Outlines of Pharmaceutical Development Process

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People and ideas for innovation in healthcare

AGENDA

1. Brief Outline of Pharmaceutical Development Path
2. R&D: why a complicated business
3. Tools and organizations of control of Pharmaceutical Development and Drug Marketing

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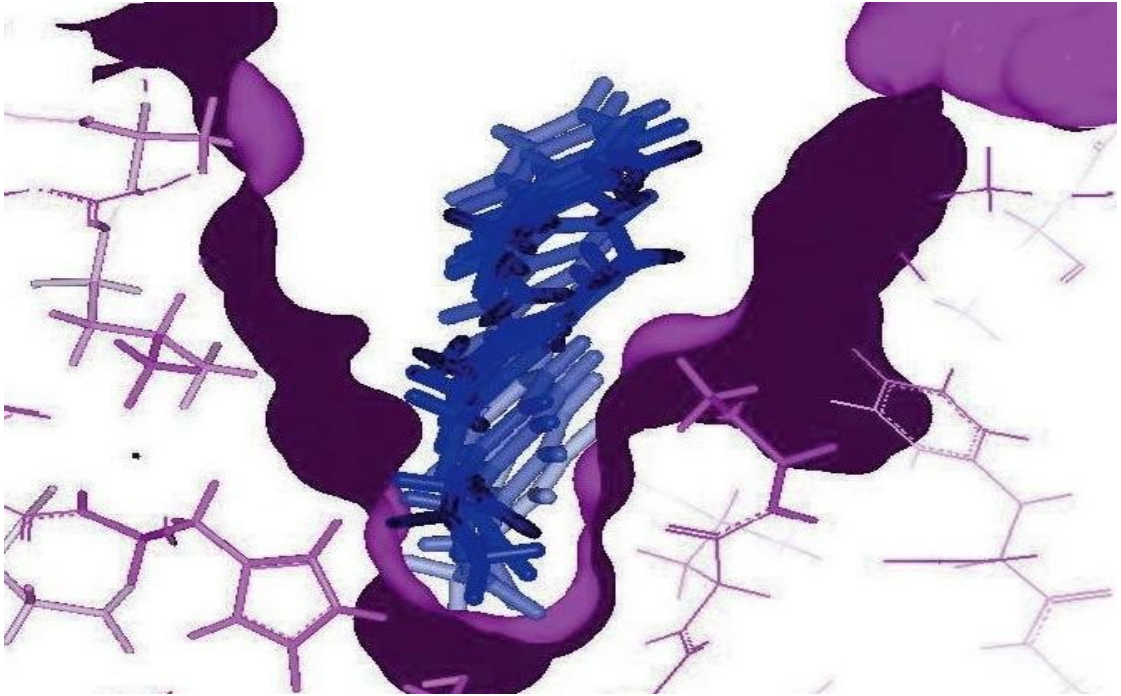
The drug (greek: φάρμακον)

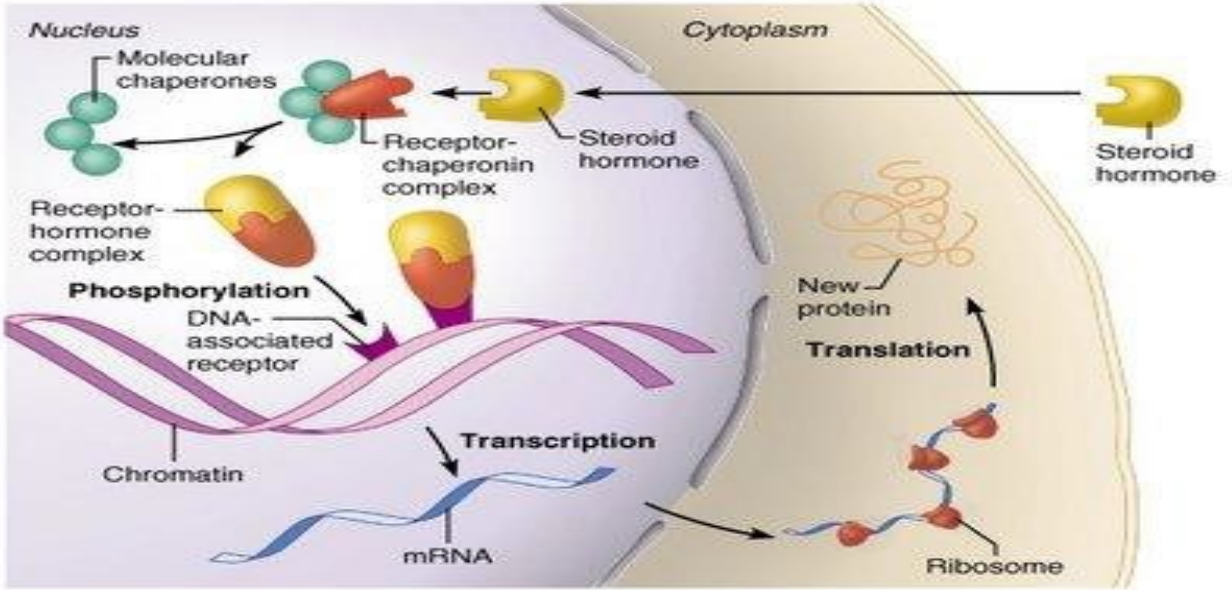
A substance that, by interacting with a biological target, modifies a physiological or pathologic process to produce a therapeutic effect, e.g.:

- 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)

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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

