R&D concepts, Definitions, Technology readiness levels and cycles (TRL) Health Economy, environnement of CRO, Pharma industry versus Agro-industries Finance & Valorization (not in this course)

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What is R&D

- in a company, everything that is on the « costs » side and not « sales » of the financial counts.
- Pharma industry : up to **15-20%** turnover, Agro-Ind: **5%**
- it does not mean the same for everybody, depending on your field.
- the more complex the technology is (space, NASA) the more advanced are the procedures
- ***« Innovation » has nothing to do with novelty, the true innovation can be seen through patents and licensing and even so...***
- ***many companies try to appropriate public knowledge (Sanofi; Rifapentine-Isoniazid)***


BILLET DE BLOG 3 AOUT 2020

Isoniazide et rifapentine: notre courrier à Sanofi

Aujourd'hui, OTMeds adresse avec Treatment Action Group (TAG) un courrier à Sanofi, qui cherche à breveter des combinaisons de deux antituberculeux, l'isoniazide et la rifapentine, alors que la firme n'a découvert aucune de ces molécules. Nous demandons à Sanofi de retirer ses demandes de brevets là où elles sont encore en cours d'examen, et ses brevets partout où ils ont été délivrés.

TAG Treatment Action Group — Observatoire

https://blogs.mediapart.fr/edition/transparence-dans-les-politiques-du-medicament/article/030820/isoniazide-et-rifapentine-notre-courrier-sanofi

Schedule

- Chap. 1: **S3 to S8** : R&D basis, TRL, definitions
- Chap. 2: **S9 to S23**: Drug R&D and companies history, regulations (outside pharmacopea)
- Chap 3: **S24 to 39 :** SARS CoV 2 Vaccines development
- Chap 4**: S40 to 64 :Quality of drugs**
- Chap 5**: S65 to 75 : History of Pharma industry**
- Chap 6: **S76 to 89:** Focus on CROs : industry services, contacts
- Chap 7: **S90 to end**: Pharma versus Agro-Biotech

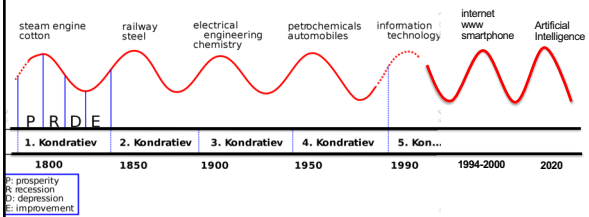
Chapter I

AI, R&D basis, Technology Readiness Level

C. Sola
Master 2 MAGB-Module MPAMB
30/01/2025

Kondratiev long wave cycles


Kondratiev (1892-1938),
Schumpeter (1983-1950)



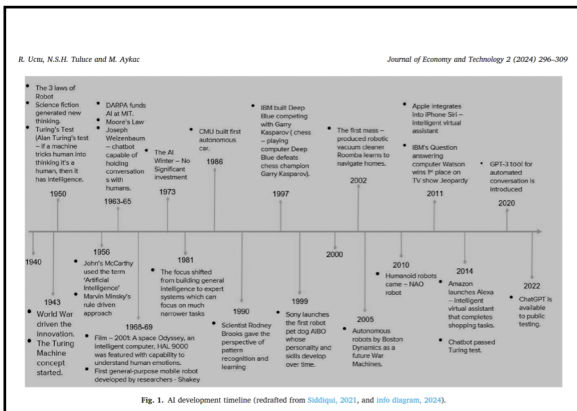


Fig. 1. AI development timeline (redrafted from Siddiqui, 2021, and info diagram, 2024).

Alan Turing 1912-1944

Artificial Intelligence

"**Computing Machinery and Intelligence**" is a seminal paper written by Alan Turing on the topic of artificial intelligence. The paper, published in 1950 in *Mind*, was the first to introduce his concept of what is now known as the Turing test to the general public.

History of Data and Data storage

https://www.youtube.com/watch?v=gg_T7EgOXkI

Data-Mining History

https://matthewrhoads.com/2017/10/14/blog-post-title-2/

predictive AI = machine learning

generative AI

Artificial Intelligence

https://en.wikipedia.org/wiki/History_of_artificial_intelligence

Chat GPT

https://docs.google.com/presentation/d/1Vo9w4ftPx-rizdWyaYoB-pO3DzK1n3250gDeXsnt0X0/mobilepresent?slide=id.g1cd15b254fd_2149_10

Main differences between predictive and generative AI

:

Predictive AI:

Goal: The aim of predictive AI is to **predict outcomes** based on historical data. It takes past or current data and uses it to forecast future events, behaviors, or trends.
Approach: Predictive AI relies heavily on **statistical models, machine learning** algorithms, and **data-driven techniques** to **identify patterns** in data and **make predictions** about unknown future events.

Examples:

- **Weather forecasting**: Predicting the weather based on historical climate data.
- **Recommendation systems**: Suggesting movies or products based on your past preferences (like Netflix or Amazon recommendations).
- **Fraud detection**: Identifying unusual patterns in transactions to predict potential fraud.

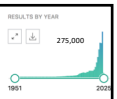
Key characteristic: Predictive AI focuses on using existing data to foresee possible future outcomes or to classify new data into predefined categories.

2Generative AI:

Goal: The primary aim of generative AI is to create new content or data that is similar to existing data. It learns patterns from training data and then **generates new, original instances** that resemble the data it was trained on.
Approach: Generative AI typically uses more advanced models, like **Generative Adversarial Networks (GANs)** or **Variational Autoencoders (VAEs)**, which enable the AI to produce new, realistic data points. It focuses on creativity and generating novel instances.
Examples:

- **Text generation**: Models like GPT-3/4 can generate new paragraphs of text based on a prompt.
- **Image generation**: AI systems like DALL·E create new images based on textual descriptions.
- **Music composition**: AI models that generate new musical pieces based on patterns learned from existing music.

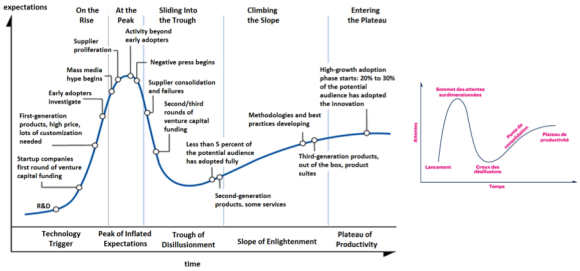
A little PubMed search... on AI



	2024	2025	
Artificial Intelligence and Diagnostics :	100,801Hits	124,000	
AI and Public Health	5,792Hits	8,467	
AI and Medicine :	63,911 Hits	85,046	
AI and Cancer :	37,541 Hits	47,319	
AI and Drug:	18,345 Hits	23,399	
AI and Drug Discovery:	5,119 Hits	6,663	
AI and Epidemiology	11,904 Hits	15,759	
AI and Precision Medicine	6,732 Hits	9,822	+23-25%
AI and Medical Education	6,382 Hits	9,596	
AI and microbiology	4,491 Hits	5,843	
AI and Drug design	4,009Hits	5,045	
AI and vaccine	1,707 Hits	2,227	
AI and environmental medicine	1,676 Hits	2364	
AI and Pesticides	507 Hits	654	
AI and vaccine design	426 Hits	ND	
AI and antimicrobial resistance	616 Hits	880	

« Hype cycle » (Gartner Inc®)

a curve that describes interest for new technology



https://fr.wikipedia.org/wiki/Cycle_du_hype#/media/File:Hype-Cycle-General.png
https://www.gartner.fr/fr/methodologies/hype-cycle

What is Innovation ? What is R&D

- **Know-hows** :
  - *Murano glass makers* (no written procedures),
  - *Michelin tire makers*, conclusion: Innovation are not always patented
- **Invention** is not **Innovation**
- **Patent** : **a Right to oppose**
- **Licence** : **a Right to do**
- **Brands, Trademarks**: **image** and **communication**
- **Goodwill:** how confidence and commitment join...
- **R&D** Definition (all expenses before turn-over ?)
  - *what is Research then, what is Development ?*
- **Business models**
- **Emergency need**

You
how do you differentiate research and development in R&D ?

