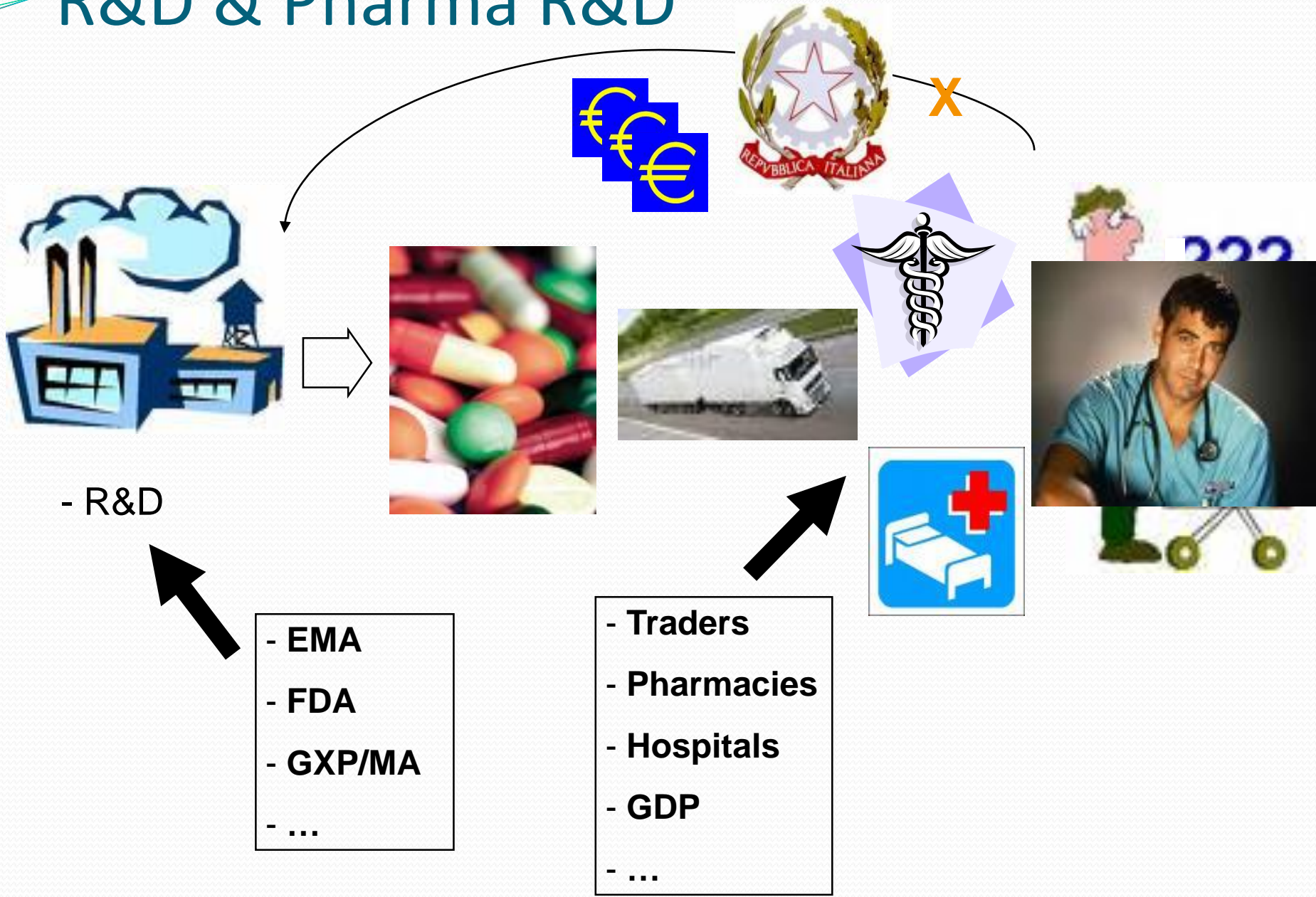


Outlines of pharmaceutical discovery and development

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R&D & Pharma R&D



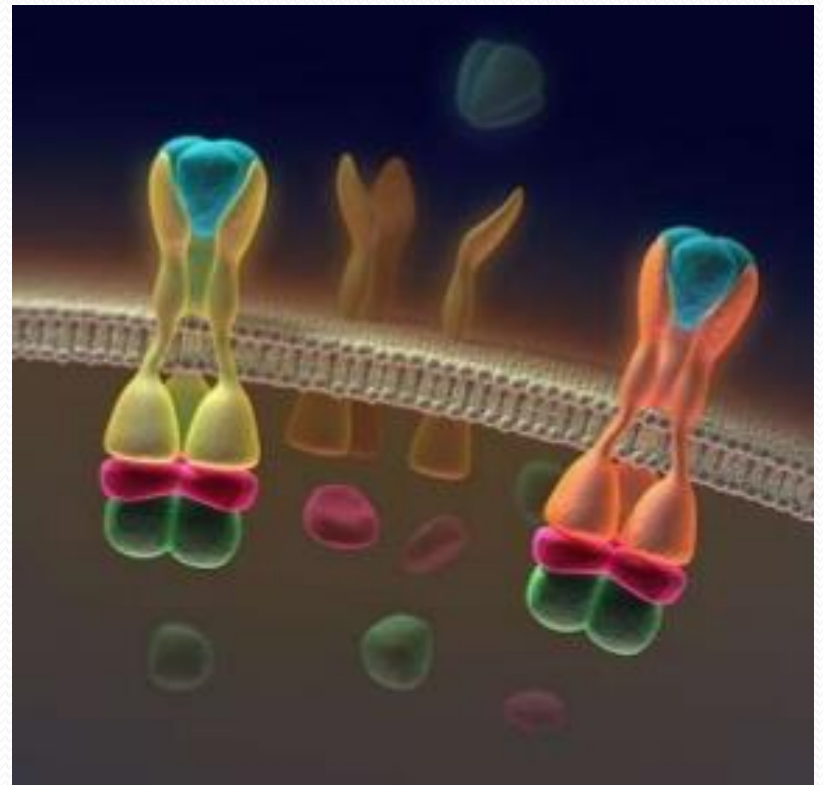
What Pharma R&D is about?

