. then *in vivo,* using animals
    3. finally on men (always volunteers)

Why?

For effective consumer protection, we need to ensure

- safety,
- efficacy,
- quality of drugs,
- relevance and accuracy of product information

  - the Elixir Sulfanilamide (1937-1938) tragedy (US): toxicity
  - the Thalidomide (1957-1961) disaster (EU): teratogenicity

Elixir sulfanilamide

- an improperly prepared sulfanilamide medicine that caused mass poisoning in the United States in 1937
- used diethylene glycol (DEG) as a solvent -> poison
- in 1938 the Food, Drug, and Cosmetic Act was introduced, which required companies to perform animal safety tests on their proposed new drugs and submit the data to the FDA before being allowed to market their products

Thalidomide

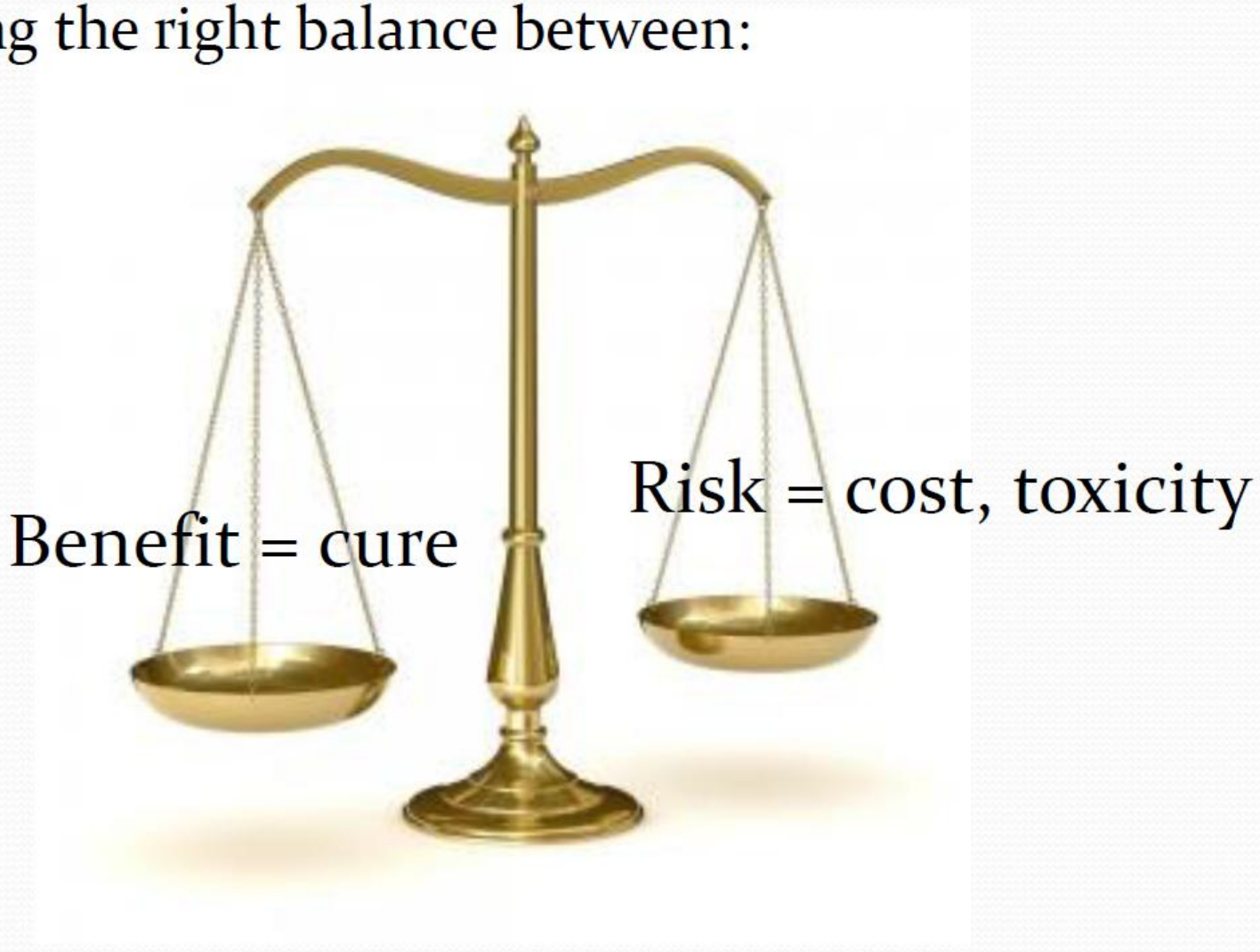
- Marketed in 1957 in 46 countries, hailed as a "wonder drug" that provided a "safe, sound sleep"
- Was also used by pregnant women to reduce morning sickness
- But it caused birth malformations, and death to babies. Any part of the foetus that was in development at the time of ingestion could be affected
- Teratogenicity studies were introduced as compuslory during new drug developments

What?

