Drug development

1. Steps of drug development
2. Control agencies in CH

Documents sur myUNIL

Stephan Kellenberger, DSB-UNIL

Figures are from « Rang and Dale's « Pharmacology », from « Principles of Pharmacology » by Golan et al., or as indicated.

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8. The drug discovery testing scheme

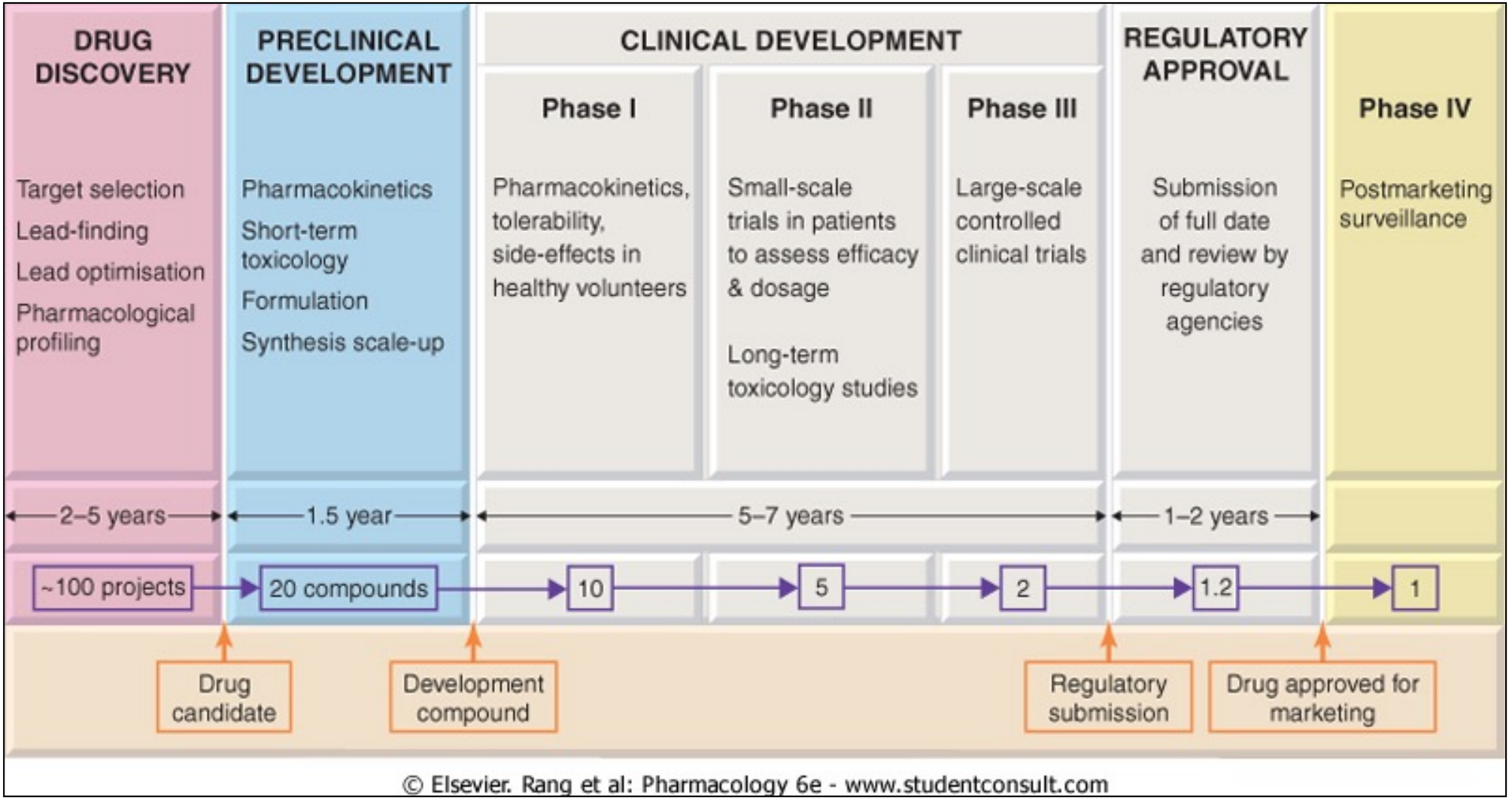

Figure 56-1 The stages of development of a 'typical' new drug, i.e. a synthetic compound being developed for systemic use. Only the main activities undertaken at each stage are shown, and the details vary greatly according to the kind of drug being developed.

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New drug approvals,USA, 1994-2024

(Nature Rev. Drug Disc. Feb 2025)

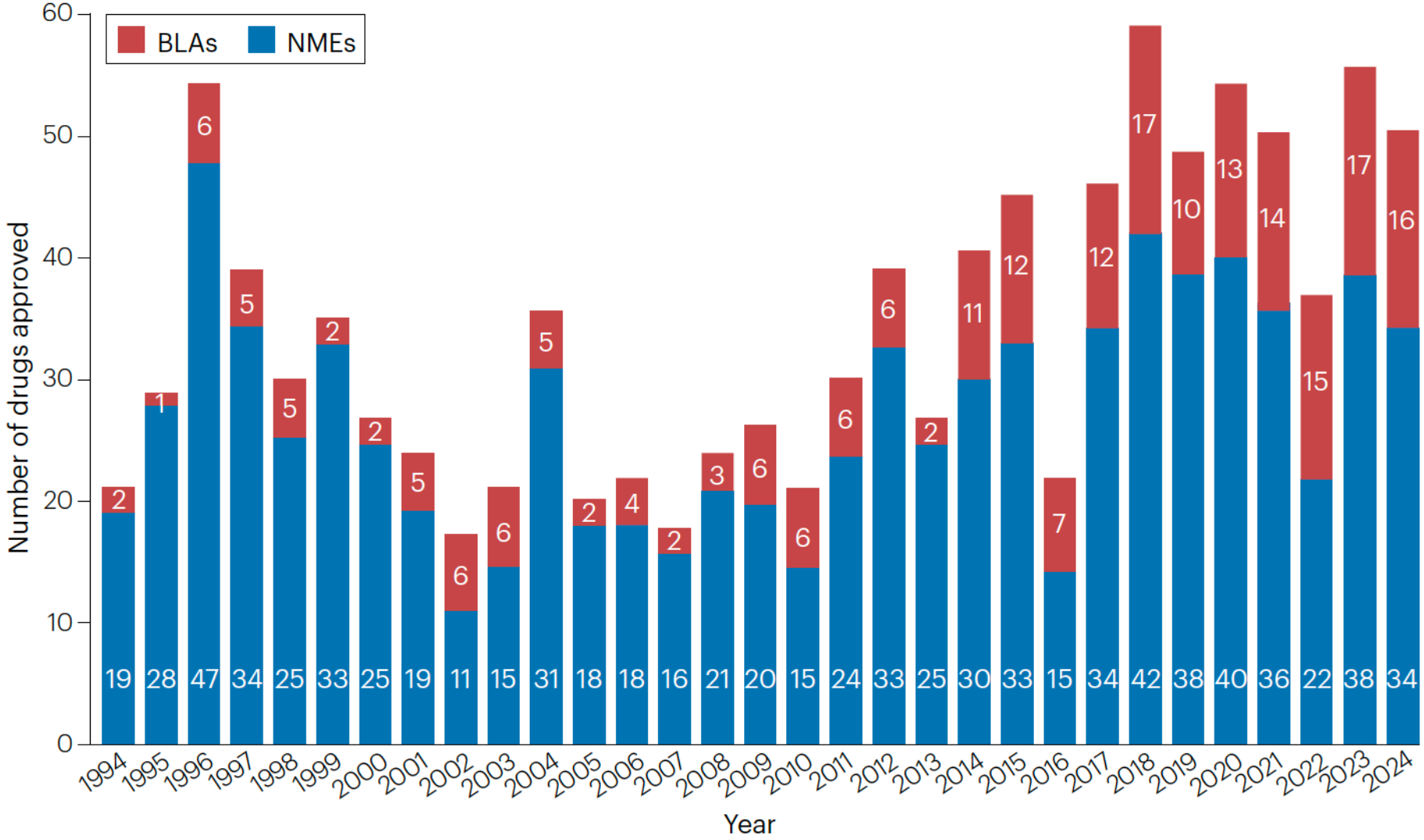

Fig. 1 | Novel FDA approvals since 1994. Annual numbers of new molecular entities (NMEs) and biologics license applications (BLAs) approved by the FDA's Center for Drug Evaluation and Research (CDER). See Table 1 for new approvals in 2024. Products approved by the Center for Biologics Evaluation and Research (CBER), including vaccines and gene therapies, are not included in this drug count (Table 2). Source: FDA.