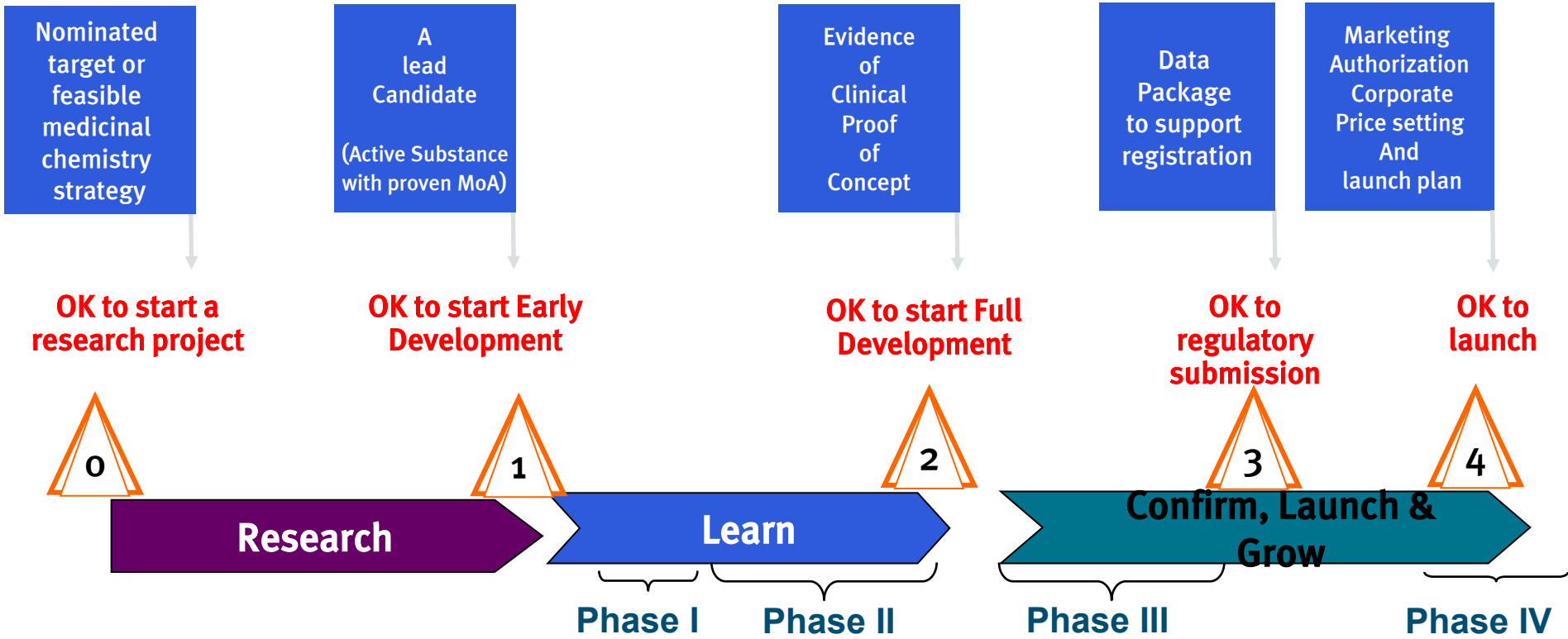
1) Research:
   - **Basic**: study of the human biological functions at a molecular / cellular level, to identify new therapeutical targets [-> the keyhole]
   - **Applied**: identification of new chemical entities with pharmacological activities on the established targets [-> the key]
2) Development: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

Typical Timeframe for Pharmaceutical New Product Development Project

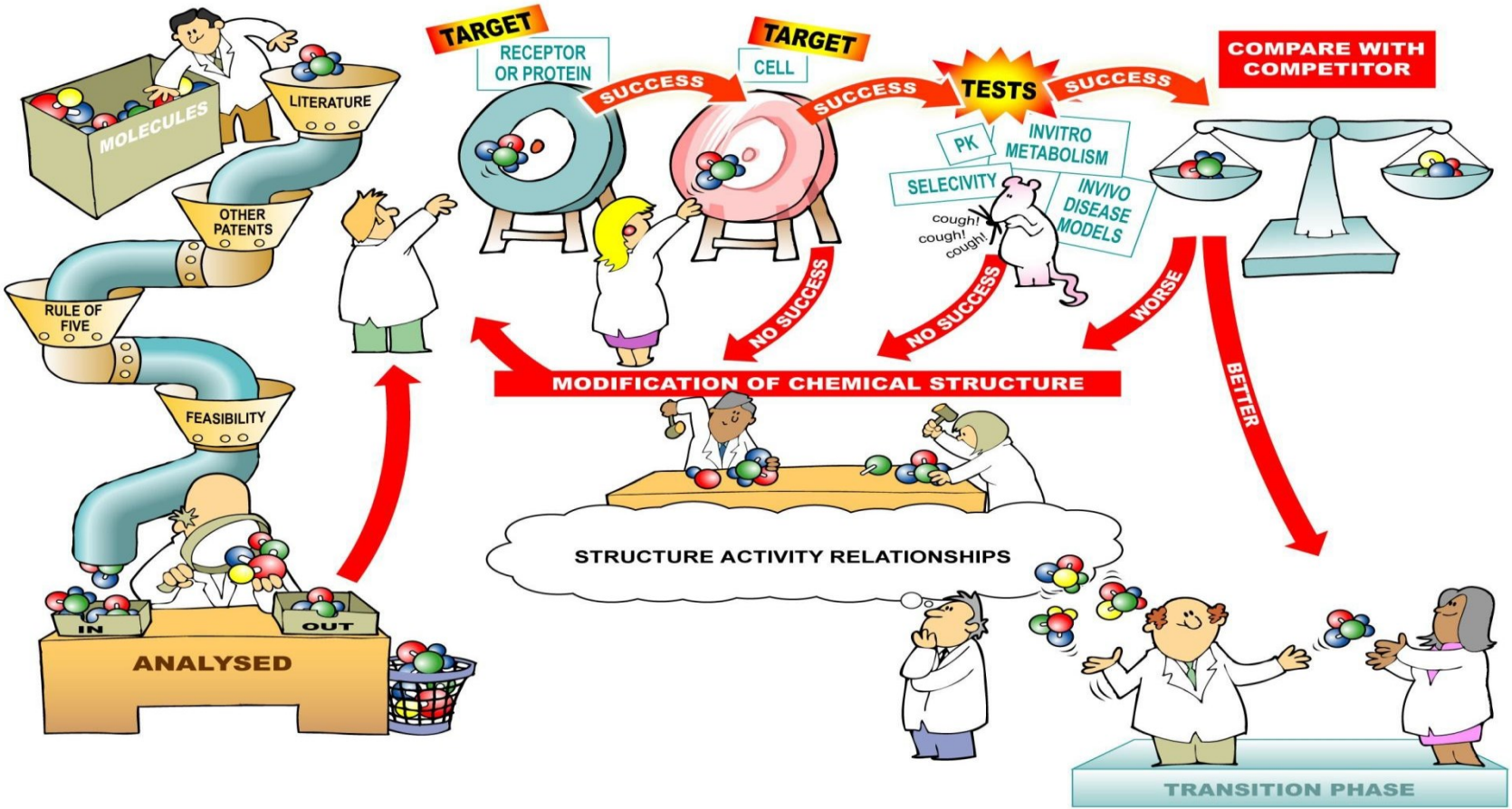
From drug discovery to manufacture

What triggers the progression: Gates as Decision Making Points

Stage Gate Processes typically provide a framework by which project teams move ideas through development to the market