- Licensing & inspection of manufacturing facilities and distribution channels,
- Product assessment and registration (Marketing Authorisation),
- Adverse Drug Reaction (ADR) monitoring (pharmacovigilance),
- QC,
- Control of drug promotion and advertising,
- Control of clinical trials

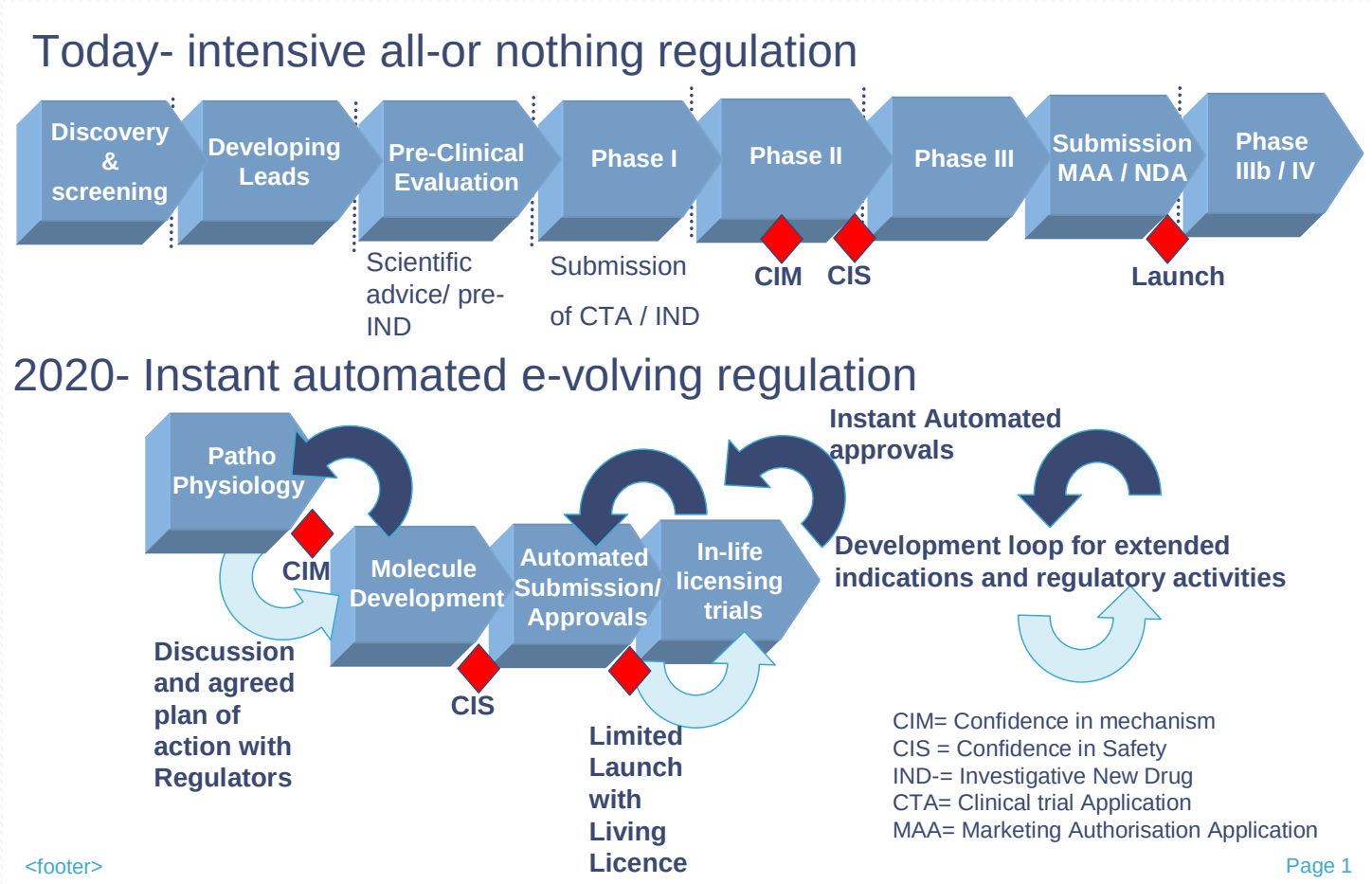
Which is the issue?

- Finding the right balance between:



The rules

The drug development is highly regulated by laws and guidelines, that are supposed to be reviewed to contain times and cost of development, keeping the risks under control in the meantime



The concern of the European Commission

Adaptive licensing – under which drugs would be approved earlier on than at present and on the basis of less evidence – would not comply with the risk-averse bent of the current legal system, said Florian Schmidt, a legal officer in the pharmaceuticals unit at the commission.