ChatGPT
Research and Development (R&D) are often used together, but they represent distinct activities within the innovation process of a company or organization. Here's how they are generally differentiated:

1. **Research (R):**
   - **Nature:** Research is primarily concerned with the discovery of new knowledge, ideas, and theories. It involves the exploration of the unknown and the pursuit of understanding.
   - **Objective:** The main goal of research is to expand knowledge, gain insights, and explore possibilities without a specific end goal in mind.
   - **Timeframe:** Research activities may have a longer timeframe, and the outcomes are often uncertain. It can involve fundamental or basic research that may not have immediate applications.
   - **Risk:** Research involves a higher degree of uncertainty and risk as the outcomes are not predetermined.
2. **Development (D):**
   - **Nature:** Development is the application of existing knowledge to create new or improved products, processes, or services. It is more focused on practical and tangible outcomes.
   - **Objective:** The primary goal of development is to turn research findings or existing knowledge into something concrete and practical. It aims at creating value, often with specific goals or applications in mind.
   - **Timeframe:** Development activities are usually more time-bound and goal-oriented. The emphasis is on efficiency and effectiveness in achieving specific objectives.
   - **Risk:** Development involves a lower level of uncertainty compared to research, as it builds upon existing knowledge and aims at solving specific problems.

In summary, research is about exploring the unknown and generating new knowledge, while development is about applying existing knowledge to create something useful or valuable. Both research and development are integral components of the innovation process, and they often work together to drive advancements in technology, products, and services. The relationship between research and development is often depicted as a continuum, where research feeds into development, and the insights gained from development activities can, in turn, influence further research.

R & D

New knowledge, Higher risk, Longer time-frame

Existing knowledge, Lower risk, Shorter time-frame

Technology Readiness Level (TRL)
ISO 16290:2013

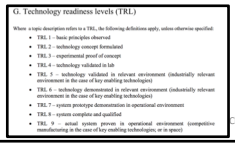
« A NASA invention to manage the technological risks »

A Technology (hardware, components, peripherals, etc.) is evaluated, in particular with a view to funding research and its development or with a **view to integrating this technology into an operational system or subsystem.**

Used by American and European government agencies, widely distributed, adopted by many organizations, companies or public institutions

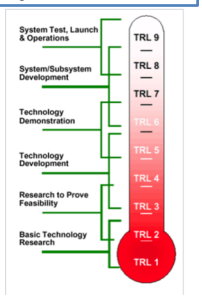
The TRL is in particular an important criterion in the Horizon Europe 2021-2027 program for funding European research by the Commission. In general, when a new technology is discovered, invented or designed, it is not immediately applicable. New technologies are generally subject to experimentation, refinement, and increasingly realistic tests.

Once the technology is sufficiently proven, it can be integrated into a system/subsystem. In 2013, the International Organization for Standardization (ISO) published a new standard defining the levels of technological maturity and their evaluation criteria.


G. Technology readiness levels (TRL)

Where a topic description refers to a TRL, the following definitions apply, unless otherwise specified:

- TRL 1 – basic principles observed
- TRL 2 – technology concept formulated
- TRL 3 – experimental proof of concept
- TRL 4 – technology validated in lab
- TRL 5 – technology validated in relevant environment (industrially relevant environment in the case of key enabling technologies)
- TRL 6 – technology demonstrated in relevant environment (industrially relevant environment in the case of key enabling technologies)
- TRL 7 – system prototype demonstration in operational environment
- TRL 8 – system complete and qualified
- TRL 9 – actual system proven in operational environment (competitive manufacturing in the case of key enabling technologies; or in space)



Concreteness and sophistication of the TRL scale gradually diminished as its usage spread outside its original context

Programme pour une Europe numérique (2021-2027)

Intelligence artificielle (IA) (1 663 956 000 EUR)
Cybersécurité et confiance (1 399 566 000 EUR)
Compétences numériques avancées (507 347 000 EUR)
Déploiement et meilleure utilisation des capacités numériques
et de l'interopérabilité (1 002 217 000 EUR)
Semi-conducteurs (1 575 000 000 EUR)

https://eur-lex.europa.eu/FR/legal-content/summary/digital-europe-programme-2021-2027.html?fromSummary=27#:~:text=Le%20programme%20s%C3%A9tend%20du,directe%20par%20la%20Commission%20europ%C3%A9enne.

Chapter 2
Drug Definitions and Basic Health Economy

The Pharmaceutical and Health professions The players,
Update on Pharmaceutical R&D in 2024

Some Key data on Pharma industries

Sector n ° 2: Economy in the world 1000 versus 2000 Billions US$ (after weapon industry) **Pfizer**

Pharma Industry : in France, one leader : **Sanofi-Aventis**

Some strong labs on certain specialties but they are generally small (**Servier**, cancerology)

In the world, some giants, (**Pfizer**, **Astra-Zeneca**, GSK, BMS, Roche, Abbott, Novartis…) however market not yet so concentrated

Insufficient private R&D (critical financial mass) complemented by public research, active environment of start-up companies (Moderna BioNtech).

High R&D costs (**12-20% turnover**), extraordinarily creative and dynamic start-up environment, few winners, « ***winner takes all*** »

42nd JP Morgan yearly healthcare conference
le Monde 17 janvier 2024

Healthcare Conference

1370 Milliards US$ investment capacity

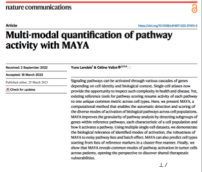
GLP-1 agonists
for type 2 diabetic patients
(marché de l'**obésité**)

1. **Fundraising:** Private equity firms raise capital from investors, creating a fund that will be used to make investments.
2. **Deal Sourcing:** Private equity firms identify potential investment opportunities, which can include acquiring a significant stake in a private company, taking a company private, or providing growth capital.
3. **Due Diligence:** Before making an investment, private equity firms conduct thorough due diligence to assess the financial health, management team, growth prospects, and potential risks of the target company.
4. **Deal Structuring:** If the due diligence is successful, the private equity firm structures the deal, determining the terms of the investment, the amount of control or ownership they will have, and other relevant details.
5. **Value Creation:** After making the investment, private equity firms work closely with the management of the portfolio company to enhance its performance and value. This may involve operational improvements, strategic guidance, and other initiatives to drive growth.
6. **Exit Strategy:** Private equity firms aim to exit their investments and realize returns for their investors. Common exit strategies include selling the company to another firm, taking the company public through an initial public offering (IPO), or selling to a strategic buyer.

France (capital risque)

https://ibionext.com/
https://www.anderapartners.com/
https://sofinnovapartners.com/

Hedi Ben Brahim
One bioSciences
Genomics Single-Cell


nature communications

Multi-modal quantification of pathway activity with MAYA

France Biolead

https://www.france-biolead.fr/content/nos-membres-et-adherents

Drug discovery in 2023-2025: Five key predictions

1. *There will be greater emphasis on diversity in clinical trials*
2. ***AI will take on a wider role***
3. *Novel therapeutic platforms will drive innovation*
4. *Personalised and precision medicines will dominate pipelines*
5. *Cell and gene therapies, exploration of new technologies like bioprinting, tissue engineering and gene editing*

https://www.ddw-online.com/drug-discovery-in-2023-five-key-predictions-21106-202212/

Drug discovery in 2024: two key predictions

1. *GLP-1 agonist will be on the rise*
2. *MAB conjugates will go on to rise in cancer therapies*

Pharmaceutical Definitions

- **Human Drug**: ***any substance or combination of substances presented as having properties for treating or preventing disease in humans, and any substance or combination of substances which may be used in or administered to humans for the purpose of making a medical diagnosis***
- **Specialty**. ***A specialty is a drug prepared in advance by a pharmaceutical laboratory, placed on the market (Marketing Authorization)*** *under a specific name and packaging*.

(Article L.511-1 du Code de la santé publique)

- **without AMM** marketing authorization possible **:** ***Temporary authorization to use*** **(ATU)**

Terms:-

Drug:-(active pharmaceutical ingredient - API)
chemical compound intended for used in diagnosis, treatment or prevention of diseases.