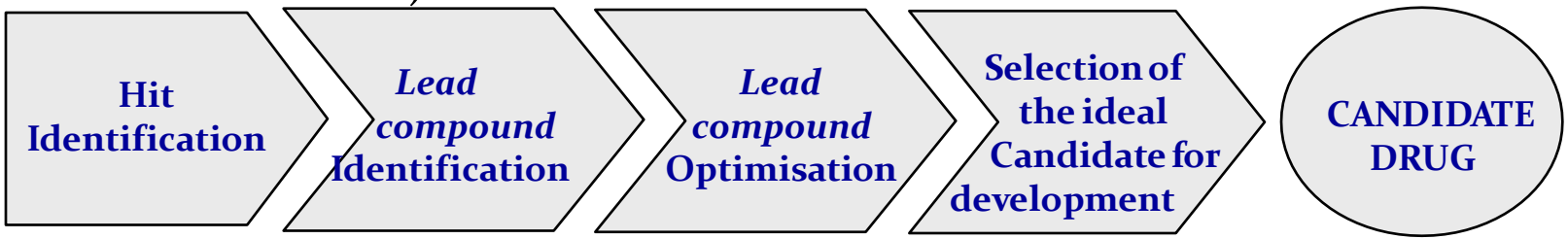


What we do in “Research”

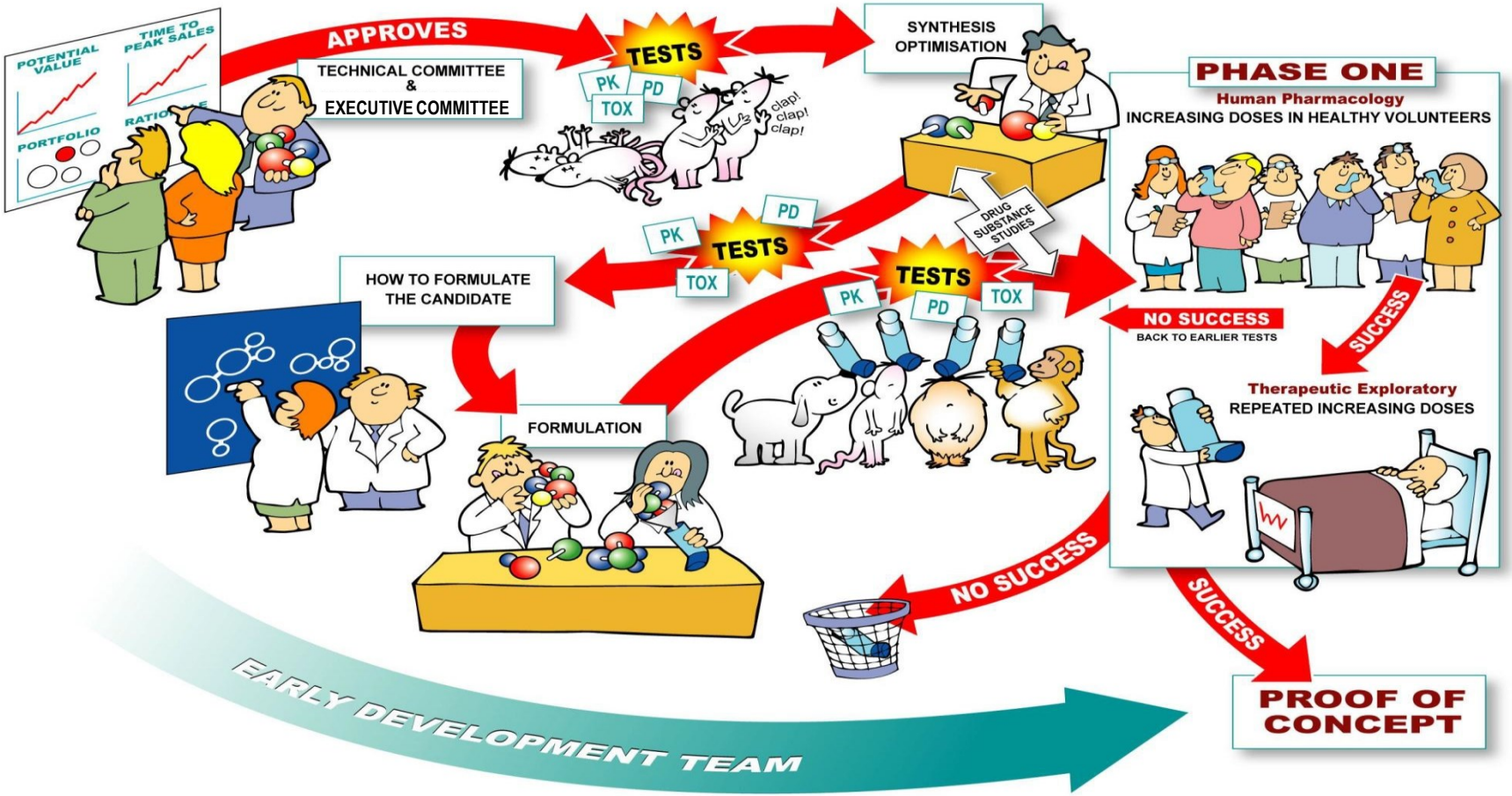


The “Research” phase

- 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)