- Our task consists 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 targets as possible (because they could lead to undesired side effects, think about hotel keys opening several rooms...)



What are the keyholes?

- Our keyholes are *receptors*, structures to which our molecules (i.e the drugs, or the keys) attach to, modifying the *biological reactions* of the cell, tissue, organ, body they belong to.
- Generally, they are proteins



The research & development process

1) **Research:**

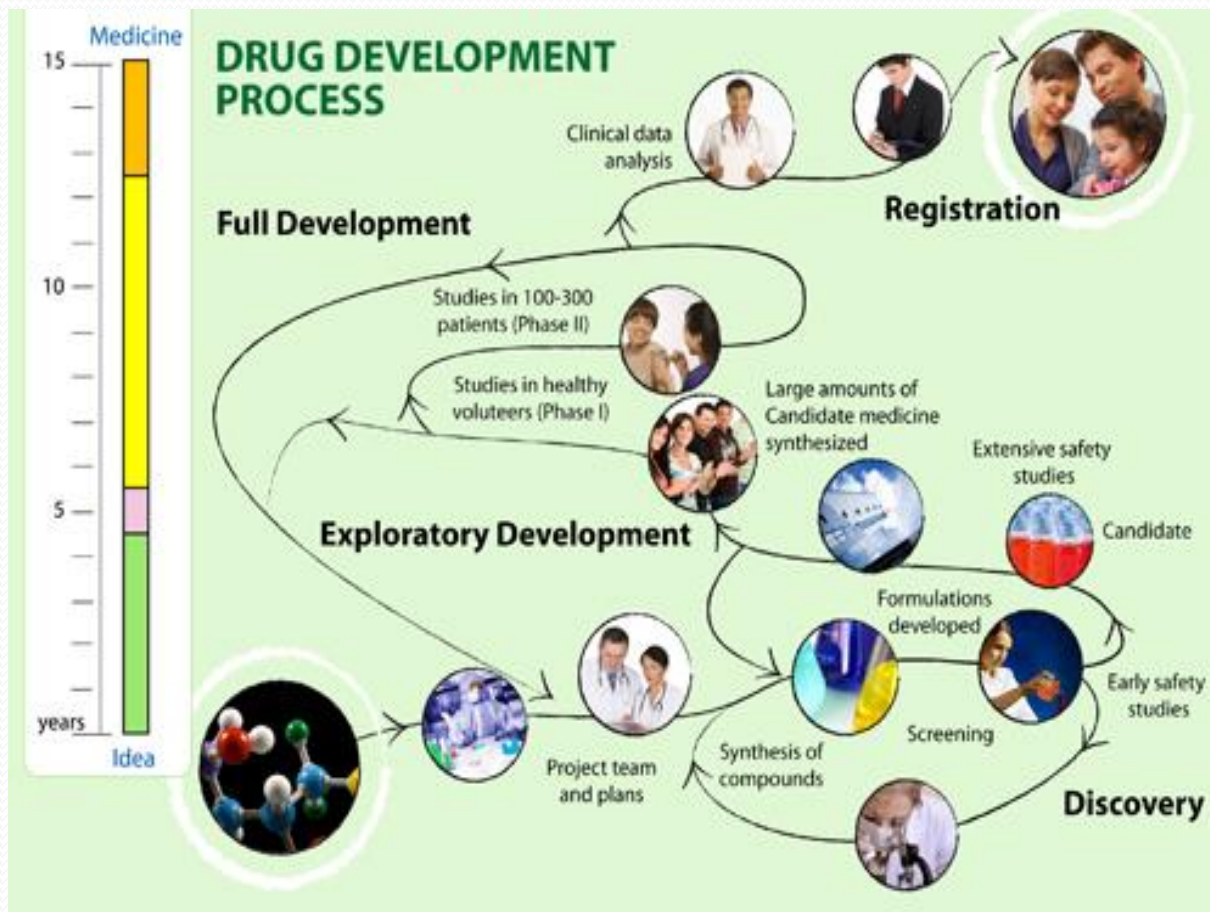
- Basic: study of the human biological functions at a molecular / cellular level, to identify new therapeutical targets [-> the **keyhole**]
- Applied: identification of new chemical entities with pharmacological activities on the established targets [-> the **key**]