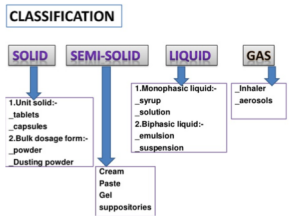
Excipients:-
(inactive pharmaceutical ingredients)
Technological, biopharmaceutical and/or stability reasons.
Diluents/fillers, binders, lubricants, desintegrants, coatings, preservants and stabilizers, colorants and flavourings

dosage form:-
Drug+excipients

https://www.slideshare.net/HARISHANKARSAHU/pharmaceutical-dosage-forms

Definitions

- **Pharmaceutical form**. *Nature and content of the container (packaging) of a specialty defined by its dosage and pharmaceutical form. Drugs intended for human or veterinary use, presented in their finished dosage form. Included here are materials used in the preparation and/or formulation of the finished dosage form*



https://www.slideshare.net/HARISHANKARSAHU/pharmaceutical-dosage-forms. (39 slides)

Definitions

Generic:

A generic drug is the strict copy of an original drug whose patent has fallen into the public domain.

The "inventors" of the new molecules file patents with the INPI (National Institute of Industrial Property) which assures them the exclusivity of their marketing for **20 years** and allows them to amortize their research and development costs. When the patent expires, the drug "falls" into the public domain.

A certified copy of the reference medicine or "princeps", the generic medicine, can be manufactured and marketed under a different name by approved pharmaceutical laboratories. The generic drug meets the same quality and safety criteria as the reference products and is controlled by the ANSM:

- **same composition in active principles**
- **galenical forms identical**

Any drug can be replaced by its generic if it exists.

Biosimilar **= generic in Biotech.**


History
Periods of Medicine and Drugs history

Hippocrate -460 -377, Galien 129-201 — Ibn Sina 980-1037

- *Ayurveda, Chinese health Tradition*
- Surgery, Dentistry, Pharmacy appear first !
- **Hippocrate, Galien, Avicenne**
- Oral tradition : Healers (ethnobotany)
- **Allo**therapy (aspirin, sulfamids, antibiotics): treat symptoms
- Birth of chemical industry (colors)
- Vaccine invention (Jenner), discovery of antibiotics (late)
- Contemporaneous period (HTDS, drug design, genetic engineering, reverse vaccinology, synthetic biology, genomic engineering (CRISPR-based genome engineering, single cell genomics)
- Food with health benefits (preventive message, probiotics)
- **but political problems** : ***drug shortage, AMR, inequalities (HIV, TB, Malaria) gender and population exclusion, environement requirements=> migration of industry***

History of drug discovery and medicine evolution

Medicines have long been extracted from plants (**Pharmacognosy**, medical material). **Plants** remain an important source of pharmaceutical innovation.

After **Mineral** and **Organic chemistry**, biochemistry, knowledge of enzymology has developed and scientific knowledge of the mode of action of active ingredients has increased (**"NCE": New Chemical Entities**)

With the development of **recombinant DNA biotechnologies**, (Insulin, growth hormone, erythropoietin, GM-CSF...) change of era (biotechnology).

Vaccines invention inaugurate new preventive Medicine production : *ancient platforms* versus *novel platforms* (mRNA)

Today: ***Medicine*** evolves together with ***Sciences*** and ***Technology (AI).***

Rare diseases remain understudied and underfinanced; **Environmental Medicine is more and more important**

History of French pharma Industry

- Grew from the *back store* of pharmacies
- No heavy chemical tradition except ***Usines du Rhône*** (Aspirin)
- In Germany, Switzerland, an industry based on fine chemicals (Bayer, BASF, Sandoz, Ciba-Geigy, Merck-Darmstadt, Boehringer-Ingelheim and Mannheim, Roche, Hoechst, etc.)
- In France, structuring of the sector by petrochemistry and Elf: creation of Sanofi (**1973**), acquisition of Aventis in **2004**, born in **1999** from the merger of the German Hoechst, the French Rhône-Poulenc and Roussel-Uclaf, of the Americans Rorer and Marion and the British Fisons.

Brief History of some drug discoveries

In 1820 **Pelletier and Caventou** discovered **Quinine** extracted from **cinchona**, a tree of the genus cinchona, which grows in the Andes between 2000 and 3000 meters, the first **antimalarial**, alkaloid extracted from the bark of ***Cinchona officinalis***

- **Adolf von Bayer** invents **Barbiturates** (hypnotic)
- **Charles Gehrardt** invents **Aspirin** (antipyretic, antiinflammatory)
- **Domagk** (Bayer) discovers the **Sulfonamides** (1936), the first true bacteriostatic agent
- In France, small industries are developing from the back of pharmacies, while in Germany and Switzerland (Bern then Basel), industrial chemistry is structured and becomes powerful
- The first war gave France (Usines du Rhône) the patent for Aspirin as compensation for war losses, while very strong chemistry in Germany (Bayer, BASF, Hoechst, Merck, Boehringer, etc.) will last (still today).

FRANCE

Medicine shortage hits as France grapples with health 'tripledemic'

France is one of several countries facing shortages of the widely used antibiotic amoxicillin and other medications, with surging illnesses among children increasing demand for the drugs.

Anti-infectieux, 21%
SNC, 19%
Anticancéreux, 14%
54%

https://www.rfi.fr/en/france/20221222-medicine-shortage-hits-as-france-grapples-with-health-tripledemic
https://www.hcsp.fr/explore.cgi/adsp?clef=1180

What drives innovation in Pharma?

- **An Active Ingredient**
- **An Indication**
- **A need !!!** **(a market)**
- **A price**
- **A market** : SARS-Cov2 vaccines, Autotests... new products !

- All these criteria at end are materialized by an active ***ingredient, specialty*** plus ***dosage form***

How is *innovation* translated into a reality ?

- The **Patent** (e.g. the mode of synthesis and a new chemical entity and an application field)
- The **License** (right to exploit a patent, limited or not in space and time)
- The **Commercial name** (do not confuse ***DCI,*** international non proprietary name and commercial name)
- real innovation, versus « ***me too*** »

What are the Phases of drug development?

- **Pre-clinical** phases: *in Silico*, *in vitro*, cell systems, animal, Toxicology, Pharmacology, Eco-toxicology
- **Clinical** Research phases (clinical trials : I-IV
- Phase of marketing authorization files building
- **Phase of negociation with health authorities** (price)
- Marketing and surveillance phase (pharmacovigilance, post commercialization)
- detection of rare secondary effects; Withdrawal ??

Ecosystems of Pharma industry

Distinction of *stakeholders* in this industry

-**Chemical Industry**: distinction between commodity and specialty chemicals (BASF, Dow, Dupont)

-Pharma Laboratories: public, private, biotechnology, start-up

-Contract Research Organizations

pre-clinical or clinical research CRO, phase I, phase II to IV, galenic specialized R&D laboratories or analytic laboratories, start-ups...

-Shapers Production laboratory

-Big Pharma: verticalization (integration)

search for functional synergies (accumulation of specialties in one or more therapeutic areas or therapeutic classes by acquisition)

-Laboratories specializing in the creation of generics

-Distributors

Chemical Industry production and requirements

- Specialty chemicals are either **single-chemical entities or mixtures of various chemical ingredients that are designed for specific applications and sometimes for specific customers**. They are sold on the basis of their performance or function rather than their composition.
- **Utility** Systems – Steam, Power, Hot Water and Chilling Water. Process industries are typically served by utility systems that **provides the necessary energy to carry out day-to-day operations**. The most common utility systems include steam, electricity and water.

VARIOUS PROCESS UTILITIES

The word "utilities" is used for the ancillary services needed in the operation of any production process. These services are normally supplied from a central site facility, and include:

1. Electricity
2. Fuel for fired heaters
3. Fluids for process heating
   a. Steam
   b. Hot oil or specialized heat transfer fluids
4. Fluids for process cooling
   a. Cooling water
   b. Chilled water
   c. Refrigeration systems
5. Process water
   a. Water for general use
   b. De-mineralized water
6. Compressed air
7. Inert gas supplies (usually nitrogen)

https://ccsuniversity.ac.in/bridge-library/pdf/Engg-CE--Subject-PUSCP-Semester-6th-PUSCP-1st-unit.pdf

Examples of Specialty Chemicals

•**Agricultural Chemicals**: Pesticides, herbicides, fungicides, and fertilizers that help optimize crop production and protect against pests.