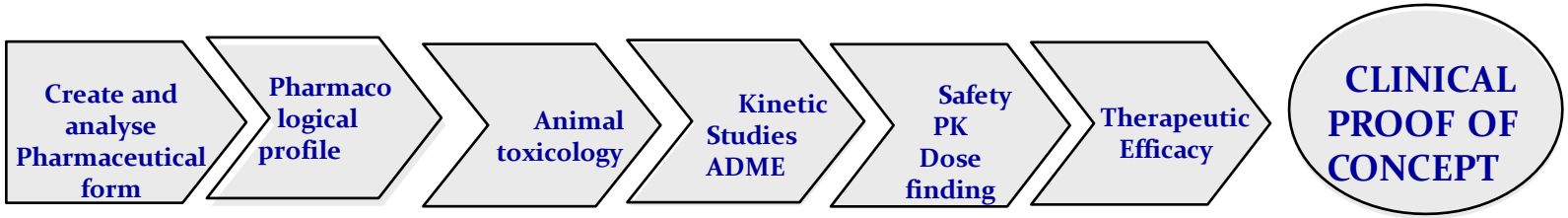


What we do in the “Learn” Phase



The "Learn" Phase: Early Development 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)

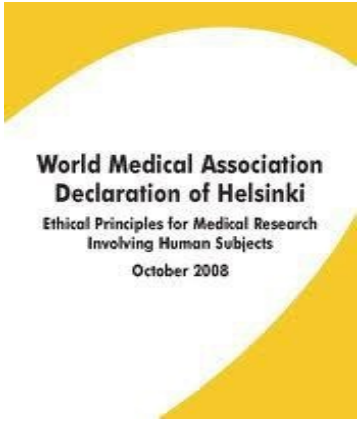


Animal welfare

- 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 and-or rarediseases)
  - 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



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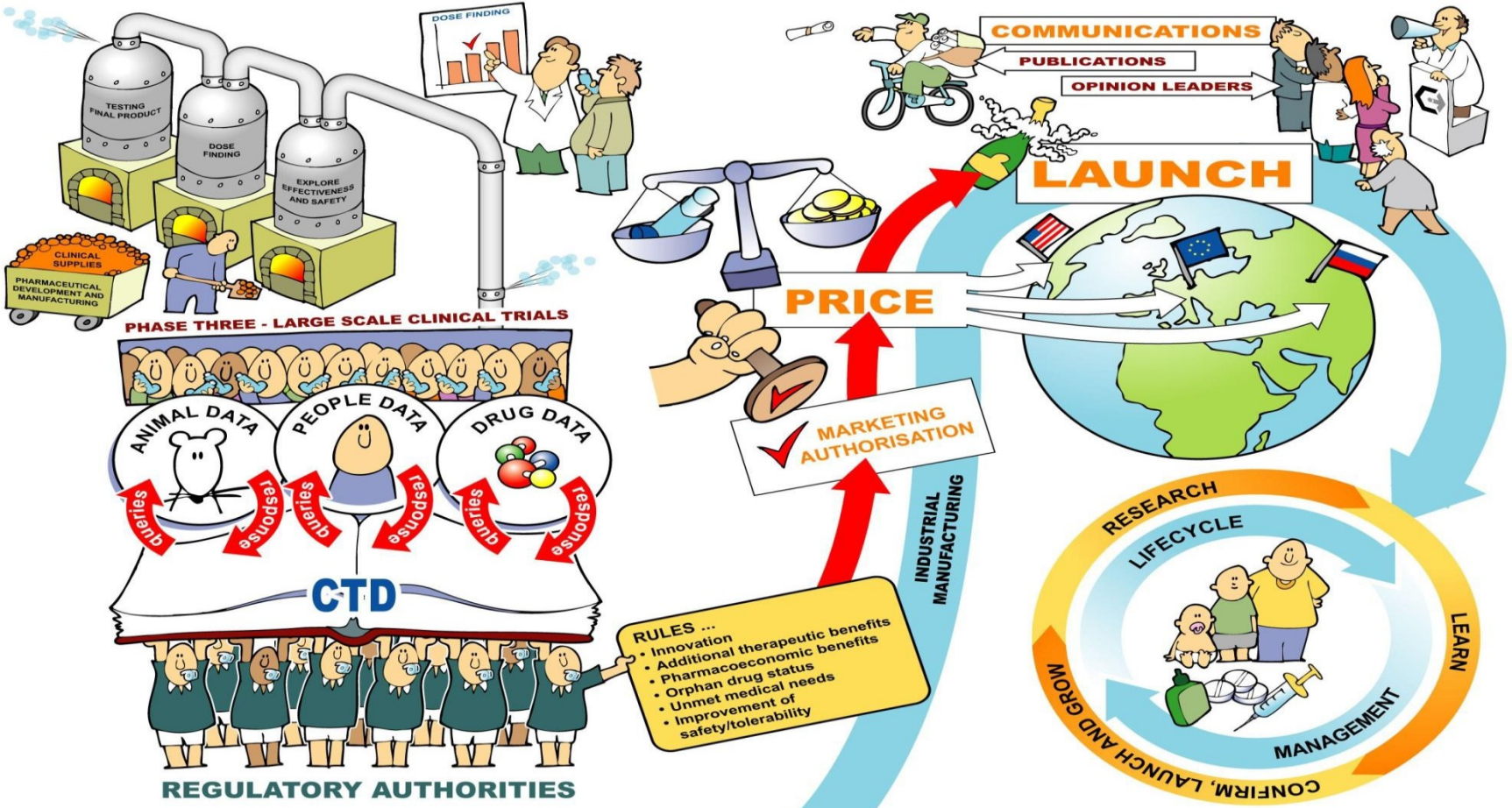
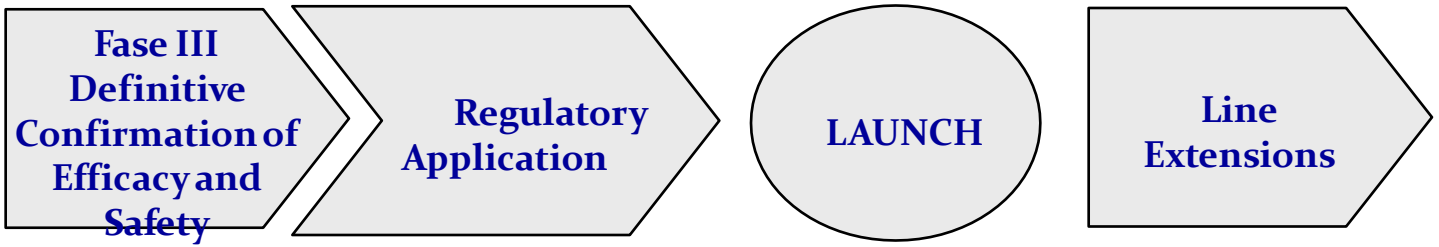
What we do in Confirm, Launch & Grow