2) **Development:**

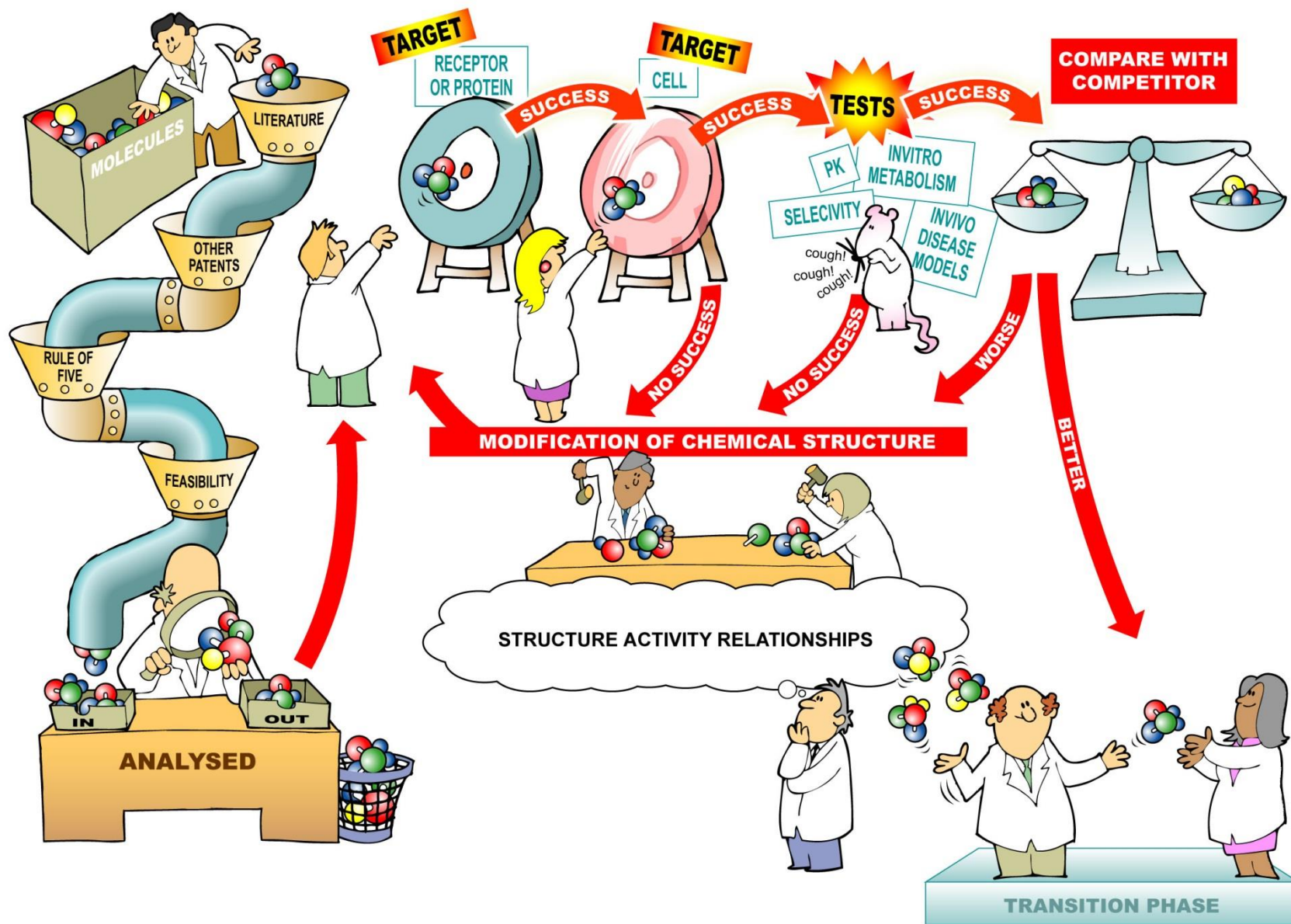
- All the activities needed to demonstrate the pharmacological and therapeutical efficacy of the new molecules
- Study of the new molecule in animal models and in men

The complex path of a new drug

The phases of development of a new drug are partially overlapped and iterative, tend to last around *15 years!*

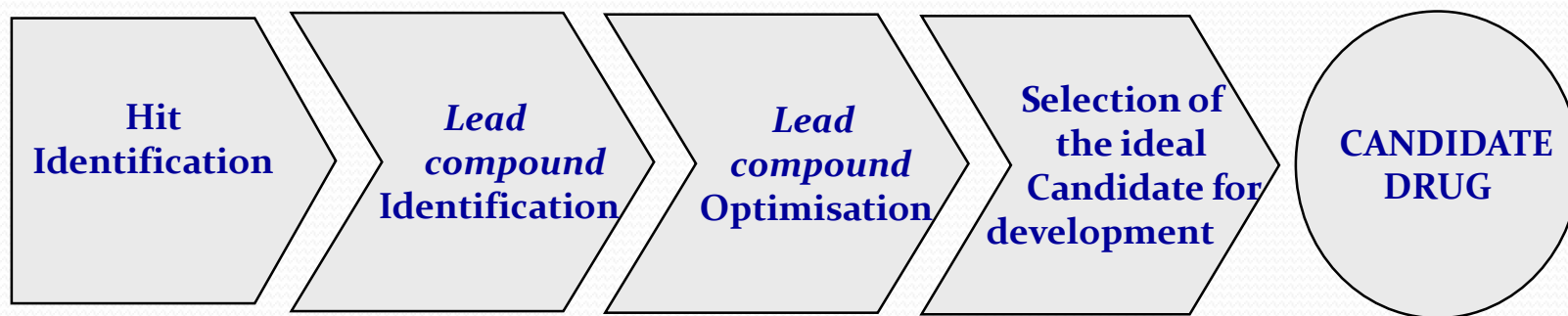


What we do in "Research"



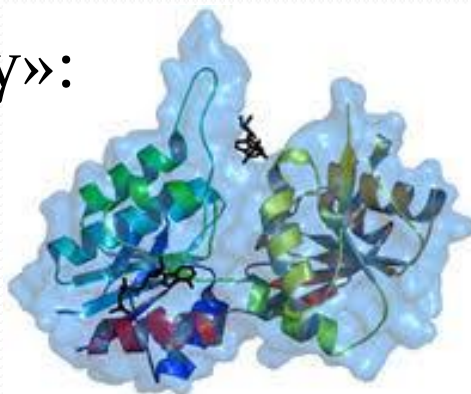
The “Research” phase

- Devoted to pharmacological innovation:
 - We define the target we want to hit (-> the keyhole)
 - We synthesise/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)