•**Performance Polymers**: High-performance plastics used in aerospace, automotive, and electronics for their durability, heat resistance, or conductivity.

•**Pharmaceuticals**: Active pharmaceutical ingredients (APIs) that are essential for drug formulations and treatments.

•**Flavors and Fragrances**: Chemicals used in food, beverage, and cosmetic industries to create specific tastes or scents.

•**Adhesives and Sealants**: Used in construction, automotive, and packaging industries, providing strong bonds and weather resistance

An exemple : Erythropoietin

treatment of anemia of renal insufficiency

- *Gene* isolated in 1986
- Molecule manufactured on engineered CHO (Chinese Hamster Ovary) cell.
- Launched in 1989: two labs, Johnson and Johnson, and Boehringer-Mannheim
- Premium for the second: less adverse events, educational investment, unsaturated market
- Definition of an oligopolistic market **(Eprex® Recormon®)**

Spécialités pharmaceutiques :

Nom commercial	DCI
Aranesp®	Darbepoetin alfa
Dynepo®	Epoetine delta
Epomax®	Epoetine oméga
Eprex®	Epoetine alfa
Eprex 4000®	Epoetine alfa
Neorecormon®	Epoetine beta
Peptides mimétiques de l'EPO	Test phase 3
Recormon®	Epoetine beta
Mircera®	CERA

Monography
-names
-therapeutical or pharmacological class
-effect, clinical pharmaco data
-indications
-clinical use
-side effects

Chapter 3

Some key aspects of New Vaccines development with emphasis on SARS-CoV2 vaccines

SARS-Cov 2 : a game changer
(*it took 4 years to develop a mump vaccine 1963-1967*)

Vaccin COVID- 19: un développement accéléré

- 31 décembre 2019: déclaration à l'OMS de la survenue d'une épidémie de pneumonies d'allure virale d'étiologie inconnue
- 9 janvier 2020, autorités sanitaires chinoises et OMS annoncent la découverte d'un nouveau coronavirus, appelé 2019-nCoV (isolé le 7 janvier), renommé SARS-CoV-2
- **11-12 janvier 2020: séquence complète du génome du coronavirus transmise par les autorités chinoises**
- 16 mars 2020: démarrage du **1er essai clinique** (Moderna, vaccin ARNm)
- 8 avril 2020 : 115 candidats vaccins dont 5 en développement clinique
- Juillet 2020: début des essais de phase 3
- 9 novembre 2020: premiers résultats d'efficacité
- 2 décembre 2020: autorisation vaccin Pfizer/BioNTech par le MHRA (Medicines and Healthcare products Regulatory Agency)
- 8 décembre 2020 : début vaccination UK
- 6 janvier 2021

- 16 candidats vaccins en phase 3
- 4 ayant une autorisation
- EMA : 2 AMM conditionnelles
  - 23/12/2020: vaccin Pfizer
  - 6/01/2021 :vaccin Moderna
  - 3e attendue pour fin janvier (AZ)
- 27 décembre 2020: début vaccination France
- 7 janvier 2021: 45 000 francais vaccinés dont 25 000 le 7/01/2021

Comirnaty market approval schedule

Exemple de compression du calendrier d'évaluation pour Comirnaty®

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Filip Josephson Co-Rapporteur: Jean-Michel Race

The CHMP confirmed eligibility to the centralised procedure on	23 July 2020
Confirmation by ETF on the eligibly to the rolling review procedure on	24 July 2020
Agreement by ETF to start the rolling review procedure on	25 September 2020
The applicant submitted documentation as part of a rolling review on non-clinical data to support the marketing authorisation application	05 October 2020
The procedure (Rolling Review 1) started on	06 October 2020
The Rapporteur's first Assessment Report was circulated to all CHMP, Peer Reviewer and ETF on	22 October 2020
The Rapporteurs circulated updated Joint Assessment reports to all CHMP, Peer Reviewer and ETF on	28 October 2020
ETF discussions took place on	29 October 2020
Adoption of first Interim Opinion on the RR via 24 hour written procedure on	06 November 2020
The applicant submitted documentation as part of a rolling review on	
The procedure (Rolling Review 2) started on	07 November 2020
The Rapporteur's first Assessment Report was circulated to all CHMP, BWP, Peer Reviewer and ETF on	19 November 2020
BWP extraordinary adobe meeting was held on	24 November 2020
Updated joint draft overview and LoQ drafted by Rapporteurs and circulated to CHMP and ETF on	25 November 2020
ETF discussions took place on	26 November 2020
Adoption of the 2nd interim opinion for this rolling review on	30 November 2020
The application for the marketing authorisation was formally received by the EMA on	30 November 2020

The procedure started on	1 December 2020
BWP extraordinary adobe meeting was held on	15 December 2020
The Rapporteur's first Assessment Report was circulated to all CHMP, BWP, peer reviewer and ETF on	16 December 2020
The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on	16 December 2020
BWP extraordinary adobe meeting with an Oral Explanation by the applicant was held on	16 December 2020
ETF discussions took place on	17 December 2020
The Rapporteurs circulated the Joint Assessment Report to all CHMP members on	17 December 2020
BWP extraordinary adobe meeting was held on	18 December 2020
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during an extraordinary meeting on	18 December 2020
CHMP extraordinary adobe meeting was held on	18 December 2020
The following GMP and GLP inspections were requested by the CHMP and their outcome taken into consideration as part of the Quality/Safety/Efficacy assessment of the product:	
– GMP inspections (distant assessments) of the sites Wyeth BioPharma, Andover (manufacturer DS, QC DS, QC DP) and Pfizer Inc., Chesterfield (QC DP, QC DP), both located in the USA, were carried out between 20 November 2020 and 02 December 2020. The outcome of the inspections carried out were issued on 15 December 2020.	15 December 2020
– A GLP inspection at a CRO in Germany between 3 to 6 November 2020. The outcome of the inspection carried out was issued on 6 November 2020.	6 November 2020

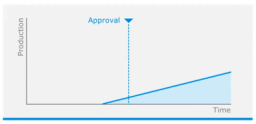
Classical versus emergency production model

STANDARD VACCINES COMPARED WITH COVID-19 VACCINES

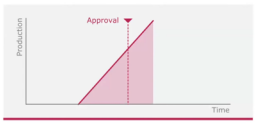
Manufacturing

Companies are **expanding** manufacturing and production **capacity** to ensure efficient vaccine deployment

STANDARD



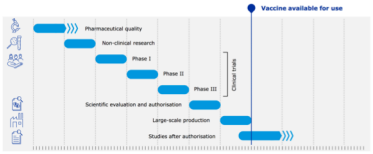
COVID-19



https://www.ema.europa.eu/en/documents/presentation/presentation-how-are-covid-19-vaccines-developed-marco-cavaleri_en.pdf

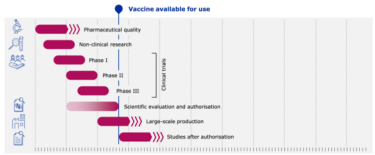
STANDARD VACCINES COMPARED WITH COVID-19 VACCINES

Indicative timeline



STANDARD VACCINES COMPARED WITH COVID-19 VACCINES

Indicative timeline



https://www.ema.europa.eu/en/documents/presentation/presentation-how-are-covid-19-vaccines-developed-marco-cavaleri_en.pdf

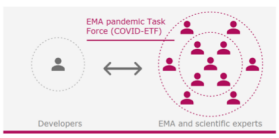
STANDARD VACCINES COMPARED WITH COVID-19 VACCINES

Expert Task Force & continuous dialogue

COVID-19 vaccine development is supported by early, continuous dialogue between developers and a dedicated group of regulatory experts **EMA COVID-19 Task Force**

STANDARD

COVID-19



https://www.ema.europa.eu/en/documents/presentation/presentation-how-are-covid-19-vaccines-developed-marco-cavaleri_en.pdf

China, Sinavac

Classical vaccine

Covid 19 Vaccines

Inactivated Virus

Safety, tolerability, and immunogenicity of an inactivated SARS-CoV-2 vaccine in healthy adults aged 18–59 years: a randomised, double-blind, placebo-controlled, phase 1/2 clinical trial

Yanjun Zhang, Gang Zeng*, Hongxing Pan*, Changgui Li*, Yaling Hu, Kai Chu, Weixiao Han, Zhen Chen, Rong Tang, Weidong Yin, Xin Chen, Yuansheng Hu, Xiaoyong Liu, Congbing Jiang, Jingxin Li, Minnan Yang, Yan Song, Xiangxi Wang, Qiang Gao†, Fengcai Zhu†*

Lancet Infect Dis 2021

https://en.wikipedia.org/wiki/CoronaVac

Russia, Gamaleya Center

Classical vaccine

Covid 19 Vaccines

Sputnik V, adenoviral-based vaccine

Currently there are over 200 different COVID-19 vaccines under development around the world.