“At the moment" the commission is "not convinced" that adaptive licensing is the best way forward, Dr Schmidt said. Legislators and society have shown through legislation introduced over the past 10 years a disposition to risk-aversity, he explained. Adaptive licensing, whereby a license would be granted under conditions of acknowledged uncertainty for an initial limited population and be broadened later on as more real-life data became available, does not meet this risk-averse leaning, he explained.

Unmet medical need, he said, should not be a reason to lower the required level of certainty, but rather it should be an incentive for greater investment in research.

"The danger is that you substitute evidence with hope."

The new course of EMA

- The Agency is presently in discussion with the EC regarding implementation of adaptive licensing (AL). IH2014 is the estimated timeline for the publication of the first implementing documents and for a call for expression of interest for participation in a pilot phase (EMA will then start a dialogue re. application of an AL approach with companies developing innovative treatments targeting unmet medical needs).
- Key elements of AL: a prospective, long-term plan for drug development and approval, agreed among a company, the Agency, HTA bodies and other stakeholders, in multi-stakeholder, parallel SA meetings starting from the early phases of the development; evidence would be firstly generated, and approval initially granted, in the subset(s) of patients where the unmet medical need is highest, if it can be demonstrated that benefits outweigh the uncertainties in the specific subset(s); the authorization will be "adapted" as more evidence is generated and submitted in compliance with the commitment; it is expected that AL will limit off-label use.
- AL differs from conditional approval (CA); the latter is used to accelerate access to drugs that target an unmet medical need in a whole population. CA is an effective tool which has been under-used and will remain available. Exceptional circumstances is definitely a different type of approval from AL, in that evidence is not expected to increase significantly after a EC approval is granted.

What others are doing

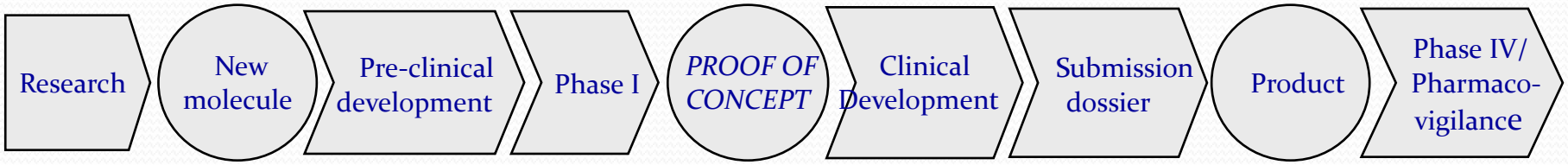
- An example: Japan for Regenerative Medicines

A new, separate approval channel for regenerative medicines has been created and introduced in 2014

- Rather than using phased clinical trials, companies will have to demonstrate efficacy in pilot studies of as few as ten patients in one study, if the change is dramatic enough, or a few hundred when improvement is more marginal
- Following approval, there will be a post-market surveillance period of seven years, after which the treatment will be evaluated again for safety and efficacy

  Every patient must be entered in a registry during that period
- If the therapies prove inefficacious or unsafe, approval can be withdrawn

Quality



- All the R&D activities, from research to pharmacovigilance, are aimed at demonstrating and guaranteeing the safety and the efficacy of the drug
- These activities are regulated by a list of "Good Manufacturing Practices», intended to protect the patient and the community

The GXPs

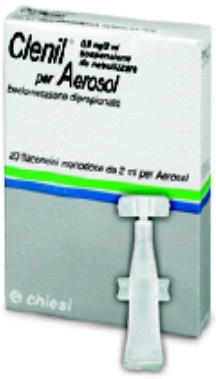
The “Good Manufacturing Practices” - or GXP - rule:

- how to conduct experiments (pre-clinical and clinical)
  - GLP: Good Laboratory Practices
  - GMP: Good Manufacturing Practices
  - GCP: Good Clinical Practices
- how to manufacture the drug:
  - active compound (DS),
  - its formulation (DP),
  - the delivery sssytem (if any)

They are similar to UNI/EN ISO standards, but not equal

The pharmaceutical products

Can vary, are not just molecules, but they need to be administred to the patient in the proper way



The pharmaceutical products

Rx - prescription drugs:

- Drugs that can only be sold with medical precription
  - patented
  - generics

Non-prescription drugs

- Drugs that do not need any medical precription
  - patented
  - generics

Hospital drugs:

- Hospital use only
  - patented
  - generics

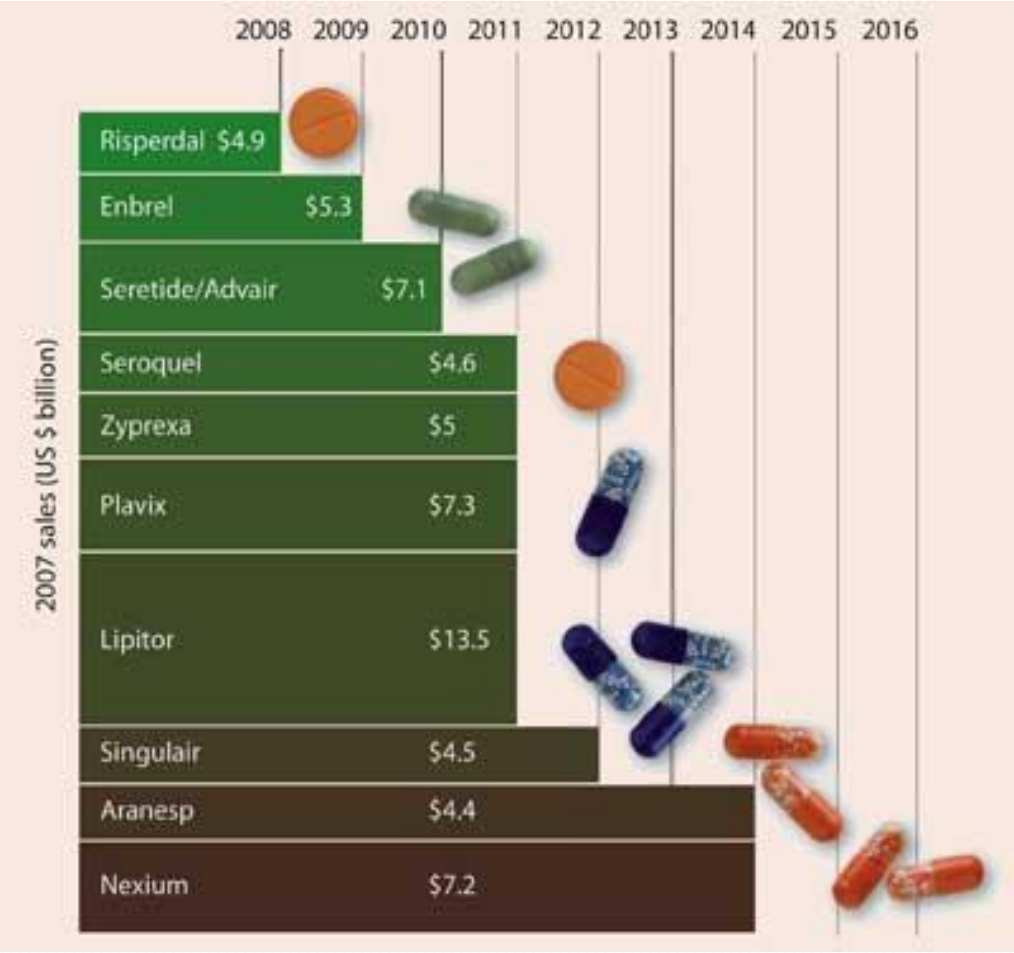
OTC (over the counter):

- Free sale → mass market

Generics

- Drugs originating from a Company's original R&D can be patented, i.e. for a period of time - generally 20 years – after they are patented they can be sold exclusively by the originating Company
- At the end of the period anybody can copy the drug (not just the molecule, but also the formulation and delivery system) and put it on the market
- To be put on the market, generics must show that they are equal to the originator, the way to do it are much easier (and cheaper) than the whole R&D process; generally are limited to *in vitro* studies or minimal *in vivo* trials
- This is why the price is much lower than the originator's

The «patent cliff»



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- This is why the price is much lower than the originator's
- …but this is also where the risk lies;
  - counterfeiting
  - bad quality (esp. on little-known particulars, e.g biosimilars)

The commercial activity

- R&D

- EMA
- FDA
- GXP/MA
- …

- Traders
- Pharmacies
- Hospitals
- GDP
- …

The third-party payer: a (almost) unique model

- Definition: “an organization other than the patient (first party) or health care provider (second party) involved in the financing of personal health services”
- The role of the third-party payer in the European pharmaceutical scenario varies:
  - universal healthcare -> public expenditure
  - co-payment by the patient
  - private insurance
- Price policies on drugs in the last decades have all converged towards cost containment:
  - positive lists
  - price cuts
  - prescription appropriateness
  - …

The present & the future

- In 2008 the world has changed: gene therapy, stem cells, cell-based therapies became “drugs”, Advanced Therapy Medicinal Products

- The information technology and its applications to the pharmaceutical chemistry (> 75 Apps scrutinised by the FDA)