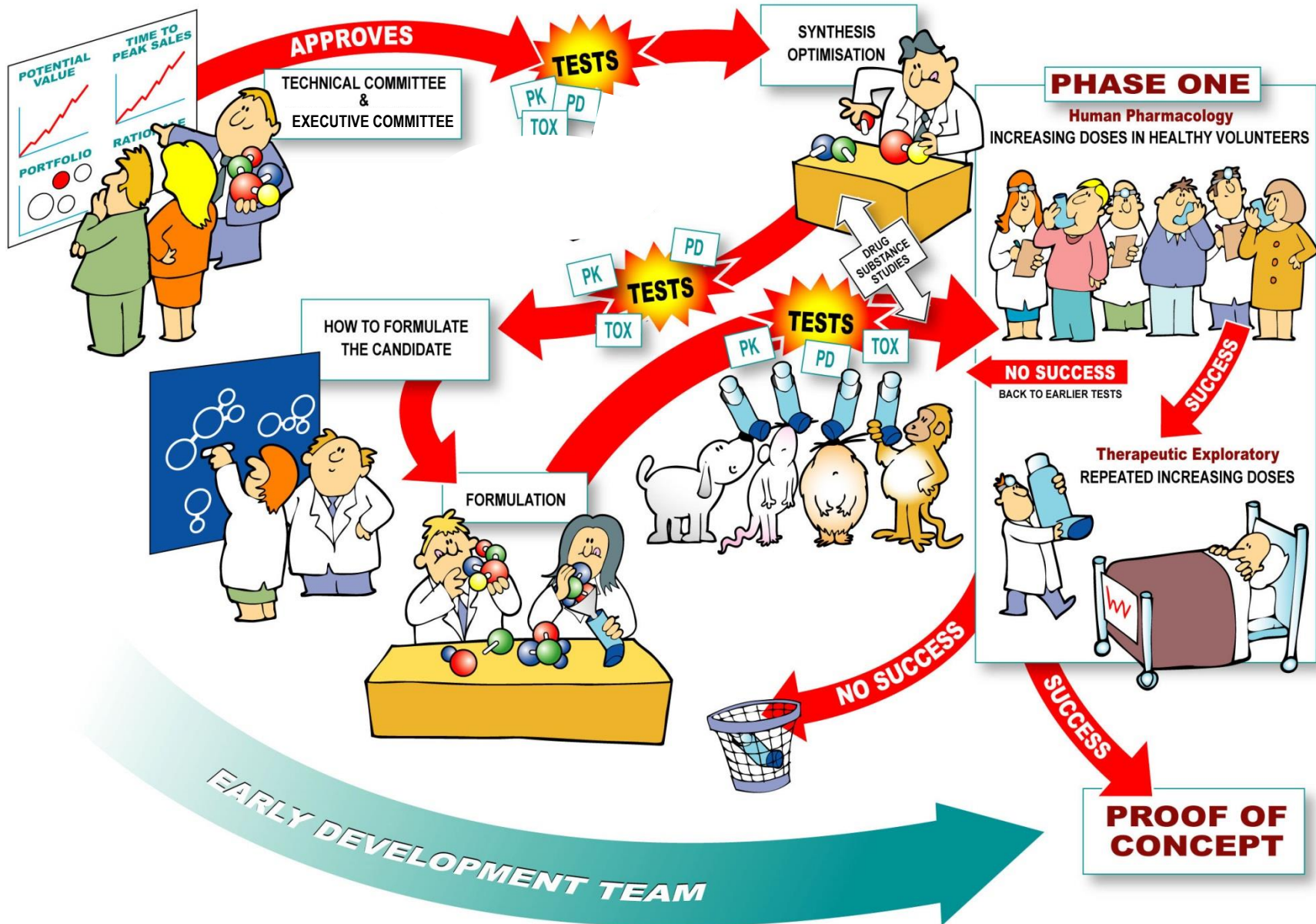


Medicinal chemistry

- Finding the «key»:

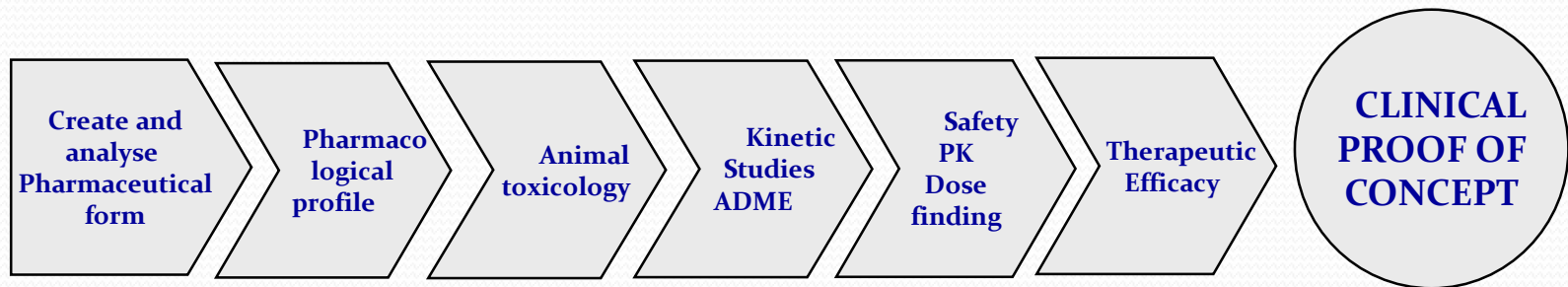


What we do in the "Learn" Phase



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)