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New drugs by therapeutic area

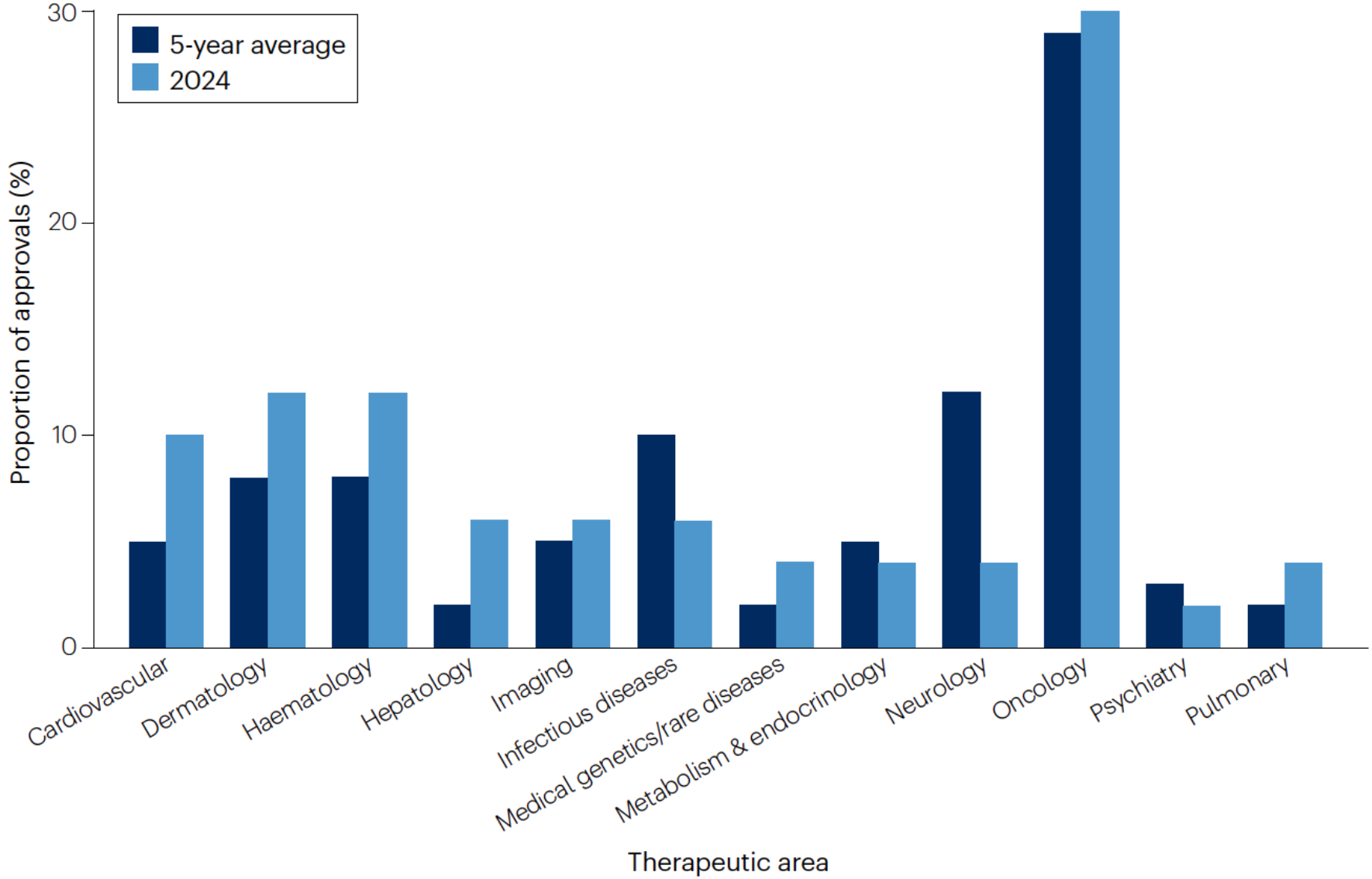
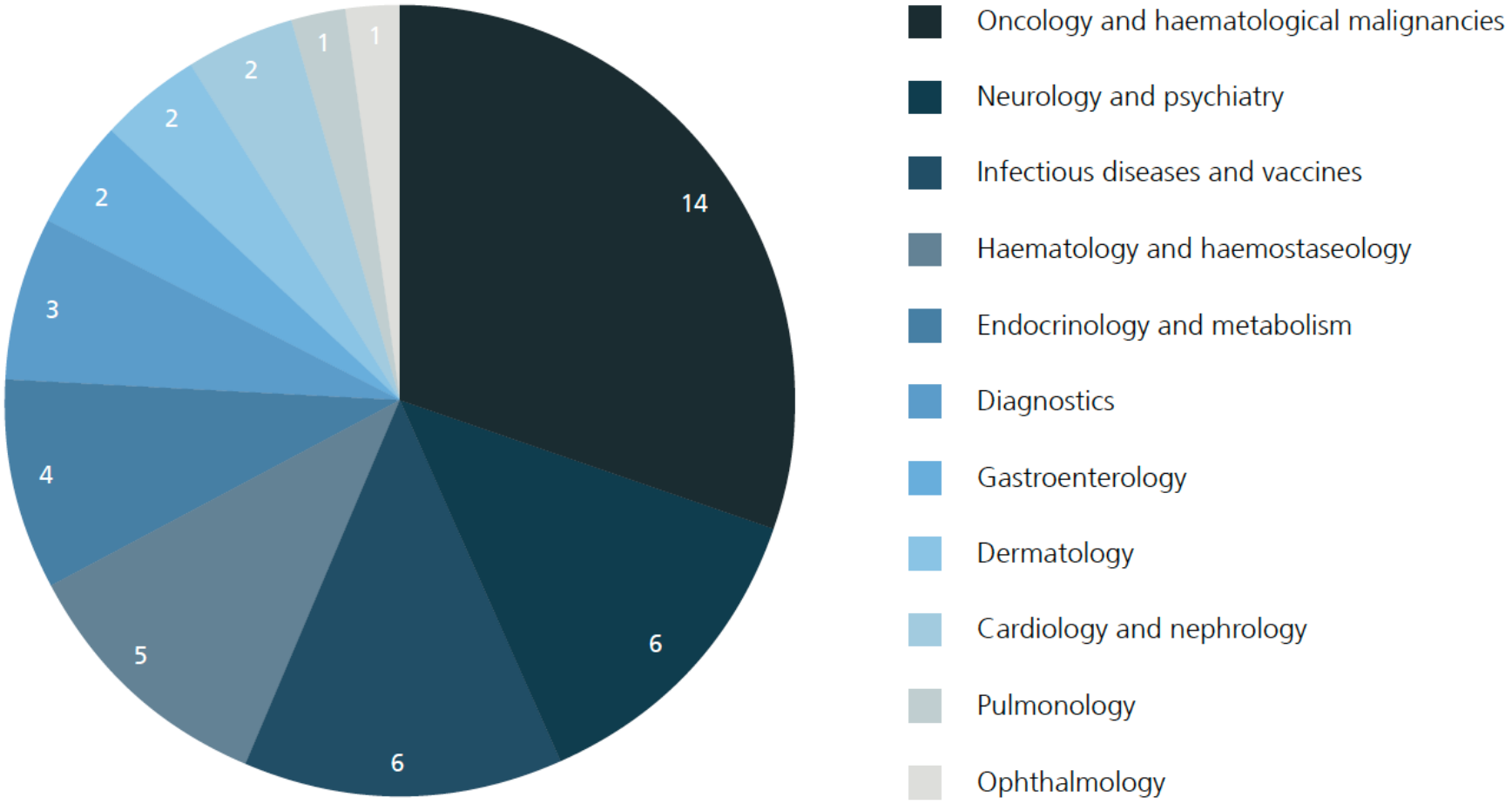


Fig. 2 | CDER approvals by therapeutic areas. Indications that span multiple disease areas are classified under only one, based on which FDA office and division reviewed the approval application. Source: *Nature Reviews Drug Discovery*, FDA.