Regulatory Scenario of ATMPs

1. EUROPE:

(a) Regulation 1394/2007 onAdvanced Therapy Medicinal Products,

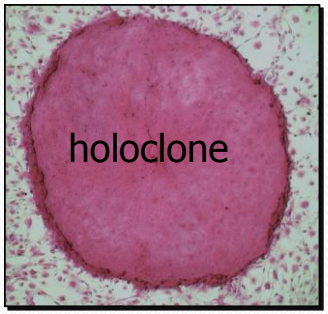
(b) Directive 2001/83 as amended by 120/2009

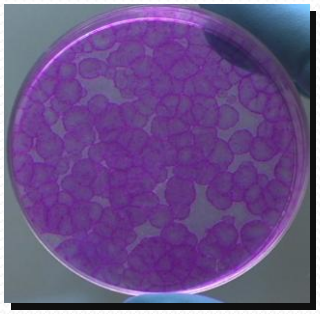
- 81 products designated as ATMP
- 93 Scientific Advices
- 10 products filed:
  - 4 approved: TiGENIX 
  - 2 gene therapy products failed (Cerepro, Advexin)
  - 1 tissue engineering failed (CAOMECS); 1 retrieved
  - 2 under evaluation (incl. Holoclar®)

2. DEVELOPMENT TIMELINES (JPN, EU, USA):
   - J-TEC: JACE 1999 -> 2009 (10 yrs)
   - TiGENIX: ChondroCelect 2000 -> 2009 (9 yrs)
   - Dendreon: Provenge 2000 -> 2010 (10 yrs)

Holostem Terapie Avanzate srl

epithelial stem cell



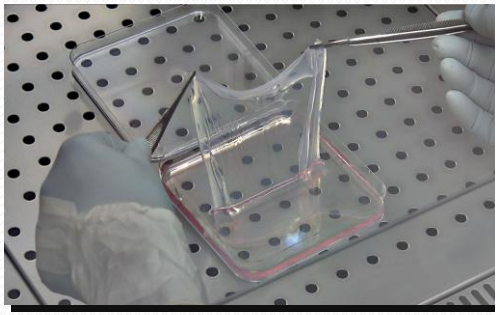


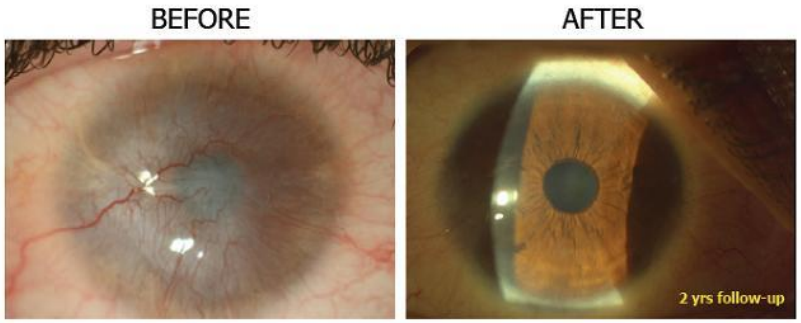
molecular characterization,
trascription factors
regulating self-renewal