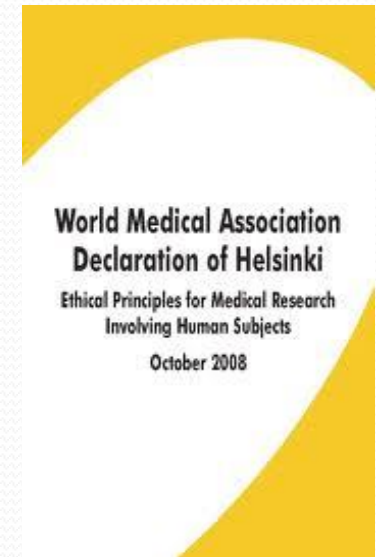


Animal welfare

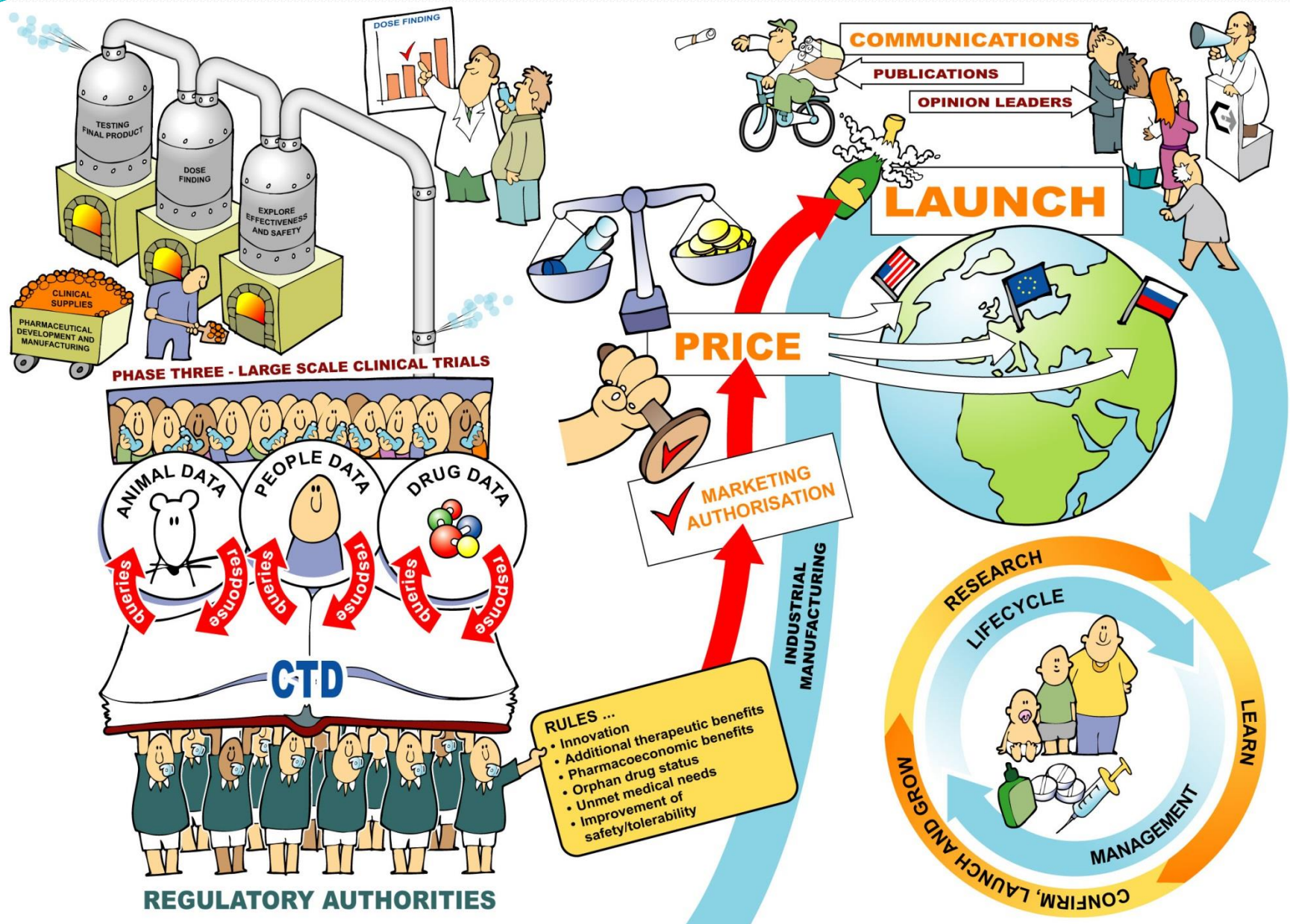
- Is regulated by;
 - rules [i.e. laws]
 - praxis
 - scientific know how
- Good «Animal» practices have been issued since the '90s
- The «3R» initiative helps create the balance between animal welfare and medical research by:
 - **Replacing** animal testing with non-animal methods whenever scientifically 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 experimentation

- All humans treated with a drug in sponsored clinical trials are *informed volunteers*
 - Phase I: **healthy** (with some exceptions, e.g. cancer)
 - Phase II-III-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



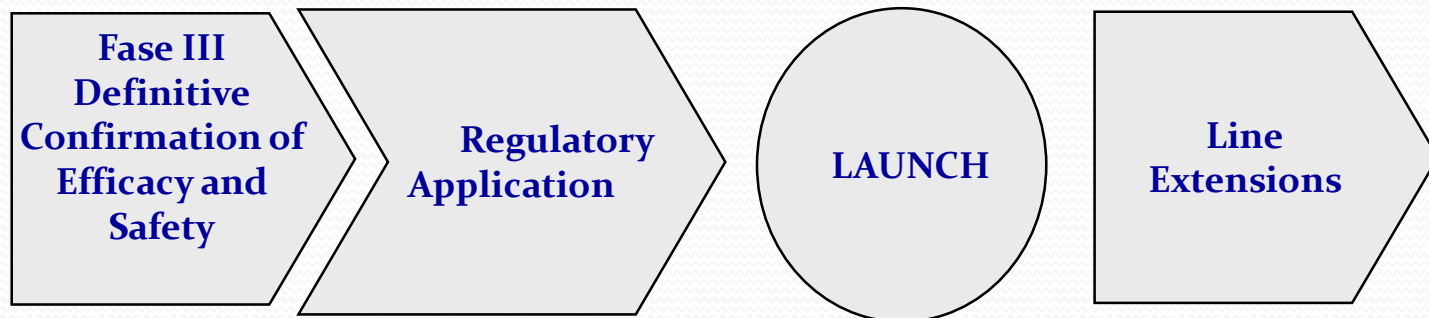
What we do in Confirm, Launch & Grow



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

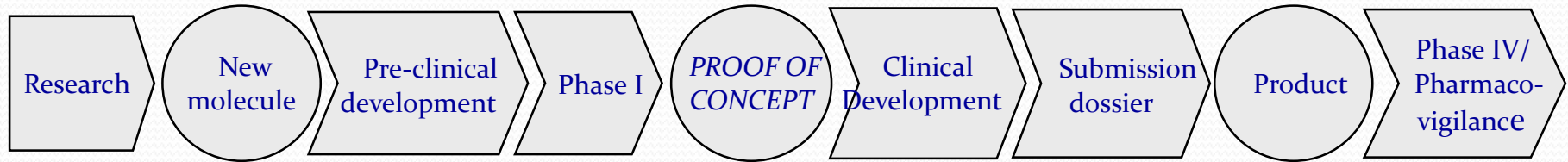
Request for Marketing Authorisation (*regulatory dossier*) submitted to the competent Regulatory Authorities (EMA, FDA et al.)