For comparison: drugs approved by Swissmedic in 2024

Figure 1: Authorised medicinal products according to indication (n=46)



Swissmedic approved 46 drugs in 2024

https://www.swissmedic.ch/swissmedic/en/home/humanarzneimittel/authorisations/information/zl-ham-nas-ie-2024.html

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New FDA-approved drugs by modality

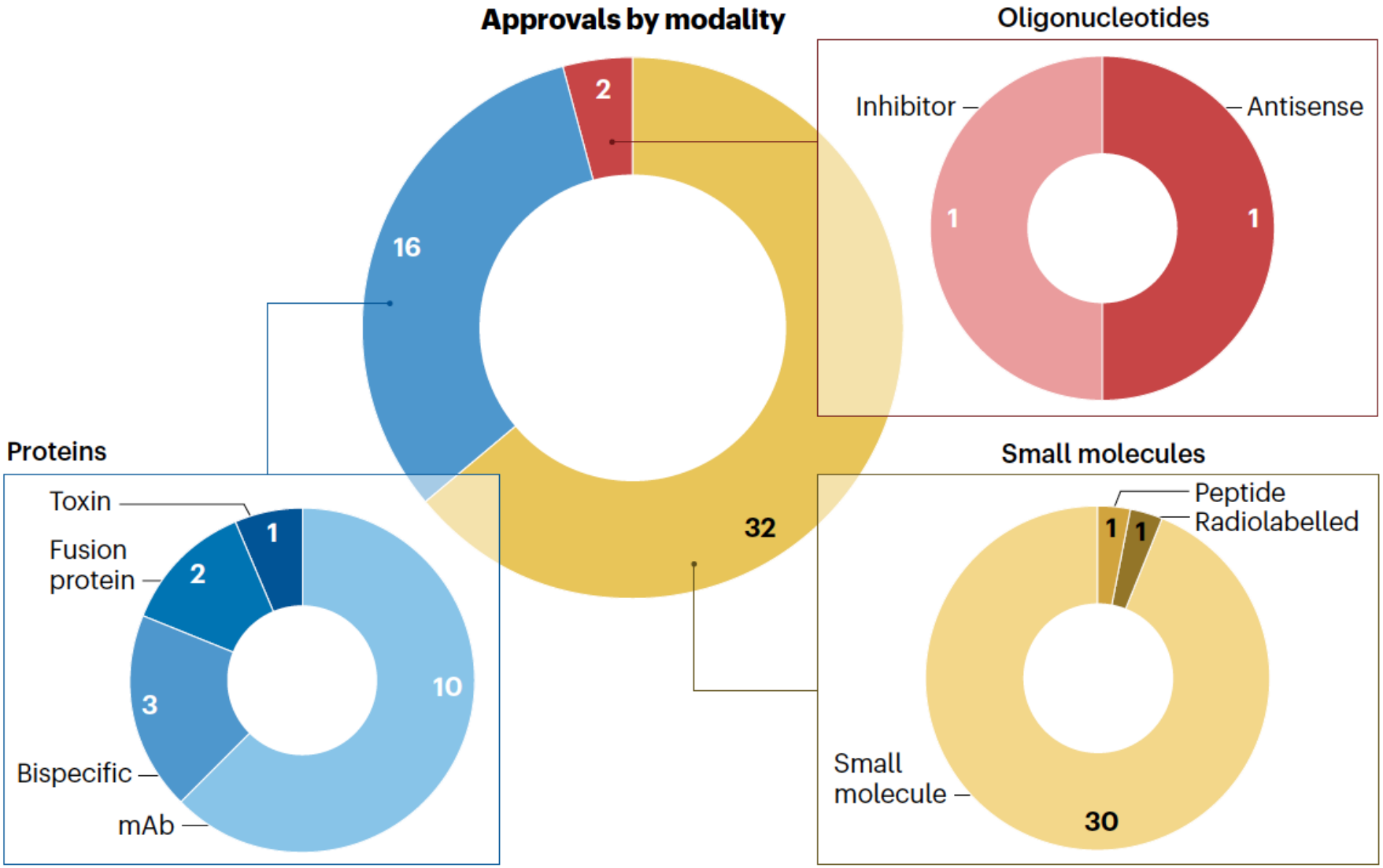

Fig. 3 | CDER approvals by modality. Small molecules, including peptides of up to 40 amino acids in length, and oligonucleotides are approved as new molecular entities. Protein-based candidates are approved through biologics license applications. mAb, monoclonal antibody. Source: *Nature Reviews Drug Discovery*.

CDER = FDA Center for Drug evaluation and research

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Selected CDER approvals

Table 1 | CDER approvals in 2024

Drug (brand name)	Sponsor	Properties	Indication
Xanomeline and trospium (Cobenfy)	Bristol Myers Squibb/Karuna	M_1/M_4 muscarinic receptor agonist plus pan-muscarinic receptor antagonist	Schizophrenia
Resmetirom (Rezdiffra)	Madrigal	Thyroid hormone receptor-β agonist	Noncirrhotic NASH with liver scarring

- Cobenfy: fixed dose combination of an M1/M4 muscarinic acetylcholine receptor agonist (Xanomeline) with a peripheral pan-mAChR antagonist (Trospium; to decrease side effects) for schizophrenia → first novel mechanism of action in this therapeutic area for decades
- Resmetirom: Thyroid receptor-β agonist for the treatment of nonalcoholic steatohepatitis (NASH, accumulation of fat and inflammation in the liver, leading to scarring and sometimes liver failure; 10-15 Mio people in the USA) → first drug that has a therapeutical effect on this disease

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Selected CBER approval

Table 2 | Selected CBER approvals in 2024

Biologic name (brand name)	Sponsor	Properties	Indication
Lifileucel (Amtagvi)	Iovance	Tumour-infiltrating lymphocyte therapy	Melanoma

Iovance Biotherapeutics's lifileucel (Amtagvi), approved by the FDA's CBER, expands the cell therapy toolbox. Researchers have for decades been building the case for tumour-infiltrating lymphocyte (TIL) cell therapies for the treatment of solid cancers.

Principle: These living therapies are made by harvesting cancer tissue, isolating the cancer-killing T cells within, and then growing these up in bioreactors to be re-infused into patients.