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

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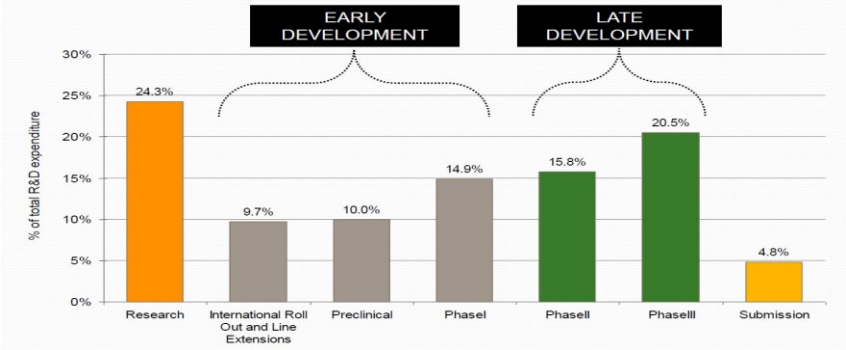
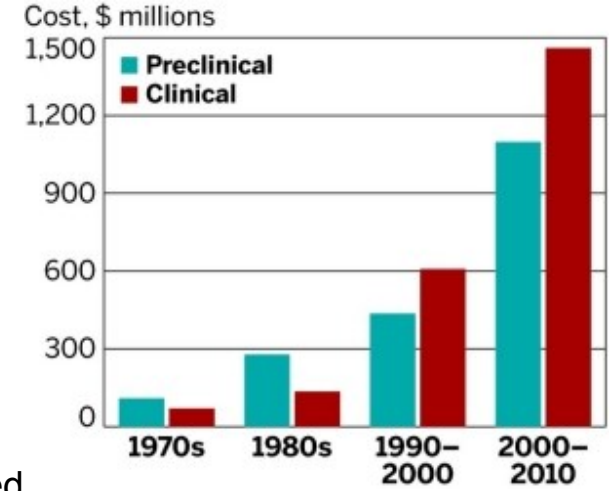
R&D: a complicated business

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

The costs of pharmaceutical development





"Deloitte and Thomson Reuters examined newly introduced drugs from the twelve pharmaceutical companies with the largest research and development (R&D) budgets**. It cost $1.3 billion to bring a newly discovered compound to market"**

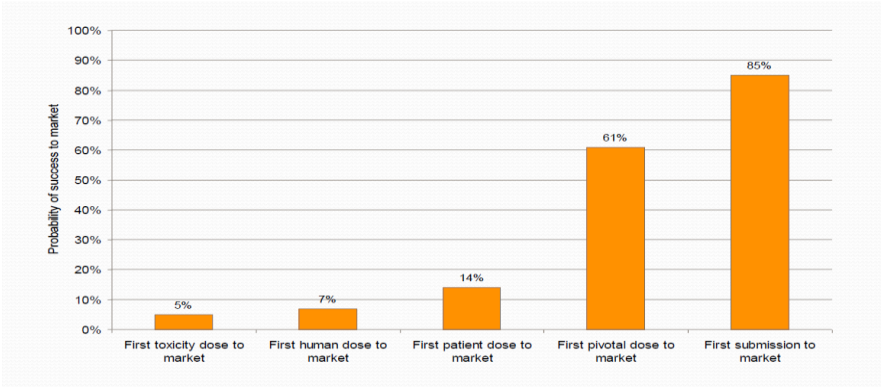
The crisis of R&D is highlighted in a new report by the **Tufts Center for the Study of Drug Development November 2014**

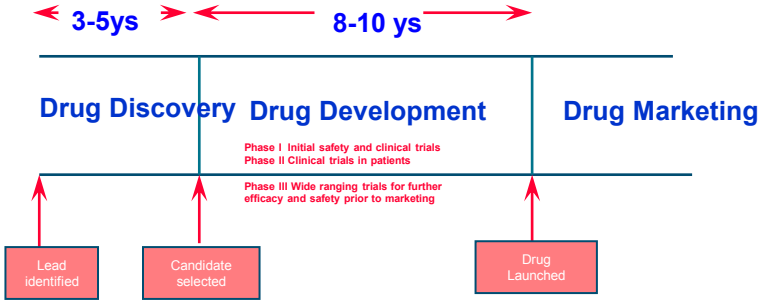
"Crisis In Pharma R&D: It Costs $2.6 Billion To Develop A New Medicine; 2.5 Times More Than In 2003"

http://www.forbes.com/sites/theapothecary/2014/11/26/crisis-in-pharma-rd-it-costs-2-6-billion-to-develop-a-new-medicine-2-5-times-more-than-in-2003/#3628d55b1641

Probability of success to market

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





Some Key business Indicator

In September, EvaluatePharma confirmed that the increasing cost of prescription drugs was concentrated in more specialized drugs. Of the top 100 selling drugs in the U.S.:

1. The median revenue per patient of the Top 100 drugs has increased **from $1,260 in 2010 to $9,400 in 2014, representing an seven-fold increase;**
2. The median patient population size served by a Top 100 drug **in 2014 is 146,000, down from 690,000 in 2010**; and
3. There are **now seven treatments priced in excess of $100,000 per patient per year in 2014, versus four in 2010**.

Given these facts, it may be understandable that the health-insurance industry is campaigning against the high prices of specialty drugs.