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

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:

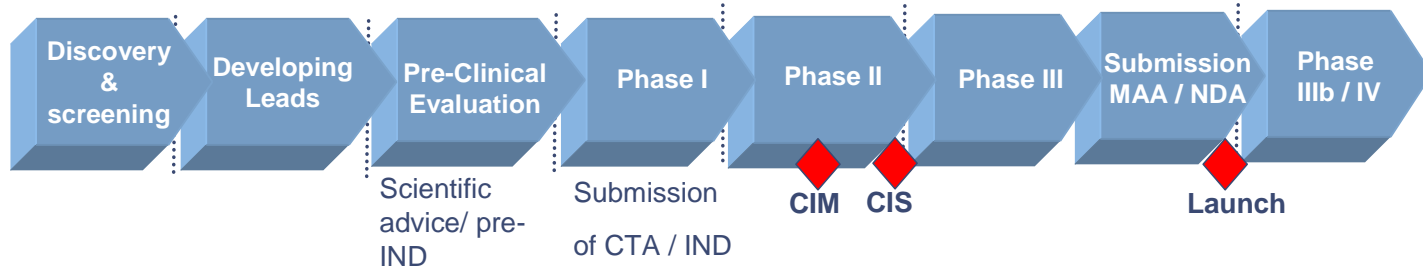
- how to conduct experiments (pre-clinical and clinical)
 - GLP: Good Laboratory Practices
 - GMP: Good Manufacturing Practices
 - GCP: Good Clinical Practices
- how to manufacture the drug:
 - active compound (DS),
 - its formulation (DP),
 - the delivery system (if any)