CBER = Center for Biologics evaluation and research

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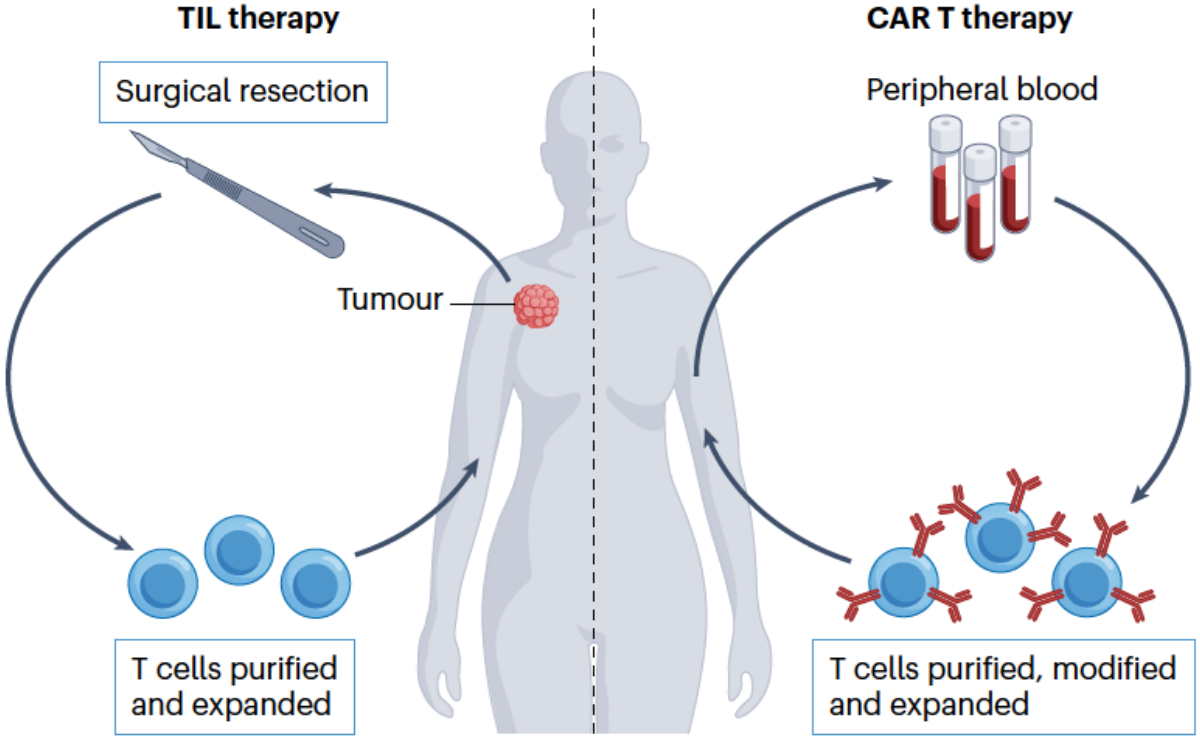
a



b

	First-generation TIL	First-generation CAR T
T cell source	Tumour tissue	Blood
Vein-to-vein time	~33 days	~21–35 days
Engineering	No engineering	Genetically modified to express a CAR
Targeting mechanism	TCRs that target unknown cancer-specific neoantigens	CARs that target a cancer-associated antigen
Cells infused per course	Billions (10^9 plus)	Millions (10^6–10^8)
Lymphodepletion protocol	Yes	Yes
Post-treatment IL-2 therapy	Yes	No
Safety signatures	IL-2-associated toxicity	CRS, neurotoxicity, off-tissue cell killing
Lead tumour types	Melanoma	B-cell cancers
Price tag	US$ 515,000	US$350,000–$500,000

Fig. 1 | TIL versus CAR T therapy. First-generation tumour-infiltrating lymphocyte (TIL) properties based on Iovance's lifileucel. Chimeric antigen receptor (CAR) T properties based on FDA-approved products. CRS, cytokine release syndrome; TCR, T cell receptor.

Volume 23 | January 2024 | 3–7 | 5
nature reviews drug discovery

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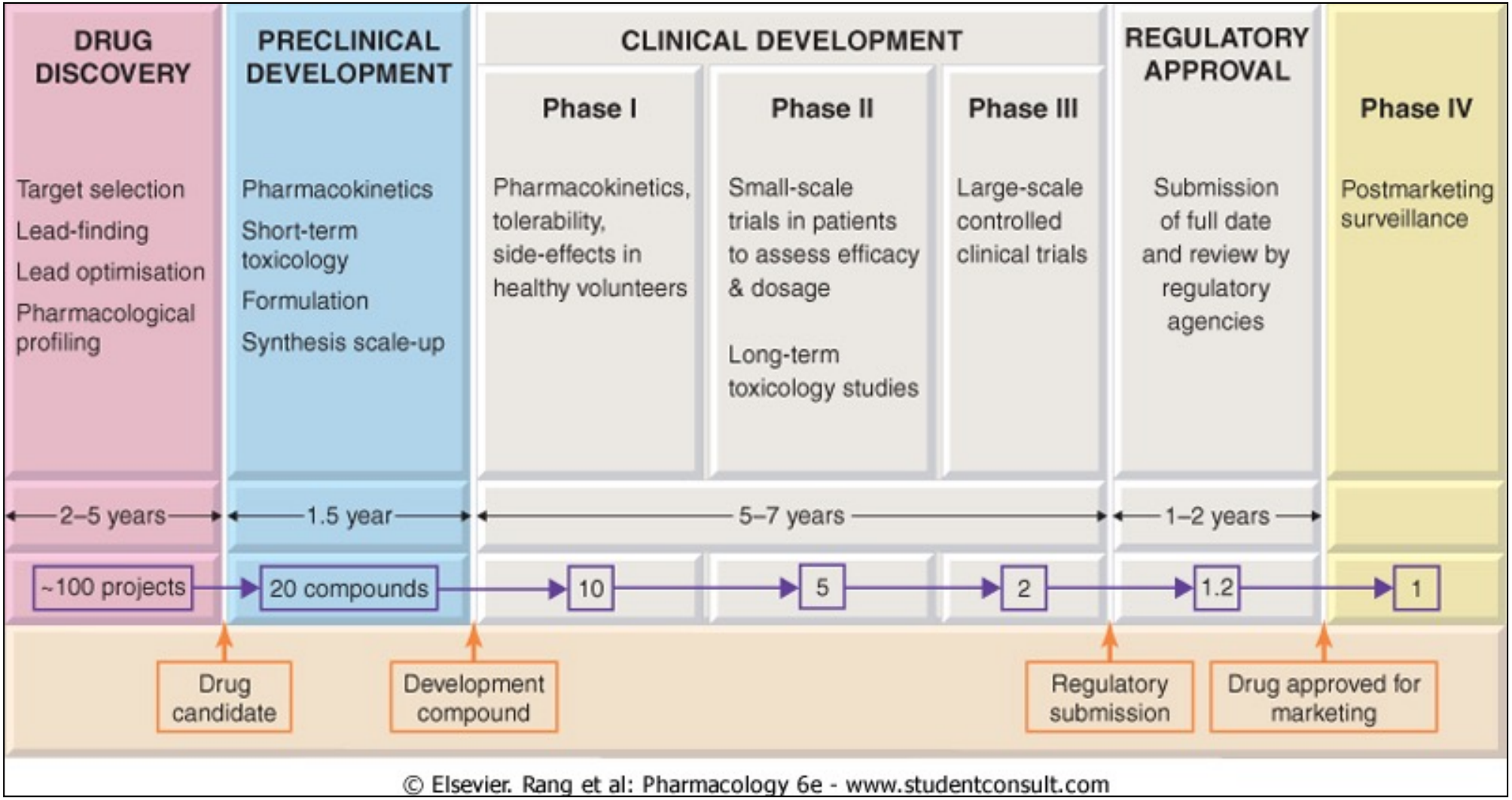

Figure 56-1 The stages of development of a 'typical' new drug, i.e. a synthetic compound being developed for systemic use. Only the main activities undertaken at each stage are shown, and the details vary greatly according to the kind of drug being developed.

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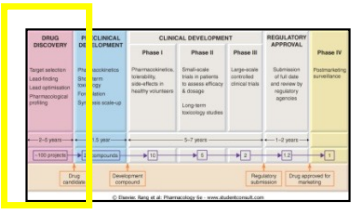
DRUG DISCOVERY



Steps in drug discovery

Target selection	based on knowledge about the disease and involved pathways
Lead finding	involves the development of an assay; testing of compound libraries.
Lead optimization	the aim is to optimize the potency of the compound for the target, as well as other characteristics (pharmacokinetics, toxicity).