How to measure success?

Value

- Fast launch to market
- Innovative medicines
- Meet stakeholder needs
- Toll-gate success rate

Resources

- Low cost to launch
- Lead times
- FTE
- Fix versus flexible costs

The Vision for R&D to enable the Strategic Shift

- Flexible, Adaptive and scalable Organisation
- Swift decisions to shift resources to high-value products implementing Portfolio Decision Management
- Increase seamless collaboration between Research, Development, Industrial Operations and Commercial
- Strategy and Process visible and transparent to the whole of the organisation
- International network of external collaborators, partners

Projects in the context of the organization & strategy

- New Product Development (NPD) projects are a key enabler of growth, bringing innovation to the market
- Successful delivery requires integrated multi-functional activities, achieved via project teams
- Stage Gate Processes typically provide a framework by which project teams move ideas through development to the market
- Project Portfolio management
- NCE development: new perspective/approaches are needed.

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Challenges of New Product Development projects

"Soft is the new hard"

- The **soft infrastructure** – people, processes and problem solving – **is more important** to sustainable innovation **than the hard** – feature, functions, technology:

- Many different functions need to work together to successfully deliver new ideas to the market:

- Successful innovations need to address unmet need(s) better than competition: Challenging!

- Technical uncertainties and risks are inherent in Development: this require
  - Flexibility and Personal Openness to the change
  - New perspective: Problem solving and Decision making,
  - Clarity on Objectives

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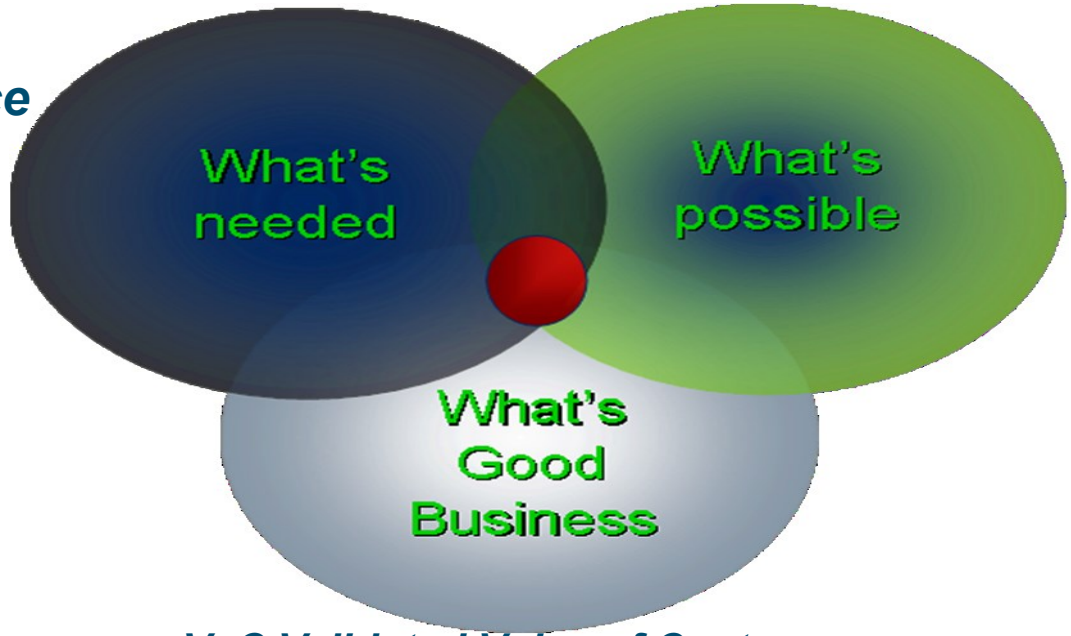
Value definition for a Project