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

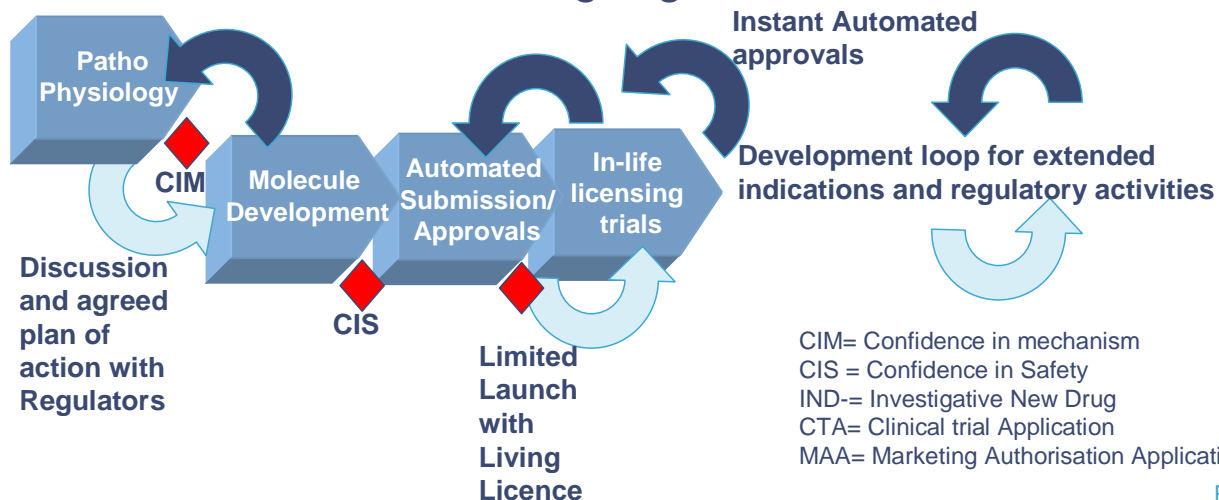
The rules

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

Today- intensive all-or nothing regulation

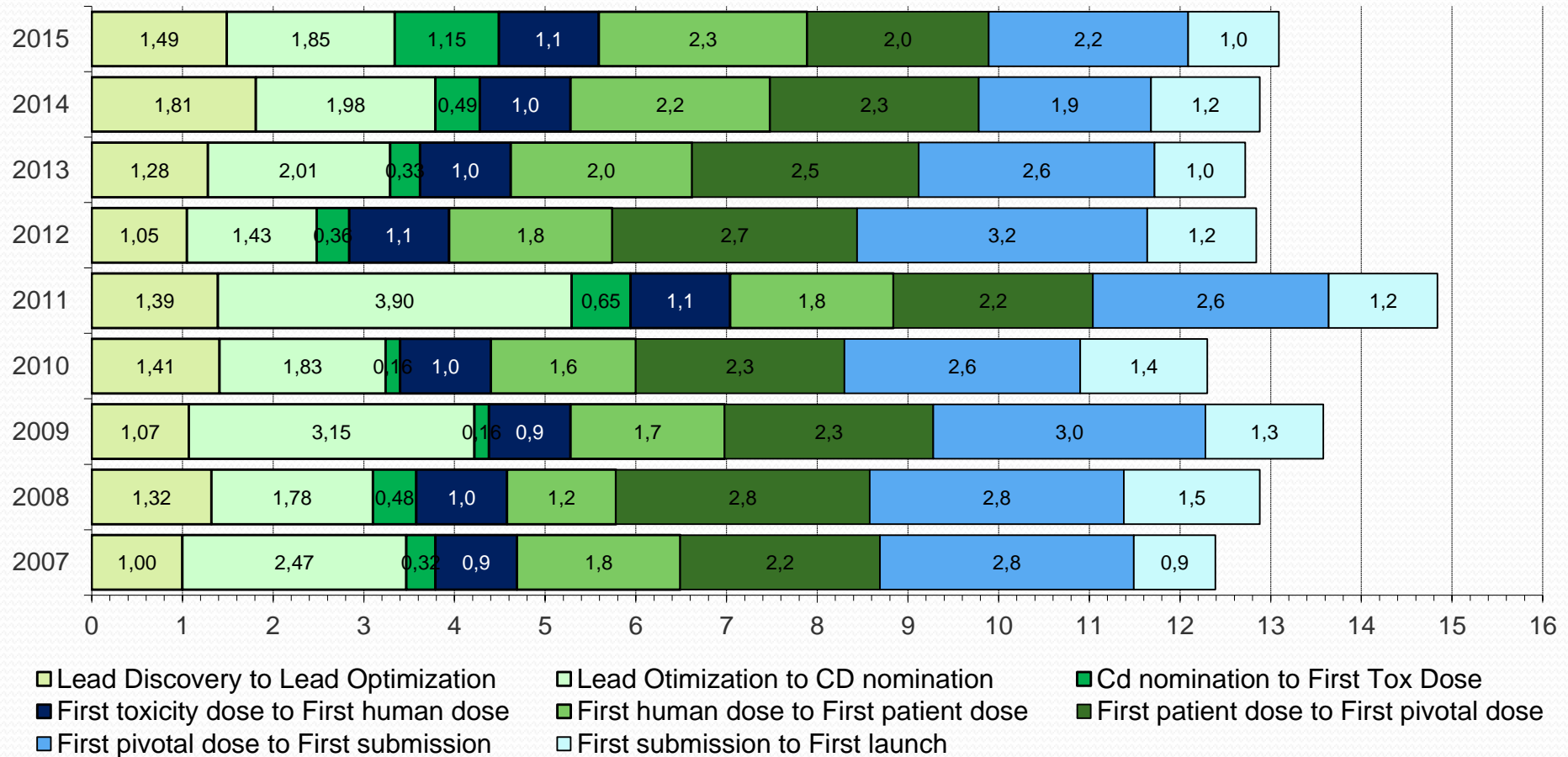


2020- Instant automated e-evolving regulation

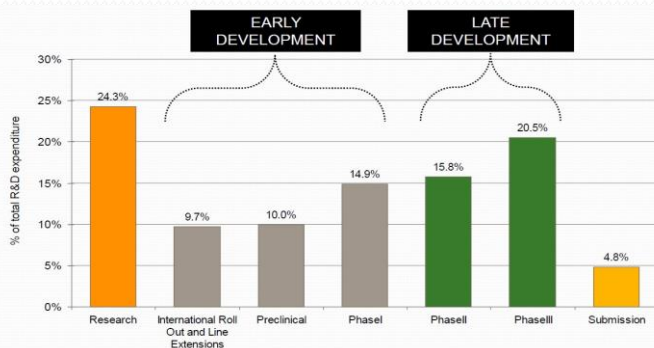


Development timelines of new drugs

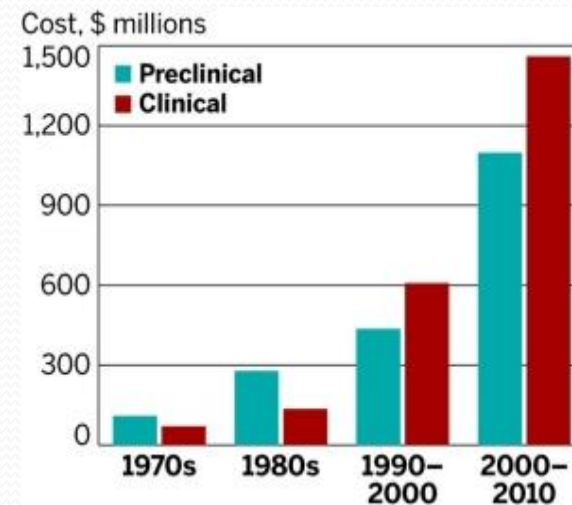
The development times of new drugs – without research – in the last 10 years is growing or stable; on average around 13 years



The cost of pharmaceutical development



“Deloitte & Thomson Reuters have examined new drugs launched on the market by the 12 biggest R&D budgets pharma companies. Putting in the market a new drug costs around 1.3 billion \$.”

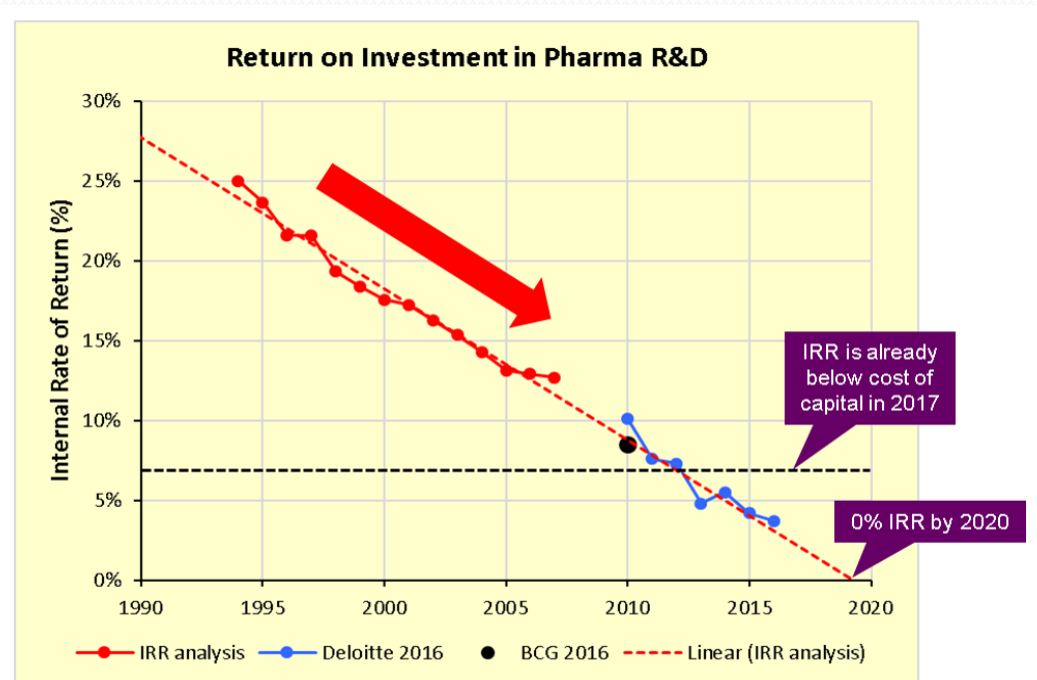


R&D productivity crisis is shown in a new report by the Tufts Center for the Study of Drug Development in November 2014