Gene therapies

different
forms of EB

corneal
distrophies



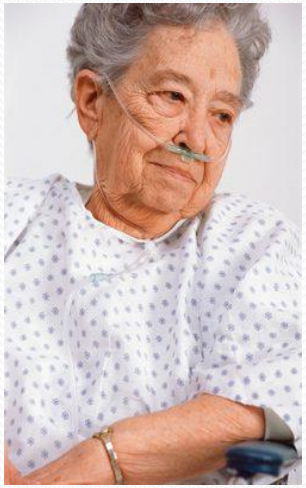


full recovery of visual acuity

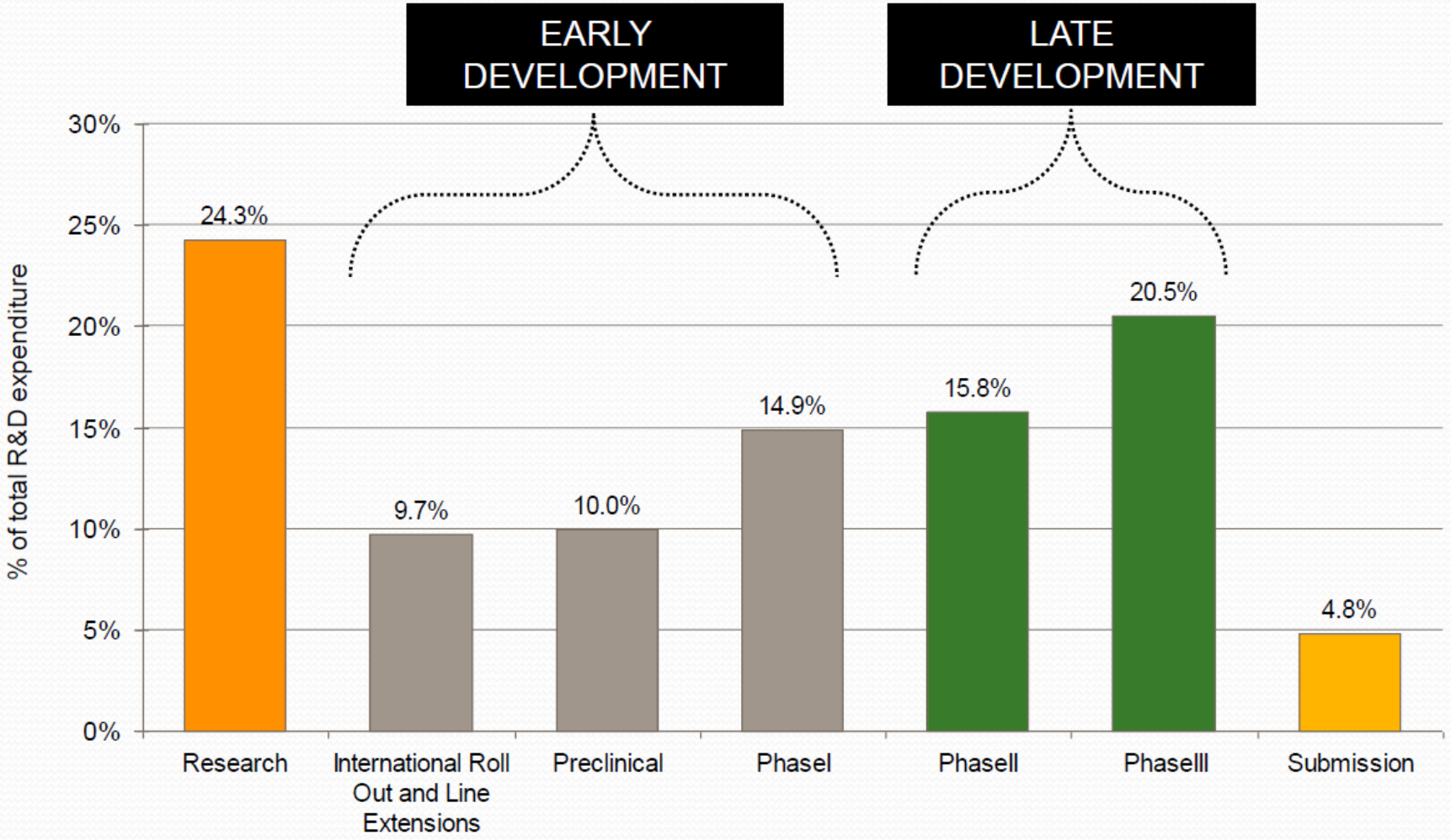
e-CLINICAL

The FORWARD study:

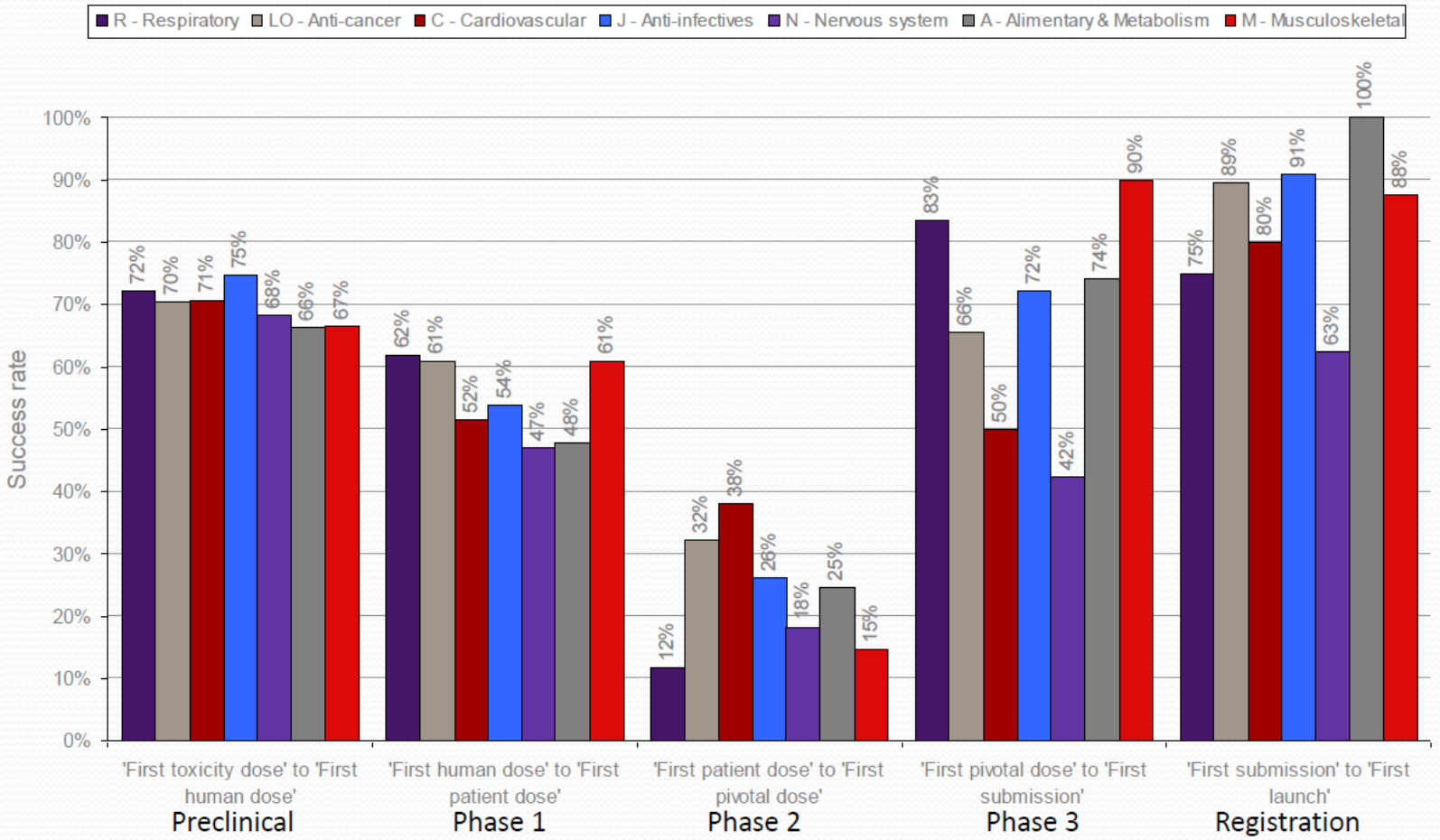
- the first application of digital Patient Related Outcome in a controlled clinical trial setting