Sputnik V is the world's first registered vaccine based on a well-studied human adenoviral vector-based platform. It currently ranks among top-10 candidate vaccines approaching the end of clinical trials and the start of mass production on the World Health Organization's (WHO) list.

The ongoing Sputnik V post-registration clinical trial in Russia involves 40,000 volunteers. Clinical trials of Sputnik V have been announced in the UAE, India, Venezuela and Belarus. This website has been created to provide accurate and up-to-date information about Sputnik V.

https://sputnikvaccine.com/about-vaccine/

Pfizer and BioNTech
Preclinical results, Sept 9th 2020

RNA vaccine

Covid 19 Vaccines

BNT162b2 mRNA-based vaccine program

Immunization of non-human primates (rhesus macaques) with BNT162b2, a nucleoside-modified messenger RNA (modRNA) candidate that expresses the SARS-CoV-2 spike glycoprotein, resulted in strong anti-viral effects against an infectious SARS-CoV-2 challenge

BNT162b2 immunization prevented lung infection in 100% of the SARS-CoV-2 challenged rhesus macaques, with no viral RNA detected in the lower respiratory tract of immunized and challenged animals. The BNT162b2 vaccination also cleared the nose of detectable viral RNA in 100% of the SARS-CoV-2 challenged rhesus macaques within 3 days after the infection

The BNT162b2 vaccine candidate induced SARS-CoV-2 neutralizing antibodies in rhesus macaques, pseudovirus neutralizing antibodies in mice, and strong, antigen-specific CD4+ and CD8+ T cells in mice and macaques

https://www.businesswire.com/news/home/20200909005570/en/

Pfizer and BioNTech
clinical III results, Nov 9th 2020

RNA vaccine

Covid 19 Vaccines

BNT162b2 mRNA-based vaccine program

Vaccine candidate was found to be more than 90% effective in preventing COVID-19 in participants without evidence of prior SARS-CoV-2 infection in the first interim efficacy analysis

Analysis evaluated 94 confirmed cases of COVID-19 in trial participants
Study enrolled 43,538 participants, with 42% having diverse backgrounds, and no serious safety concerns have been observed; Safety and additional efficacy data continue to be collected
Submission for Emergency Use Authorization (EUA) to the U.S. Food and Drug Administration (FDA) planned for soon after the required safety milestone is achieved, which is currently expected to occur in the third week of November

Clinical trial to continue through to final analysis at 164 confirmed cases in order to collect further data and characterize the vaccine candidate's performance against other study endpoint

https://www.pfizer.com/news/press-release/press-release-detail/pfizer-and-biontech-announce-vaccine-candidate-against

Moderna

RNA vaccine

Covid 19 Vaccines

mRNA-1273, our vaccine candidate against the novel coronavirus.

COVID-19 vaccine (mRNA-1273)

Last program update: November 16, 2020

https://fr.wikipedia.org/wiki/MRNA-1273

Astra Zeneca-Oxford

Classical vaccine

AZD1222

Covid 19 Vaccines

Replication-deficient chimpanzee viral vector based on a weakened version of a common cold virus (adenovirus) that causes infections in chimpanzees and contains the genetic material of th SARS-CoV-2 virus spike protein

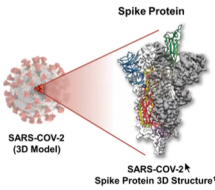
Positive high-level results from an interim analysis of clinical trials of AZD1222 in the UK and Brazil showed the vaccine was highly effective in preventing COVID-19, the primary endpoint, and no hospitalisations or severe cases of the disease were reported in participants receiving the vaccine. There were a total of 131 COVID-19 cases in the interim analysis. One dosing regimen (n=2,741) showed vaccine efficacy of 90% when AZD1222 was given as a half dose, followed by a full dose at least one month apart, and another dosing regimen (n=8,895) showed 62% efficacy when given as two full doses at least one month apart. The combined analysis from both dosing regimens (n=11,636) resulted in an average efficacy of 70%. All results were statistically significant (p<0.0001). More data will continue to accumulate and additional analysis will be conducted, refining the efficacy reading and establishing the duration of protection. An independent Data Safety Monitoring Board determined that the analysis met its primary endpoint showing protection from COVID-19 occurring 14 days or more after receiving two doses of the vaccine. No serious safety events related to the vaccine have been confirmed. AZD1222 was well tolerated across both dosing regimens.
AstraZeneca will now immediately prepare regulatory submission of the data to authorities around the world that have a framework in place for conditional or early approval. The Company will seek an Emergency Use Listing from the World Health Organization for an accelerated pathway to vaccine availability in low-income countries.
In parallel, the full analysis of the interim results is being submitted for publication in a peer-reviewed journal. Professor Andrew Pollard, Chief Investigator of the Oxford Vaccine Trial at Oxford, said: "These findings show that we have an effective vaccine that will save many lives. Excitingly, we've found that one of our dosing regimens may be around 90% effective and if this dosing regime is used, more people could be vaccinated with planned vaccine supply. Today's announcement is only possible thanks to the many volunteers in our trial, and the hard working and talented team of researchers based around the world."
Pascal Soriot, Chief Executive Officer, said: "Today marks an important milestone in our fight against the pandemic. This vaccine's efficacy and safety confirm that it will be highly effective against COVID-19 and will have an immediate impact on this public health emergency. Furthermore, the vaccine's simple supply chain and our no-profit pledge and commitment to broad, equitable and timely access means it will be affordable and globally available, supplying hundreds of millions of doses on approval."
The pooled analysis included data from the COV002 Phase II/III trial in the UK and COV003 Phase III trial in Brazil. Over 23,000 participants are being assessed following two doses of either a half-dose/full-dose regimen or a regimen of two full doses of AZD1222 or a comparator, meningococcal conjugate vaccine called MenACWY or saline. The global trials are evaluating participants aged 18 years or over from diverse racial and geographic groups who are healthy or have stable underlying medical conditions.
Clinical trials are also being conducted in the US, Japan, Russia, South Africa, Kenya and Latin America with planned trials in other European and Asian countries. In total, the Company expects to enrol up to 60,000 participants globally. The Company is making rapid progress in manufacturing with a capacity of up to 3 billion doses of the vaccine in 2021 on a rolling basis, pending regulatory approval. The vaccine can be stored, transported and handled at normal refrigerated conditions (2-8 degrees Celsius/ 36-46 degrees Fahrenheit) for at least six months and administered within existing healthcare settings. AstraZeneca continues to engage with governments, multilateral organisations and collaborators around the world to ensure broad and equitable access to the vaccine at no profit for the duration of the pandemic.