“Crisis in Pharma R&D: to develop a new drug costs \$2.6 bln; more than twice as much as in 2003”

Pharmaceutical R&D productivity

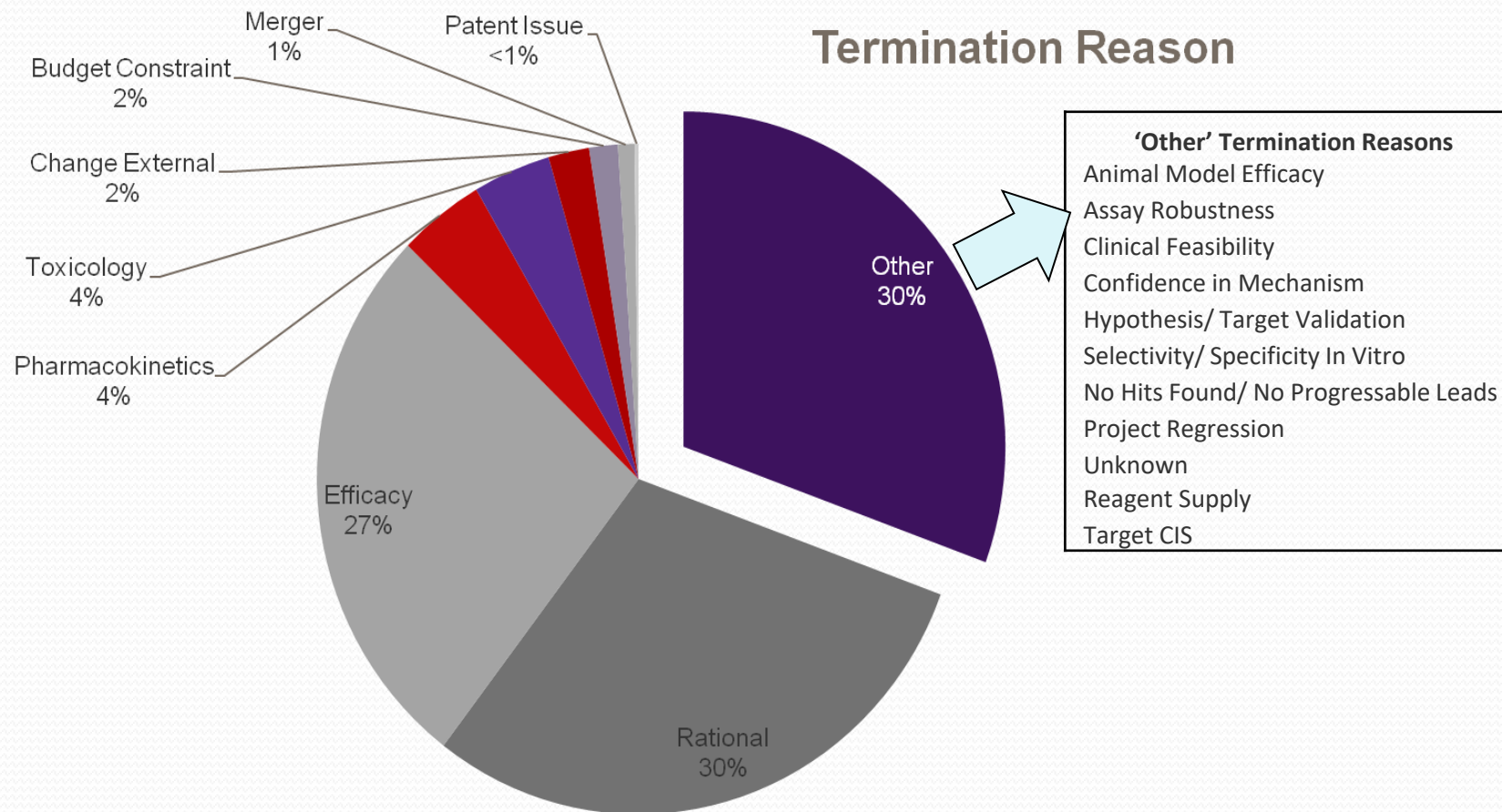
The Return On Investment on the R&D investments in pharmaceutical R&D is reducing to zero ... although it is cumulative data implying a series a dynamics...



Source: EvaluatePharma, IRR analysis

Reasons of failure

Most of the times either the products is not working, or the rational was wrong



Data are shown for projects terminated between 2008-2013. Success rates were calculated at the discovery project level using the PDM methodology. A maximum of three termination reasons can be selected per terminated project.

The pharmaceutical products

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



The pharmaceutical products

Rx - prescription drugs:

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

Non-prescription drugs

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

Hospital drugs:

- Hospital use only
 - patented
 - generics

OTC (over the counter):

- Free sale → mass market

The third-party payer: an (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

Main drivers of change in the future:

- In 2008 the world has changed: gene therapy, stem cells, cell-based therapies became “drugs”, Advanced Therapy Medicinal Products (ATMPs)
- The information technology and its applications to the pharmaceutical (> 100 Apps scrutinised by the FDA, big data, AI, ...)

The digital revolution is coming...



..let's ride it!