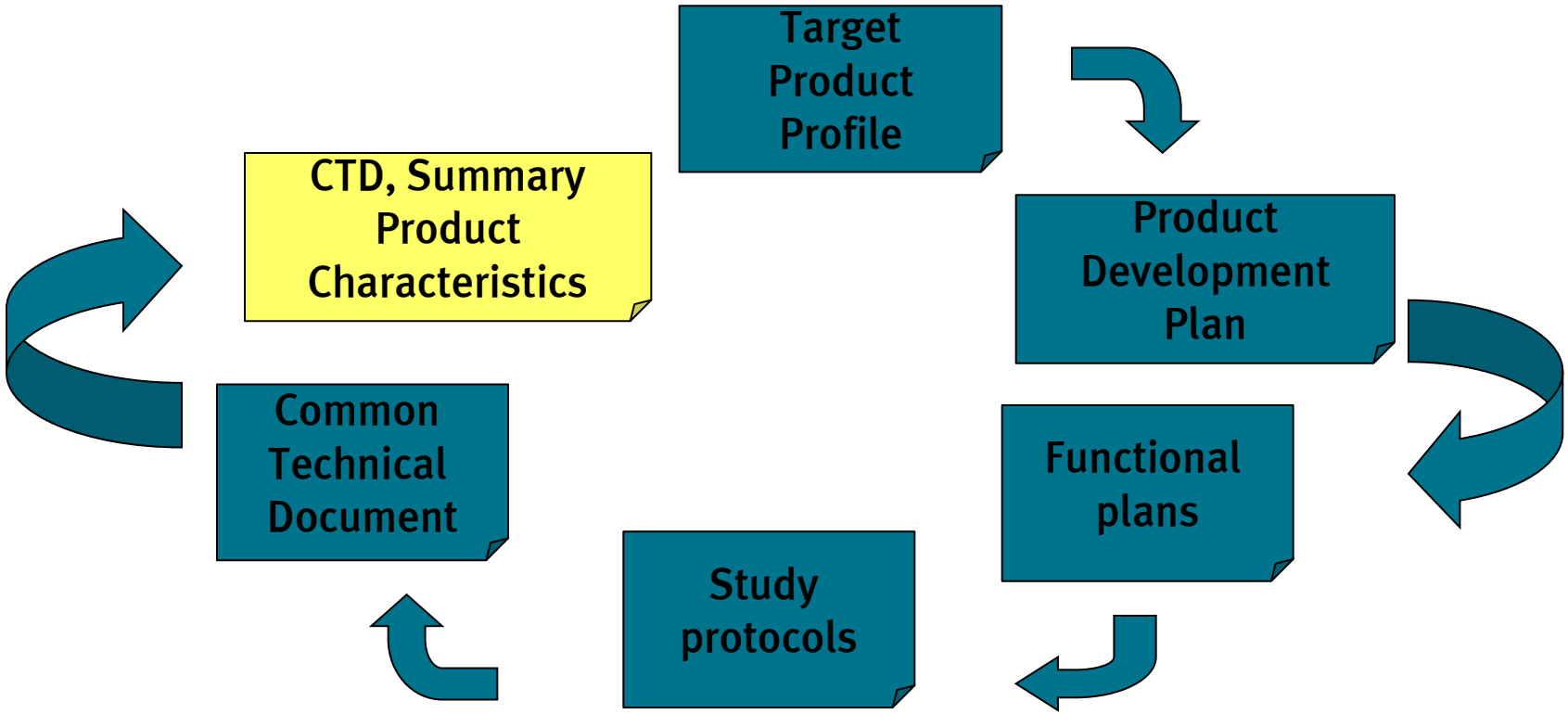
The Science

Budget
$ and time



vVoC Validated Voice of Customers

New Product Development projects are a key enabler of growth, bringing innovation to the market



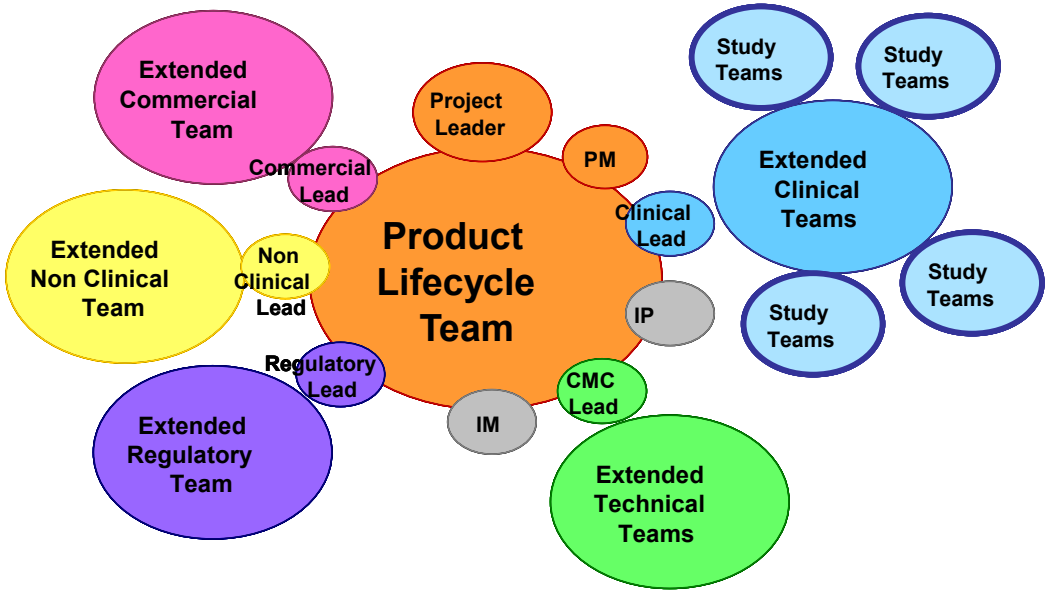
Successful delivery requires integrated multi-functional activities, achieved via project teams

Membership

- Project Leader (PL)
- Project Manager (PM)
- Functional Core Members

Responsibility

- Target Product Profile
- Project Card
- Product Development Plan
- Functional Plans
- Common Technical Document (CTD)



Change is the name of the game

1. Cultural evolution
   - Multidisciplinary
   - project driven
   - breaking down barriers
   - sense of urgency and responsiveness
   - real delegation
2. Process improvements
3. Scientific enhancements
4. Reward success on project (ie final deliverable) rather than reward success on pieces/ intermediate milestones of project

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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 Humans (always volunteers)

Why?

For effective consumer protection, we need to ensure

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

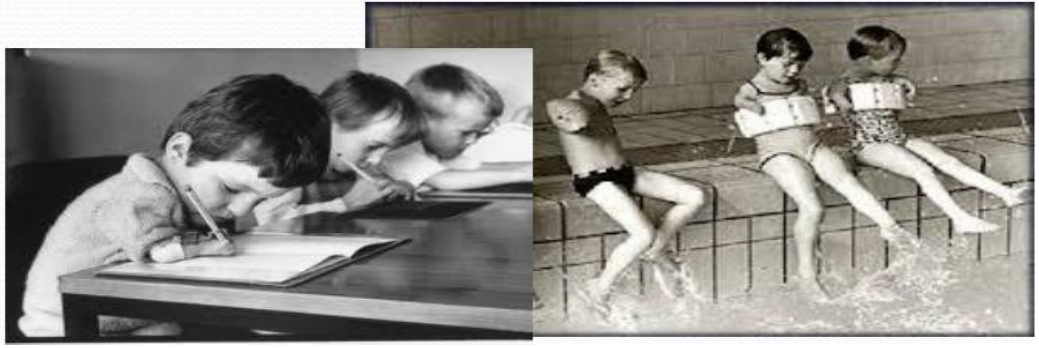
  - the Elixir Sulfanilamide (1937-1938) tragedy (US): toxicity
  - the Thalidomide (1957-1961) disaster (EU): teratogenicity