https://www.astrazeneca.com/media-centre/press-releases/2020/azd1222hlr.html

Optimization of Genetic Sequence

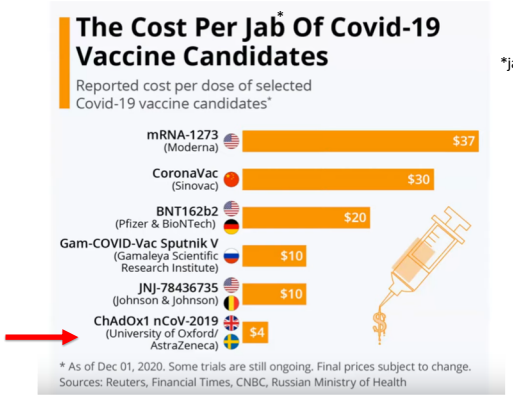
Selection of Pfizer/BioNTech COVID-19 Vaccine BNT162b2

Initially Four Vaccine Candidates

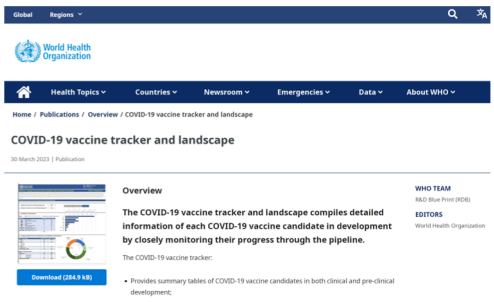


	Variant	Target	RNA Construct	Regimen
1	162a1	RBD subunit	uRNA	Prime/boost
2	162b1	RBD subunit	modRNA	Prime/boost
3	162b2	P2-mutated full spike protein	modRNA	Prime/boost
4	162c2	P2-mutated full spike protein	saRNA	Single injection

RNA: unmodified mRNA
modRNA: nucleoside modified mRNA saRNA: self-amplifying mRNA
1. Wrapp et al., 2020, *Science*.



*jab=piqure



https://www.who.int/publications/m/item/draft-landscape-of-covid-19-candidate-vaccines

conference in french

https://www.youtube.com/watch?v=q2C6GimlSts&feature=youtu.be

Omicron could change SARS-Cov disease to become endemic and global vaccinal strategy is not yet final

https://www.ecdc.europa.eu/en/covid-19/variants-concern

https://www.who.int/publications/m/item/covid-19-epidemiological-update-edition-175

VirusVariant
P.1
B.1.1.7
B.1.351
P.3
B.1.427/B.1.429
B.1.525
B.1.621
B.1.617.2
C.37
B.1.1.529
BA.5
BA.2
BA.1
BA.4
BA.2.75
BQ.1
XBB
XBB.1.5
XBB.1.5-like+F456L
BA.2.86
JN.1

Chapter 4
Steps of drug development
pre-clinical
clinical

Exemple of preclinical Research

Research of an inhibitory activity on enzymes or something else...

- ***High throughput Screening (HTS)* of molecule banks**

to Find inexpensive high-throughput tests to test thousands (tens of thousands) of molecules for their activities, for example enzyme inhibitors. It is a method still widely used to find therapeutic activities

- **Serendipity**

James Schlatter Chemist of G. D. Searle & Company discovers the sweetness of aspartame (1965)

Revisiting the safety of aspartame, **Choudhary and Pretorius: Nutr. Rev 2017**

the safety of this sweetener should be revisited. Most of the literature available on the safety of aspartame is included in this review. Safety studies are based primarily on animal models, as data from human studies are limited. The existing animal studies and the limited human studies suggest that aspartame and its metabolites, whether consumed in quantities significantly higher than the recommended safe dosage or within recommended safe levels, may disrupt the oxidant/antioxidant balance, induce oxidative stress, and damage cell membrane integrity, potentially affecting a variety of cells and tissues and causing a deregulation of cellular function, ultimately leading to systemic inflammation

Exemple of preclinical Research
« *research of a biological activity* »

***In Silico* Drug-design** (*in silico research*)

This involves studying (by modeling) the structure / function relationship of the molecule of interest by seeking to visualize the molecular interactions between the therapeutic target and the molecule:

we can for example study co-crystals (crystallography then analysis X-rays and modeling).

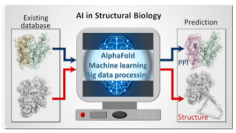
we can *in silico* improve (test) the interactions before deciding to synthesize and then test *in vivo* a new molecule

AlphaFold first availability : 2021

DeepMind

Article

Highly accurate protein structure prediction with AlphaFold



https://deepmind.google/technologies/alphafold/

Alphafold 2 and 3: version 3 allows to predict molecules interactions

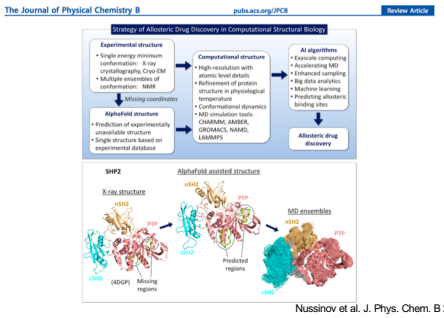
***predicted Local Distance Difference Test**

If AlphaFold predicts a protein with an **Average pLDDT*** of **85**, it means the overall structure is predicted with reasonable confidence, but there may be some regions with lower confidence where the pLDDT is below 70. In these areas, the predicted structure may need to be interpreted with more caution.

AlphaFold, Artificial Intelligence (AI), and Allostery

Published as part of The Journal of Physical Chemistry virtual special issue "Protein Folding and Dynamics—An Overview on the Occasion of Harold Scheraga's 100th Birthday".

Ruth Nussinov,* Mingzhen Zhang, Yonglan Liu, and Hyunbum Jang



Nussinov et al. J. Phys. Chem. B 2022, 126, 6372−6383

Computational methods

Advances and challenges in drug design against tuberculosis: application of in silico approaches

- *Together with the geometric growth of protein structural and sequence databases, computational methods have become a powerful technique accelerating the successful identification of new ligands*

Alexey Aleksandrov Hannu Myllykallio

JAMA | Original Investigation

Estimated Research and Development Investment Needed to Bring a New Medicine to Market, 2009-2018

*After accounting for the costs of failed trials, the median capitalized research and development investment to bring a new drug to market was estimated at **$985.3 million** (**95%CI, $683.6 million-$1228.9 million**), and the mean investment was estimated at $1335.9 million (95%CI, $1042.5 million-$1637.5 million) in the base case analysis*

Wouters et al. JAMA 2020

Exemple of preclinical Research

Study of the mode of action of a molecule on a specific cell type

- Ex: developement of a Platelet antiaggregant: **cyclooxygenase COX / lipoxygenase LOX** activity (balance between prostacyclin PGI2 / thromboxane B2 TXB2) in umibilical cord primary cultures using Mass Spectromety of protaglandins.

Assay after incubation on endothelial cells in the presence of the molecule of interests PGI2/TXB2, of various metabolites of the COX/LOX pathways

Review > Biochimie. 2019 Apr;159:55-58. doi: 10.1016/j.biochi.2018.08.009. Epub 2018 Sep 1.

Biological relevance of double lipoxygenase products of polyunsaturated fatty acids, especially within blood vessels and brain

Michel Guichardant [1], Evelyne Véricel [1], Michel Lagarde [2]

Preclinical research research of activity

- **Ethnopharmacology, ethnobotany**
- Based on traditional pharmacopoeias, we can collect both new plants and analyze them (**pharmacognosy** / medical material) and link the results to ancestral medical practices which can give indications on the activity of plants and therefore molecules

EUROPEAN SOCIETY OF ETHNOPHARMACOLOGY
MEDICINAL PLANTS • TRADITIONAL PHARMACOPOEIAS • MEDICAL ANTHROPOLOGY

Ethnopharmacology studies natural medicines derived from plants and other substances that have been traditionally used by groups of people to treat various human diseases.

https://ethnopharmacology.org/

Preclinical Research importance

- **Acute toxicity**
- **Chronic toxicity**
- **Pharmacology (mode of action)**
- **Pharmacodynamics (fate of drug in the organism)**

Enhancing the Utility of Preclinical Research in Neuropsychiatry Drug Development

Arie Kaffman[1], **Jordon D. White**[1], **Lan Wei**[1], **Frances K. Johnson**[1], **John H. Krystal**[1]
[1]Department of Psychiatry, Yale University School of Medicine, New Haven, USA

Methods Mol Biol. 2019 ; 2011: 3–22

Toxicology

- **Acute Toxicology** (research of ***letal dosis 50***)

No Observable Adverse Effect Level, *NOAEL*

Predictive and explanatory themes of **NOAEL** through a systematic comparison of different machine learning methods and descriptors.
Qian J, Song FL, Liang R, Wang XJ, Liang Y, Dong J, Zeng WB.
Food Chem Toxicol. 2022 Oct;168:113325. doi: 10.1016/j.fct.2022.113325. Epub 2022 Aug 10.
PMID: 35963474

- Sub-acute Toxicity
- Chronic toxicity: Research on animals (pathology and anatomy)
- Mutagenic toxicity (Test of Ames)
- Immunotoxicity
- food toxicity (**admissible daily intake**/DJA)
- Dose-dependent Accumulation in the organisms (nanoparticles)

Do Nanoparticles Accumulate in the Body?