The costs of pharmaceutical development

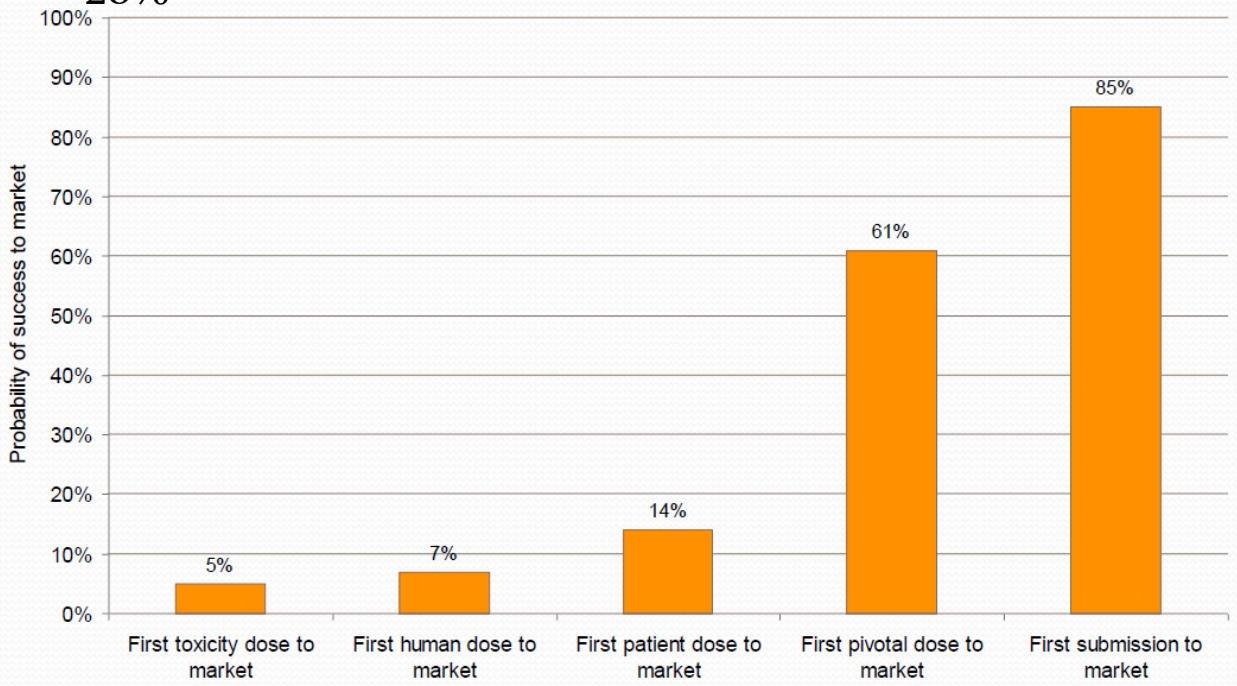


Risks of the pharmaceutical research

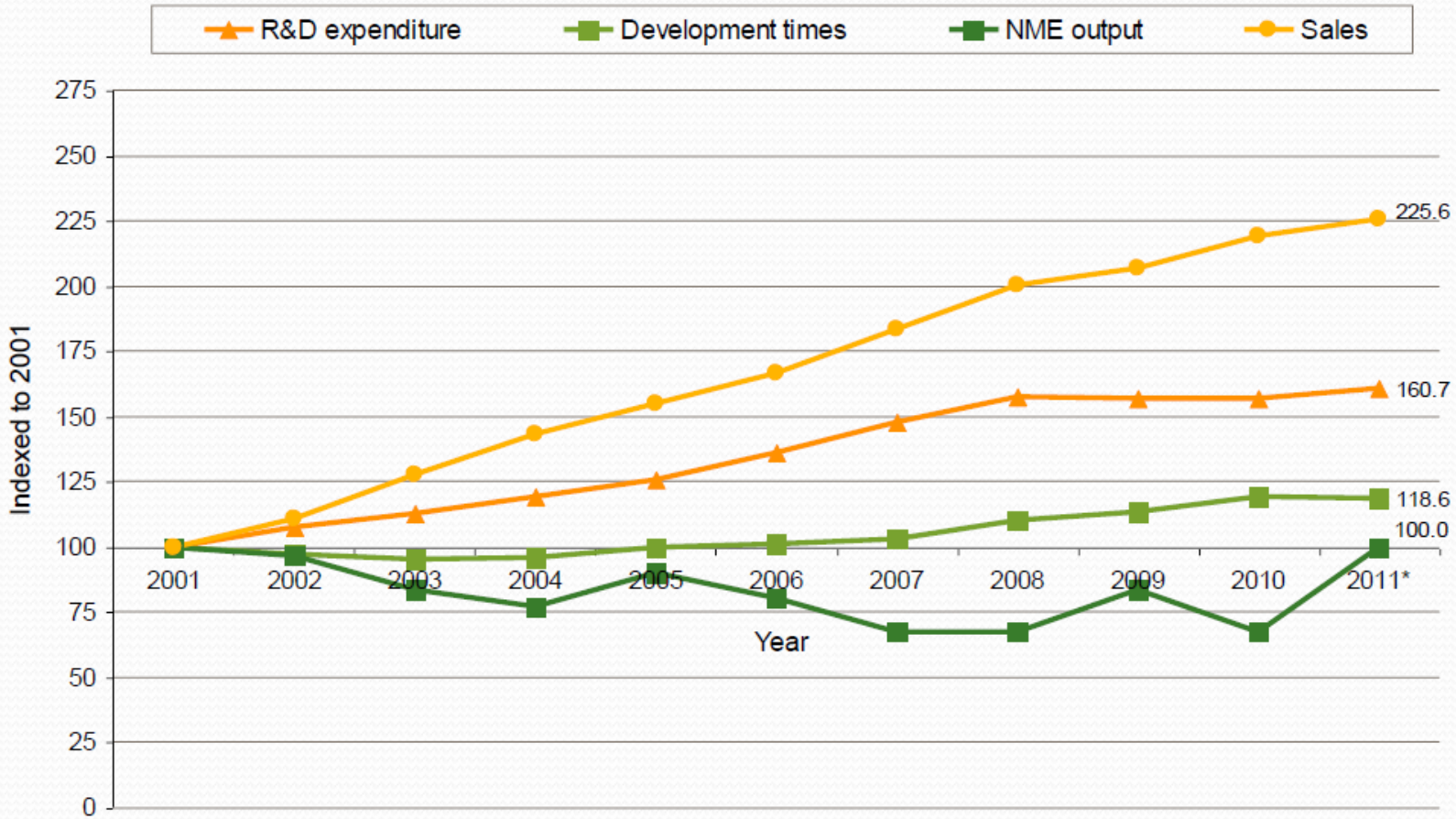


Probability of success to market

- Reasons for dropping drugs:
  - Toxicology: 45%
  - Pharmacokinetics: 10%
  - Clinical profile: 25%
  - Commercial issues: 20%



The costs of discovering of new drugs



Thank you!

What is this all about?

One example in neonatology