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Example preclinical development: inhibitors of HIV protease

- In 1987, researchers decide to target the HIV protease, because
  - essential for HIV replication
  - unusual substrate specificity (cleaves a Phe-Pro bond; rare cleavage site for mammalian proteases)
- In 1989, the crystal structure of the HIV protease was published (by Merck), and could be used as a model for the development of the inhibitor → a substance that sits in the active site of the protease, but is not cleaved
- In 1996 the FDA approved ritonavir for marketing

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development of ritonavir, as discussed in the drug targets class

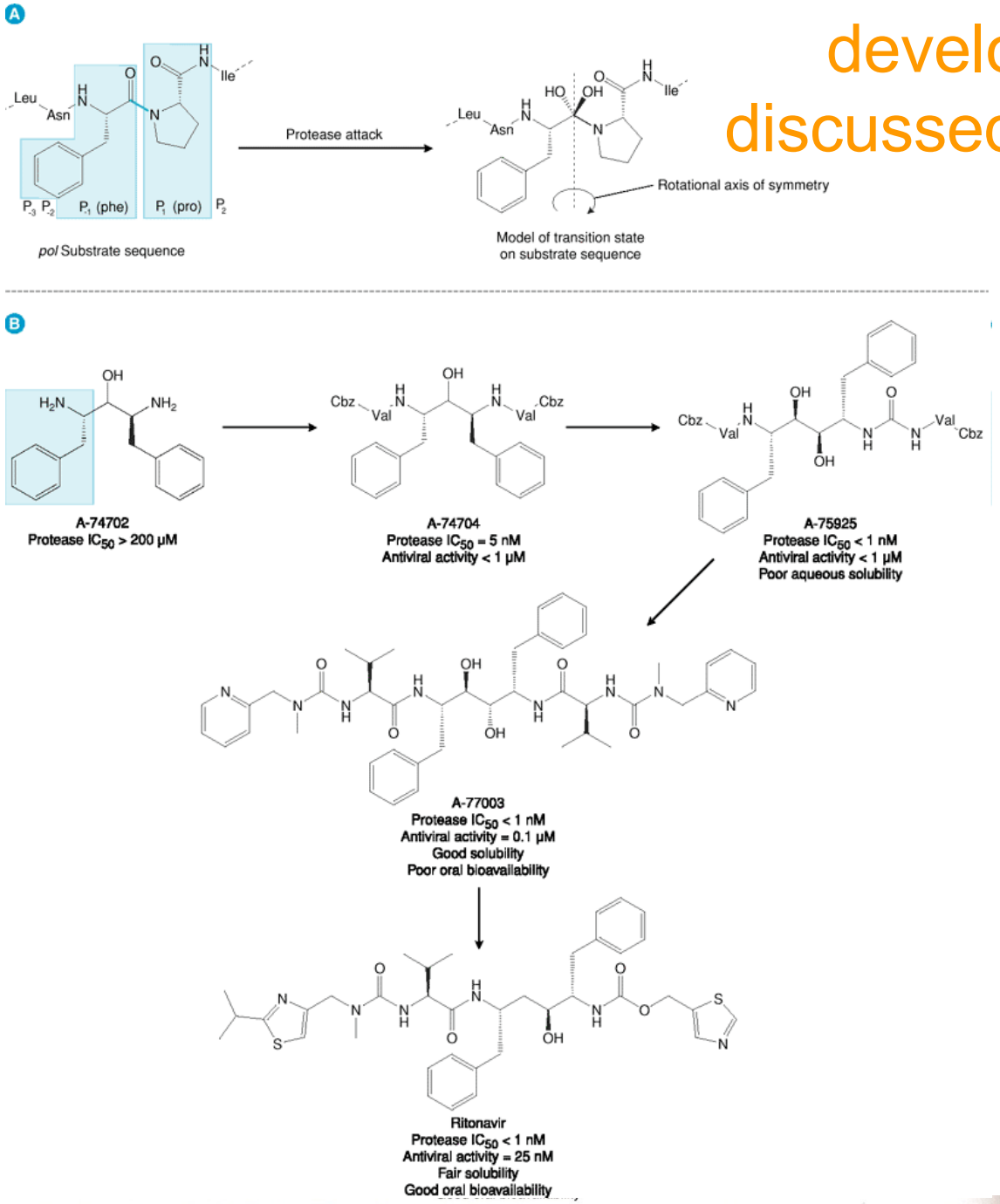


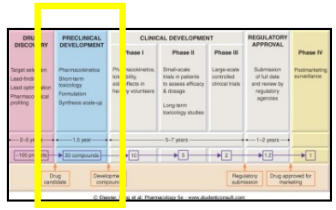
Figure 34-8. Steps in the Evolution of Ritonavir. **A.** The HIV *pol* gene product has a phenylalanine (phe)-proline (pro) sequence that is unusual as a cleavage site for human proteases. HIV protease cleaves the phe–pro bond. The transition state of this protease reaction includes a rotational axis of symmetry. **B.** Structure-based development of a selective HIV protease inhibitor began with a compound (A-74702) that contained two phenylalanine analogues with a CHOH moiety between them. This compound was then modified to maximize antiprotease activity (measured as IC_{50}, the concentration required to cause 50% inhibition of the enzyme), while also maximizing antiviral activity, aqueous solubility, and oral bioavailability. See Box 34-3 for details.

BOX 34-3. Development of Ritonavir

The development of ritonavir is an example of structure-based ("rational") drug design. Scientists began with a model of the transition state that forms during the cleavage of a substrate by HIV protease (Fig. 34-8). An analogue of the transition state was designed, using just one residue on each side of the cleavage site. Knowing that HIV protease is a symmetric dimer, the scientists chose to use the same residue—phenylalanine—on both sides of the cleavage site, with a CHOH group that mimics the transition state as the center of symmetry. This molecule, A-74702, was a very weak inhibitor of HIV protease, but adding symmetrical groups at both ends to form A-74704 (Fig. 34-8, where Val is valine and CBZ is carbobenzyloxy) resulted in a > 40,000-fold increase in potency (IC_{50} = 5 nM). Attempts to modify A-74704 to improve aqueous solubility reduced potency, however, so a related potent inhibitor, A-75925, in which the center of symmetry was a C-C bond between two CHOH groups, became the scaffold for further modifications. Symmetric changes to both ends of the molecule resulted in a soluble, highly potent inhibitor, A-77003. This compound was not orally bioavailable, however. Further modifications, which removed a central OH group and altered other moieties at each end, resulted in a compound—ritonavir—that was less soluble but had improved antiviral activity and good oral bioavailability. Therapeutically achievable plasma concentrations of ritonavir greatly exceed the concentration required for antiviral activity. In the process of structure-based drug design, successive modifications to these molecules took advantage of X-ray structures of HIV protease complexed to each inhibitor. By examining these structures, scientists were able to make informed guesses about what chemical groups to add or subtract. The result was a therapeutically useful HIV protease inhibitor, ritonavir.