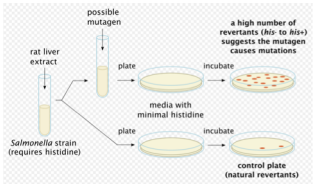
- Yes, nanoparticles **can accumulate in the body**, but the extent and location of accumulation depend on several factors, including the type of nanoparticle, its size, surface properties, and route of exposure.
- Because nanoparticles are so small (typically between **1 to 100 nanometers**), they can easily enter the body through various exposure routes such as **inhalation, ingestion, dermal contact, or injection**.
- Once inside the body, nanoparticles can accumulate in various tissues and organs, especially if they are **biologically persistent** (i.e., they don't break down or are not easily cleared from the body). Some nanoparticles are cleared relatively quickly, while others may accumulate over time, potentially leading to long-term effects.

Carbon Nanotubes (CNTs), Silver Nanoparticles, Titanium Dioxide

Ames test

Review > Mutat Res. 2000 Nov 20;455(1-2):29-60. doi: 10.1016/s0027-5107(00)00064-6.

The Ames Salmonella/microsome mutagenicity assay



> Mutat Res Genet Toxicol Environ Mutagen. 2019 May;841:43-48. doi: 10.1016/j.mrgentox.2019.05.007. Epub 2019 May 15.

The test that changed the world: The Ames test and the regulation of chemicals

Chromosomal aberration test

> Methods Mol Biol. 2019;2031:121-134. doi: 10.1007/978-1-4939-9646-9_6.

Chromosomal Aberration Test in Human Lymphocytes

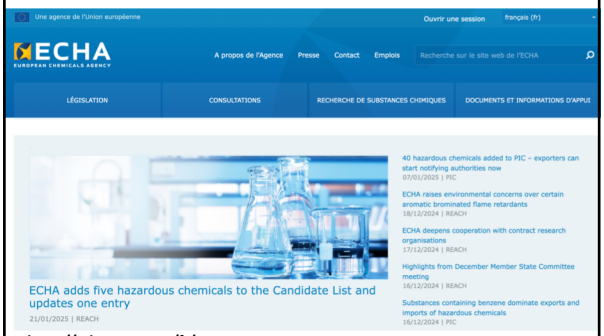
Christian Johannes [1], Guenter Obe [2]

Abstract

Human peripheral lymphocytes (HPL) are non-cycling primary cells (G0 cells). They are easily collectable by venipuncture. In the presence of suitable culture media and stimulants in vitro HPL enter the cell cycle and divide mitotically. Metaphase-like stages can be arrested using the spindle fiber poison colcemid and prepared on microscopic slides. Following appropriate staining, chromosomal aberrations can be analyzed in the microscope. These aberrations may either be induced in vivo by environmental or occupational influences or in vitro after experimentally controlled manipulations in order to detect or to test the mutagenic potency of various agents.

Keywords: Biological dosimetry; Chromosomal aberrations; Culture media; Human peripheral lymphocytes; Human primary cells; Mutagenicity testing; Stimulation.

European Chemical Agency (2007, Finland)



https://echa.europa.eu/fr/

REACH= Registration, Evaluation, Authorization, and Restriction of Chemicals

The REACH is a comprehensive legislation in the European Union (EU) that aims to ensure the safe use of chemicals. Compliance with REACH involves various testing requirements depending on the specific circumstances of each chemical substance. The testing requirements includes

- **Data Gathering and Registration:**
- **Chemical Safety Assessment (CSA):**
- **Testing Proposals and Information Sharing:**
- **Substance Evaluation:**
- **Authorization:**
- **Restriction:**
- **Downstream User Obligations:**
- **Communication in the Supply Chain:**
- **Notification of Substances in Articles**

- **Data Gathering and Registration:**
  - Collecting and submitting information on the properties and uses of the chemical.
  - Identifying and registering substances with the European Chemicals Agency (ECHA) if the annual production or import volume exceeds certain thresholds.
- **Chemical Safety Assessment (CSA):**
  - Conducting a Chemical Safety Assessment for substances produced or imported in quantities of 10 tons o more per year.
  - Performing exposure assessments for workers, consumers, and the environment.
- **Testing Proposals and Information Sharing:**
  - Proposing testing when data gaps are identified.
  - Sharing available data with other registrants to avoid unnecessary animal testing.
- **Substance Evaluation:**
  - Subjecting substances to evaluation by EU member states when concerns arise regarding their risks.
  - Providing additional information if requested by authorities.
- **Authorization:**
  - Applying for authorization if a substance is listed in Annex XIV and its use is not exempted.
  - Submitting substitution plans for authorization applications.
- **Restriction:**
  - Complying with restrictions on the manufacture, placing on the market, or use of certain substances listed in Annex XVII.
- **Downstream User Obligations:**
  - Complying with information received from suppliers (e.g., Safety Data Sheets) and using substances in accordance with the provided information.
- **Communication in the Supply Chain:**
  - Providing information on safe use down the supply chain, including updating Safety Data Sheets.
  - Complying with communication requirements for articles containing substances of very high concern (SVHCs) in concentrations above 0.1% weight by weight.
- **Notification of Substances in Articles:**
  - Notifying ECHA if an article contains a **substance of very high concern (SVHC)** in concentrations above 0.1% weight by weight, and the total amount is greater than 1 ton per year

Registration, Evaluation and Authorisation of Chemicals (REACH) (Nanoparticles and Toxicity in Pubmed returns 42,624 hits)

Aluminium as potentially toxic agent, **Titanium dioxyde** and **Nanoparticles**

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5551928/pdf/Dsch_Arztebl_Int-114-0653.pdf

Titanium dioxide (TiO_2), which exists in micrometric and nanometric form, is used in the composition of a large variety of products such as paints, cosmetics, sunscreens but also drugs, toothpaste, confectionery and more generally as a coloring alimentary **declared as cancerigen since 2016 by ECHA**

Subchronic and chronic toxicity evaluation of inorganic nanoparticles for delivery applications

Mohammadpur et al. Adv Drug Deliv Rev 2019 Apr;144:112-132. doi: 10.1016/j.addr.2019.07.006.

Legal Clinical Research Framework (see Barbier-Jolaine slideshow, 2014)

https://slideplayer.fr/slide/3055185/

- Nuremberg Code, 1947
- Helsinki Declaration, 1964 (World medical association elaborate ethical code
- Manilla Declaration, 1981 (WHO, international guidelines)
- Helsinki Declaration 2008
- Loi française de Santé Publique 2004
- Loi française de Bioéthique 2011

Clinical Research Framework (see Barbier-Jolaine slideshow, 2014)

Clinical trials - Regulation EU No 536/2014

https://slideplayer.fr/slide/3055185/

- Huriet Law 1988, Directive 2001/20 /
- EC of the European Parliament and of the Council of April 4, 2001
- Written consent (informed consent)
- Distinguished research without direct individual benefit from research with direct individual benefit
- Obligation to submit the protocol to a CCPPRB
- Obiogation of distinction of roles: Promoter (finances research) and Investigator (carries out research, a priori completely independently)
- Promoter's insurance obligation
- Obligation to manage pharmaceutical batches of therapeutic trials
- (dispensing, counting, recovery)
- Documentation obligation
- (basis of the AMM / CRF file)
- Obligation to demonstrate an improvement in the service provided (the novelty must prove to be superior to the existing reference medicine)

https://health.ec.europa.eu/medicinal-products/clinical-trials/clinical-trials-regulation-eu-no-5362014_en

Clinical research

- **Phase I** = trial without direct individual benefit
- **Phase II** (IIa et IIb) = trial with direct individual benefit. Study of pharmacokinetics and pharmacodynamics. It is at this stage that many side effects are discovered initially and the trials stop
- **Phase III** : extension of phase II to more patients, often multicentric, studies used to build the marketing authorization dossier, detection of rarer adverse effects
- **Phase IV**: post-AMM, pharmacovigilance.