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

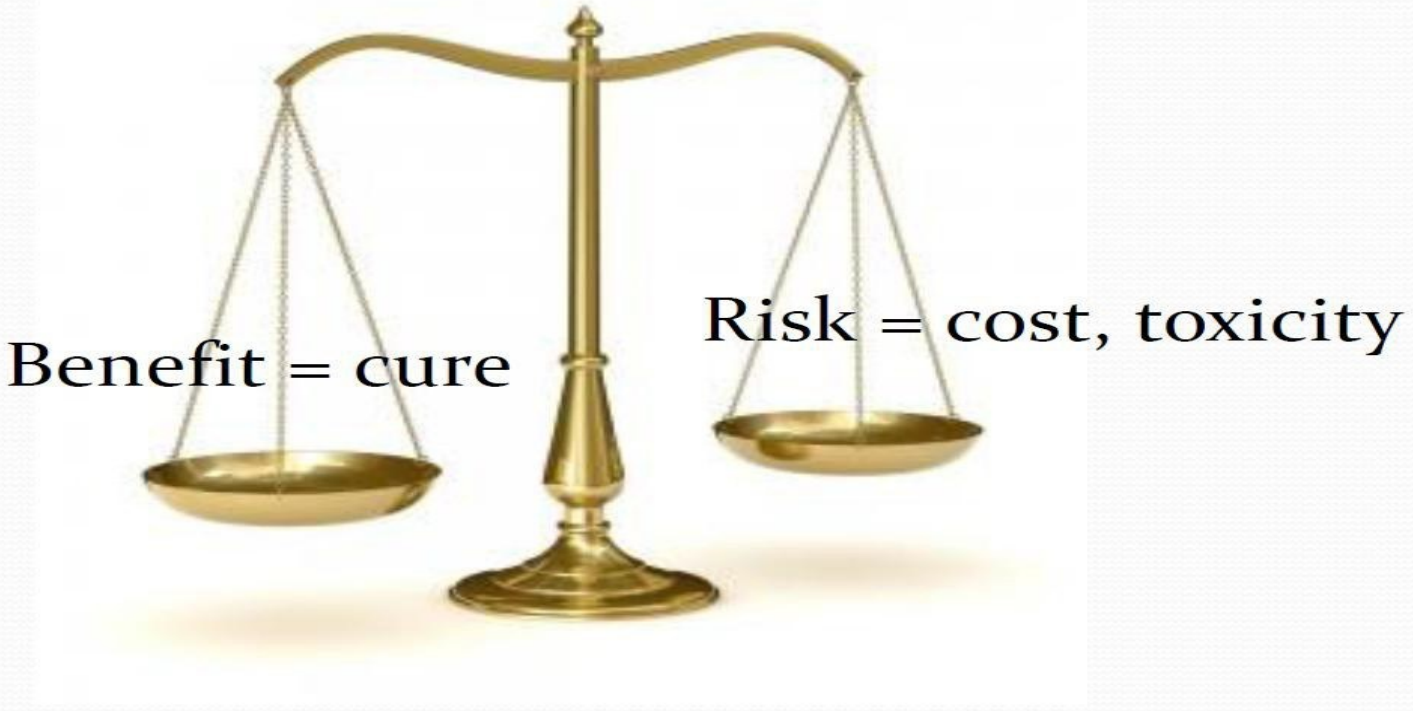


What?

- 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

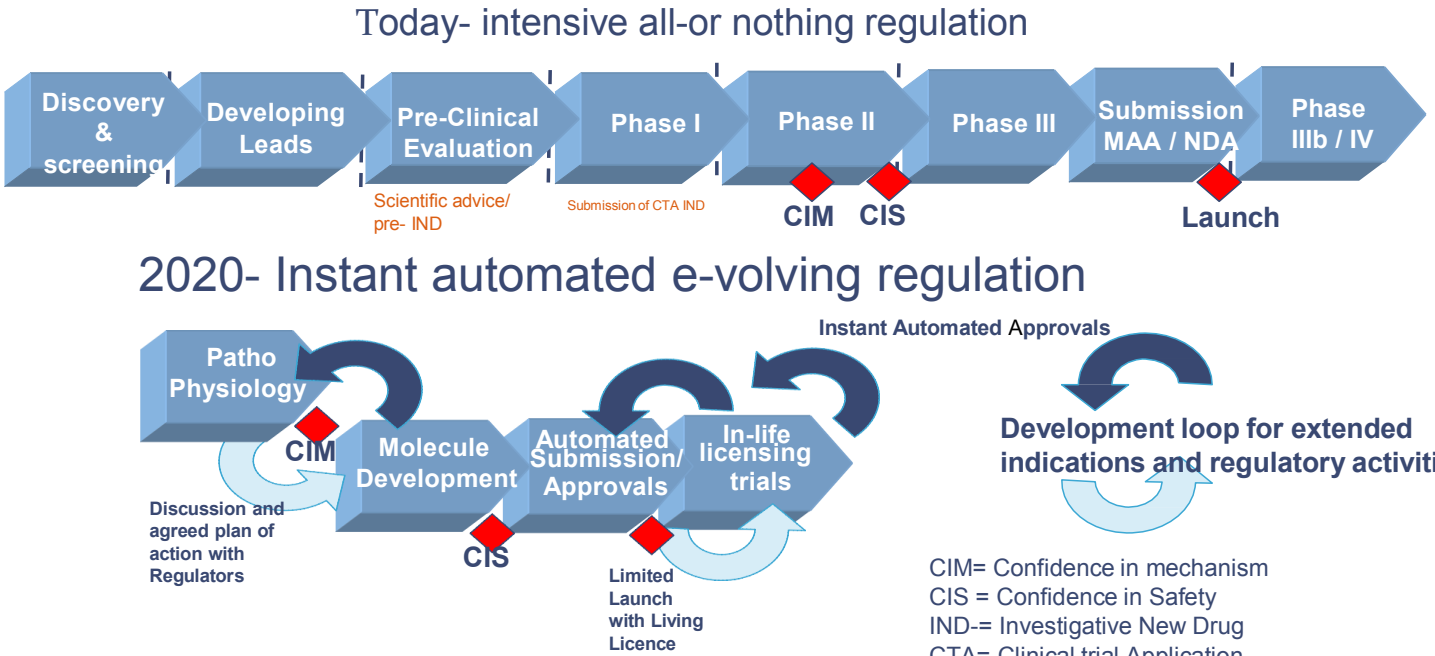
Which is the issue?

- 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 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 ssytem (if any)

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

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

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- …but this is also where the risk lies;
  - counterfeiting
  - bad quality (esp. on little-known particulars, e.g biosimilars)

Thank you!