New drug development : preclinical studies

General aim: to meet all the requirements for first tests in humans



6 phases can be distinguished:

1. Characterization of the therapeutic agent (selectivity, potency, mode of action)
2. Assessment of basic biological properties of the compound, such as protein binding.
3. Pharmacokinetics and Toxicokinetics of the compound and its metabolites (ADME).
4. Acute toxicity. Dose escalation, to find the maximally tolerated dose.
5. "GLP studies", including
   a. Chronic toxicities (duration depending on the intended duration of use of the drug), in at least two species (mouse or rat, and dog or monkey)
   b. Safety pharmacology (Cardiovascular system, CNS, respiratory system)
   c. Reproduction
   d. Carcinogenesis
6. Local tolerance, drug-induced photosensitivity, abuse liability, pediatric use

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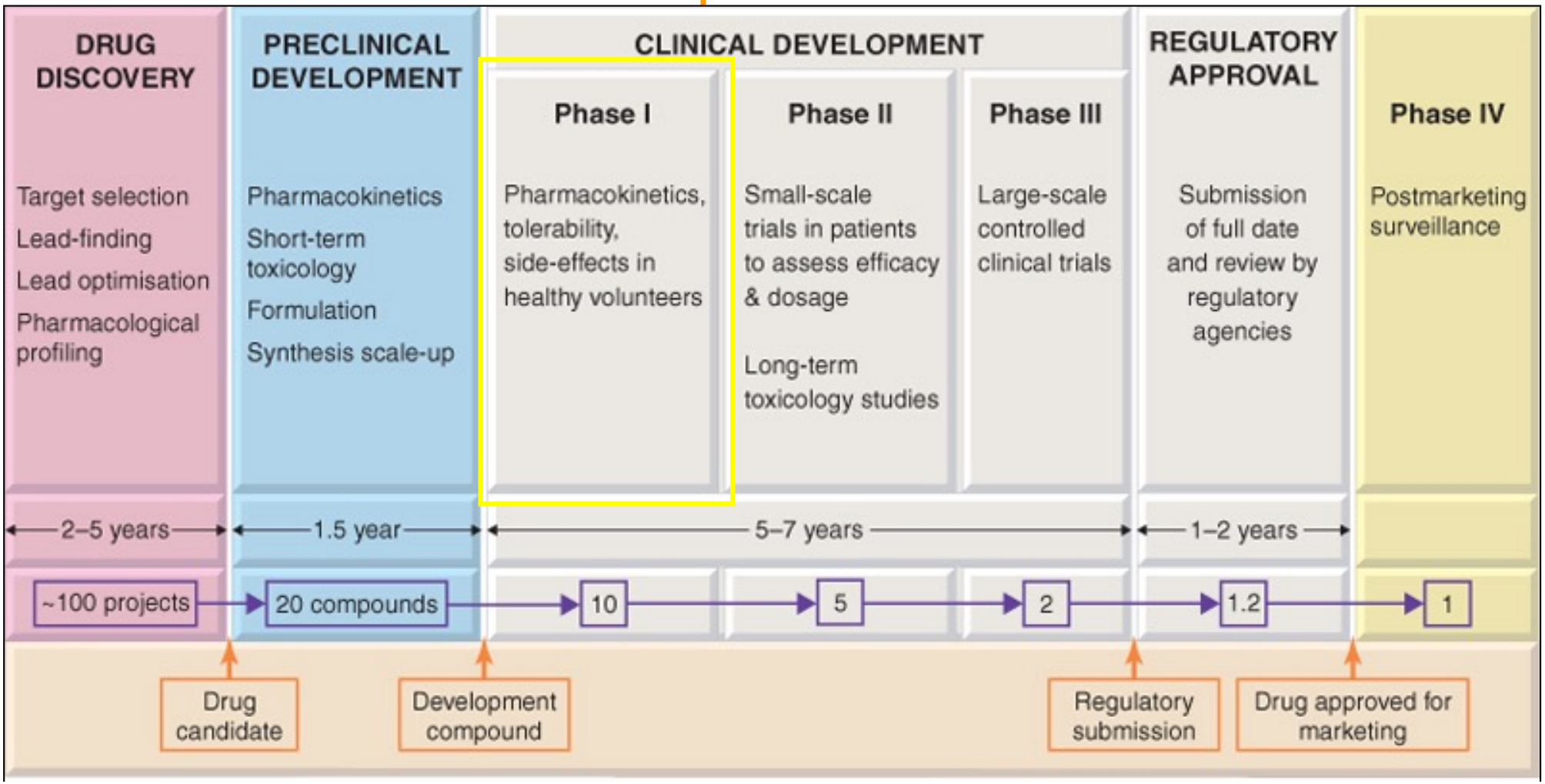
Clinical development : clinical trials



Phase I trials

- performed on a small group of normal healthy volonteers
- tests at increasing doses
- aims : safety (potentially dangerous effects), tolerability (unpleasant symptoms), pharmacokinetic properties.

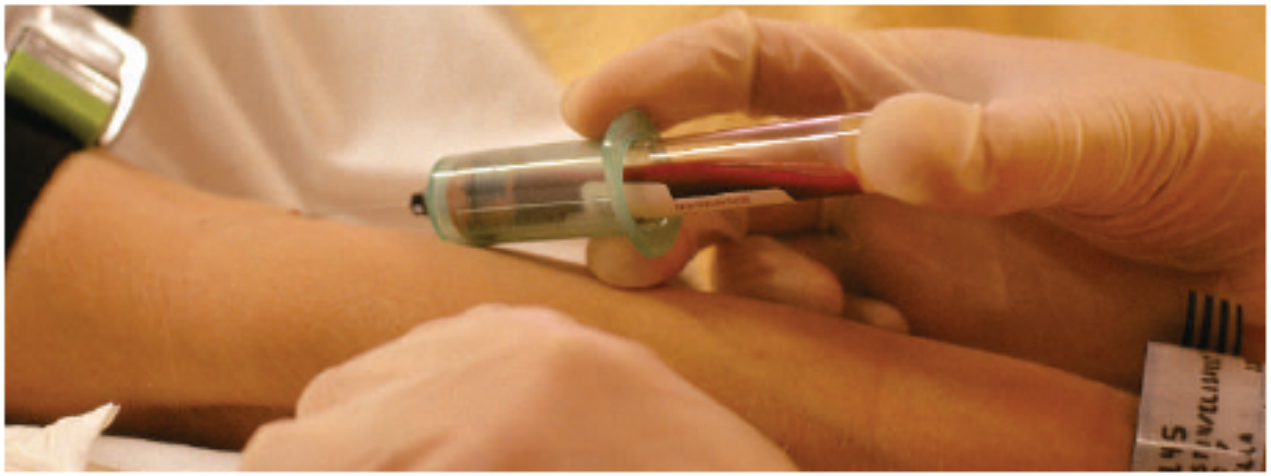
TGN1412 catastrophic Phase I trial; London, March 14, 2006

London's disastrous drug trial has serious side effects for research

A drug trial that took a shocking turn in London last week may have far-reaching effects on policy. Its failure, experts say, could change restrictions on clinical research and increase scrutiny of the private companies that carry out the majority of clinical trials.

"There's going to be a lot of soul searching," says Thomas Murray, a bioethicist at the Hastings Center, a think tank in Garrison, New York.

As *Nature* went to press, two previously healthy young men were in critical condition and another four seriously ill at Northwick Park Hospital in London. On 13 March, they received intravenous injections of TGN1412, an antibody made by Boehringer Ingelheim for TeGenero, a small, privately owned biotechnology firm in Würzburg, Germany. The drug was being developed to fight autoimmune diseases and leukaemia. Parexel International, a contract research organization based in Waltham, Massachusetts, that operates in 39 countries, was running the trial for TeGenero.



IMAGESTATE/ALAMY

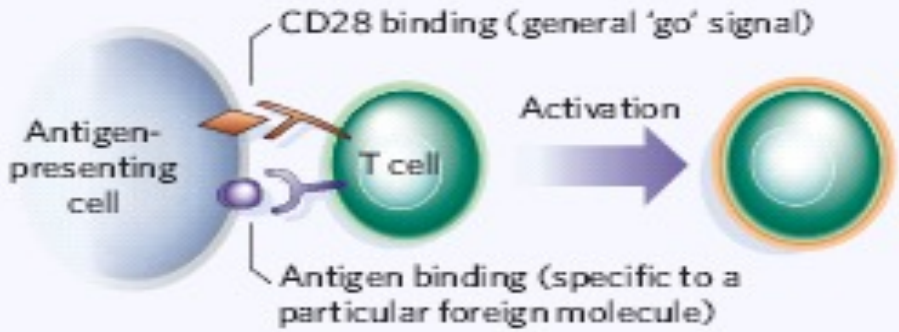
"Was informed consent adequate? Were the right subjects selected? Were the right doses given? This better have been done right, or some tough questions are going to come up for the private, commercialized research sector," says Arthur Caplan, a bioethicist at the University of Pennsylvania, Philadelphia.