Patient Information Sheet (required to get informed consent)

- **Extremely important**: must present the issues, risks, benefits, must be understandable, even if it is the investigator who ultimately seeks or not to convince the patient to enter a study, for his own good
- But more and more, the drug is no longer free, it is bought by public hospitals: private research and public therapeutic research must collaborate, often the public funds private research ...

Insurance Obligation

- **Thalidomide** historical scandal (1950-1960)
- **Distilben** scandal(1948-1977, 200.000 women)
- **Mediator** scandal (1976-2009, 2.000.000 people)

In fact: obligation to report known adverse effects. But this is statistical, hence the surprises may come AFTER marketing

The risks concerning SARS-CoV 2 vaccines are not carried by private companies

Cancer and Environmental medicine

Endocrine Disruptors examples (bisphenol A, chlodecone)

2011

Bisphénol A, les dessous d'un scandale sanitaire

Repérés dès le milieu des années 1990, les effets nocifs du BPA ont été systématiquement minorés.

2018

Scandale sanitaire aux Antilles : qu'est-ce que le chlordécone ?

Ce pesticide ultra-toxique a été utilisé pendant plus de vingt ans dans les bananeraies en Guadeloupe et Martinique. Il a contaminé sols, rivières, bétail, poissons, crustacés, légumes-racines... et la population elle-même.

2020

Critical Review

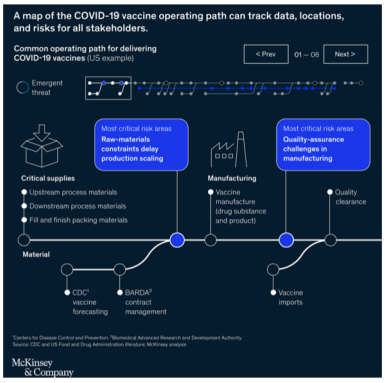
Per- and Polyfluoroalkyl Substance Toxicity and Human Health Review: Current State of Knowledge and Strategies for Informing Future Research

https://www.lemonde.fr/planete/article/2011/10/28/bisphenol-a-un-scandale-mondial_1595537_3244.html

https://www.lemonde.fr/planete/article/2018/06/06/scandale-sanitaire-aux-antilles-qu-est-ce-que-le-chlordecone_5310485_3244.html

https://setac.onlinelibrary.wiley.com/doi/pdfdirect/10.1002/etc.4890?src=getftr

from Emergency Use Authorization to Risks coverage



https://www.mckinsey.com/business-functions/risk/our-insights/the-risks-and-challenges-of-the-global-covid-19-vaccine-rollout#

Health industry: some professions

What Types of Jobs are there in the Pharmaceutical and Medical Device Industry?

By: Donagh Fitzgerald and Claire Wilson. Last Updated: April 2022

- CEO, CFO
- Director of R&D, Technology Director (CTO)
- Medical Department (writer, Medical director)
- Therapeutic trials monitor (clinical monitor)
- Project Manager Medical / Scientific Writer
- Research assistant
- Pharmacovigilance manager
- Quality managers, Quality Insurance, Auditors
- Biometrician
- Regulatory Affairs staff (Regulatory Affairs Director, Redactor)
- Marketing staff (product manager, brand manager, group manager, range manager) Commercial, Marketing research
- (Medical information, Regional directors, Zone directors)
- Logistics function
- Production: Responsible pharmacist, Director of production site
- Quality control technicians
- Business Development Manager

https://www.getreskilled.com/types-of-pharma-jobs/

What are the conditions required to being a drug to the market ?

-Marketing authorization (DMA)

Quality-Efficacy-Safety

NCE, formulation, dosing, manufacture

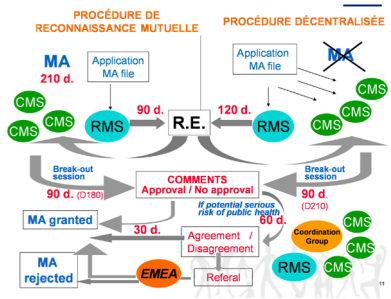
-A price

https://solidarites-sante.gouv.fr/IMG/pdf/amm-assises-Lechat.pdf. **30 Pages, little bit outdated**

https://ansm.sante.fr/var/ansm_site/storage/original/application/ae1f0487eee12fc471179ecda8ccb21d.pdf **52 pages, procedure**

Procedure to get Market Approval in Europ for a new drug

la réglementation du médicament, Chap 4, LEEM



MA= market approval CMS=concerned member state, RMS= Reference Member State, RE=evaluation report

Therapeutical Innovations -1

- **New drugs must show that they provide more than the reference drug in the therapeutic class**, we are no longer satisfied with activity compared to a **placebo**, but with activity compared to the reference drug.
- Concept of MRS = **Medical Service Rendered**
- If a medicine has an MRS that is too low it can be erased from the reimbursment list (i.e. homeopathic drugs)

Therapeutical Innovations -2

- Other types of pharmaceutical innovations: improvements in specialties (vectorization, technical improvements: insulin in pen, etc.) *en route* to « **Medical Devices** »
- Example: pegylated interferons compared to the initial interferons which cause a reduction in the frequency of administration in the treatment of active chronic hepatitis C
- another example : change of mode of administration of a drug

Therapeutical Innovations -3

- other kind of innovation: the **FDC** (*fixed drug combinations*), (e.g. to treat tuberculosis in developing countries) Combination of 4 molecules (Rifampicin, Isoniazid, Ethnambutol, Pyrazinamide) in a single tablet
- Treatment of TB: 4 atb for 2 months then 2 atb for 4 months, heavy treatment…
- the new formulation improves **compliance** (monitoring of the medication taken by the patient), same for insulin: changes of modes of administration
- nowadays : new regimen (oral) BPaLM for MDR-TB

« Medical Devices » (ISO 13485)

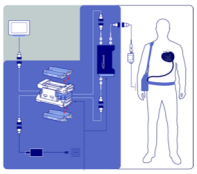
*A **medical device** is any device intended to be used for medical purposes*

- **Medical Devices**: think in terms of *care against pathologies* and no longer only in terms of pharmaceutical treatments…
- It is a synthetic approach that includes treatment, good compliance and / or good dosage controls, therapeutic monitoring methods, self-assessment of the evolution of the pathology for example. Example: diabetics

file:///Users/christophe.sola/Downloads/the-complete-guide-to-iso-13485-for-medical-devices.pdf

Medical Devices Example

Carmat (Aeson®) 50 pat.



stryker

WRIGHT

Guidance on the vigilance system for CE-marked medical devices

DSVG 05

1979

Stryker acquiert Osteonics Corporation

Motiva
Mentor
Polytech Health
Allergan
Sebbin
Arion
Eurosilicone/Nagor

Insulin Infusion Pumps and Integrated meter systems

« *in Vitro* Diagnostics »

Understanding Europe's New IVDR 2017/746

IVDs are used to analyze human samples such as blood and saliva, either by measuring the concentration of specific substances, or analytes (such as sodium and cholesterol), or by detecting the presence or absence of a particular marker or set of markers, such as a genetic mutation or an immune response to infection.[2] Clinicians regularly use IVDs to diagnose conditions, guide treatment decisions, and even mitigate or prevent future disease (for example, through screening tests that indicate a patient's risk of developing a given condition in the future).

https://www.pewtrusts.org/en/research-and-analysis/issue-briefs/2019/05/what-are-in-vitro-diagnostic-tests-and-how-are-they-regulated