Within one to two hours of being injected, the six volunteers suffered violent reactions that included headache, backache, nausea, a drop in blood pressure and, ultimately, multiple organ failure. The trial was the first test of the drug in humans; it was immediately suspended by the UK Medicines and Healthcare Products Regulatory Agency, which is now investigating.

Thomas Hanke, chief scientific officer for TeGenero, says that the company had "no preclinical evidence whatsoever" that the drug might be unsafe, and that no adverse effects had been observed in rabbit and monkey studies.

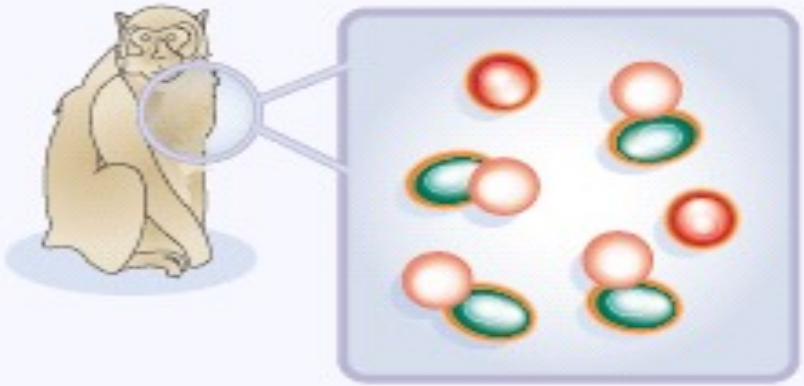
TGN1412 catastrophic Phase I trial; London, March 14, 2006

Normal T-cell activation
To switch on a T cell, two signals are required: a general activation trigger and a specific 'antigen' from a molecule recognized as being foreign.

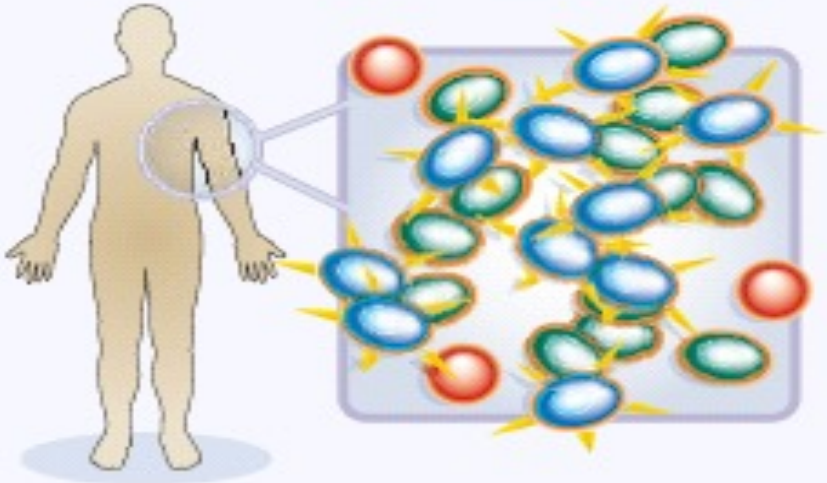


Super-antibody T-cell activation
This overrides both signals and potentially activates all T cells with a CD28 receptor, not just those specific for a particular antigen.

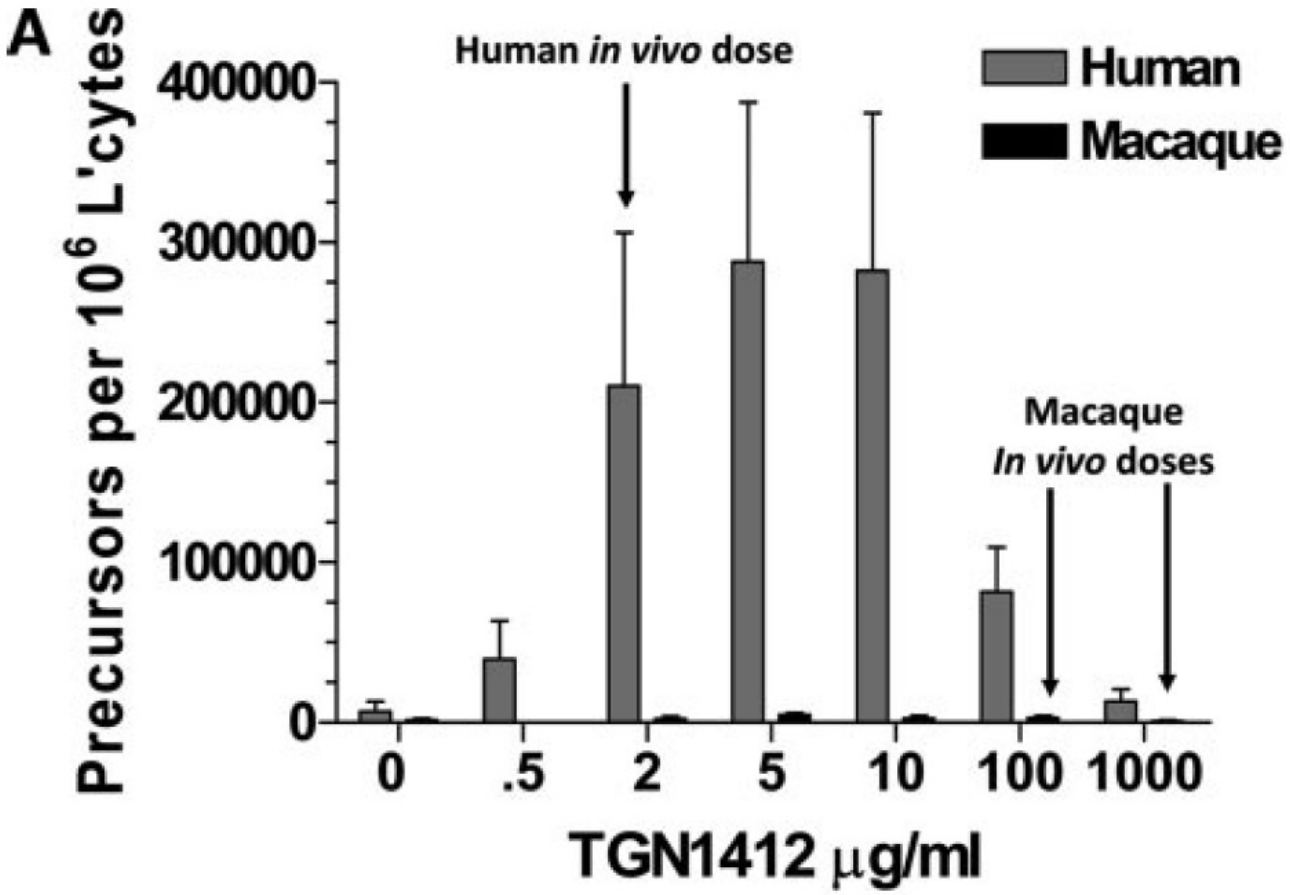
What happened in animal trials
In monkeys, TGN1412 activated only regulatory T cells, which damp other elements of the immune response. So the researchers hoped the drug would help treat autoimmune diseases by suppressing the inflammatory immune cells (red) that attack the patient's own tissue.



What probably happened in the London trial
As well as activating regulatory T cells, TGN1412 switched on helper T cells (blue), which produce chemical messengers called cytokines that boost other elements of the immune response. This mass activation of T cells caused a devastating 'cytokine storm' — a flood of inflammatory molecules that swept through the patients' bodies.



Difference in Dose response between humans and macaques



(Experiments done after the clinical study, to try to understand the reason for the reaction

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Clinical Trial disaster in Rennes, January 2016

- One person is dead and five more have been hospitalized, after a phase I clinical trial in France went horribly wrong; several of the surviving volunteers have remaining impairments (memory impairment, cerebellar syndrome).

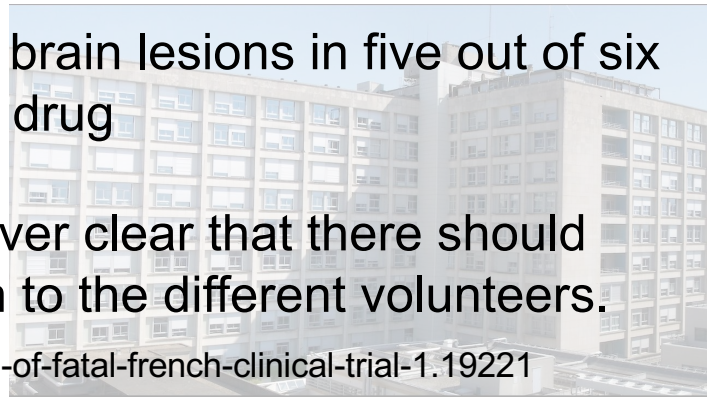
- The drug candidate: BIA 10-2474 inhibits fatty acid amide hydrolase (FAAH) enzymes. Blocking these enzymes prevents them from breaking down cannabinoids in the brain. The drug candidate was planned to be used for the treatment of neurological and psychiatric pathologies.

- Phase I clinical trial by the company Biotrial on six volunteers, 28-49 years old. 84 volunteers had already received the drug candidate at various (lower) doses without apparent adverse effects.

- The 6 volunteers were the first to receive the highest dose. The first dose was given on January 7, symptoms appeared on January 10. When the symptoms appeared, all 6 volunteers had already received the dose.

- The drug candidate caused hemorrhagic and necrotic brain lesions in five out of six men in a group who received the highest doses of the drug

- The reasons for this outcome are unknown. It is however clear that there should have been more time between the drug administration to the different volunteers.



http://www.nature.com/news/researchers-question-design-of-fatal-french-clinical-trial-1.19221

What was learnt from this case for first-in-human studies?

- Restrict the maximum dose to a small multiple of the dose that achieves the maximal desired pharmacological activity.
- Identify the mechanisms of potential toxicity (in the case of BIA 10-2474, the exact mechanism is still not known)
- Since several FAAH inhibitors were shown before to be ineffective, it might have been reasonable not to take this compound to clinical trials
- A final lesson from this case is for all involved in phase I studies, especially first-in-human studies, to remain vigilant at all times

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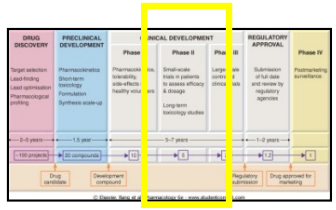
Clinical development: phase II trials



- Performed on group of patients (100-300)
- Test the therapeutic efficacy, identify the therapeutic indications
- Set posology, set the doses to be used (dose finding)
- Identify the levels of toxicity

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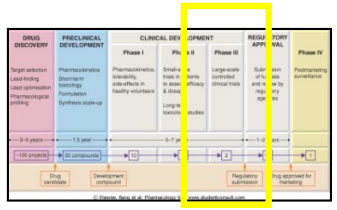
Clinical development : phase III trials



- Double-blind randomised trials (drug versus placebo or reference drug), multicenter, large number of patients
- Aim: confirm data of phase II trials, compares new drugs with common treatments

Selection of *endpoints*

Primary end points : survival, evolution of symptoms/disease, remission

Surrogate end points (marqueurs intermédiaires) : markers of the disease, (blood pressure, HbA_c, viral mRNA, plasma cholestérol, etc.…), should predict the evolution of disease.

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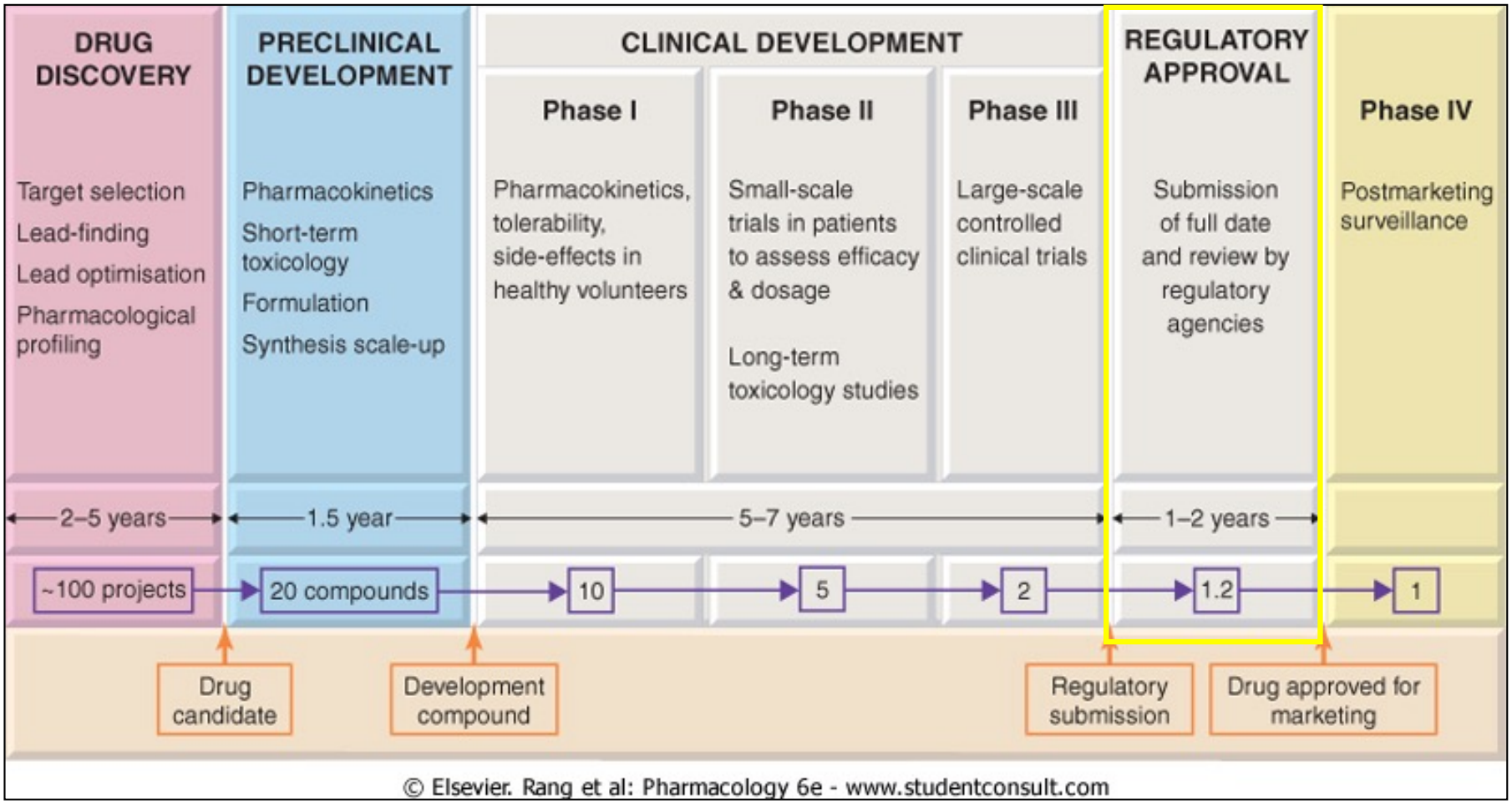
Regulatory approval



Submission to Swissmedic

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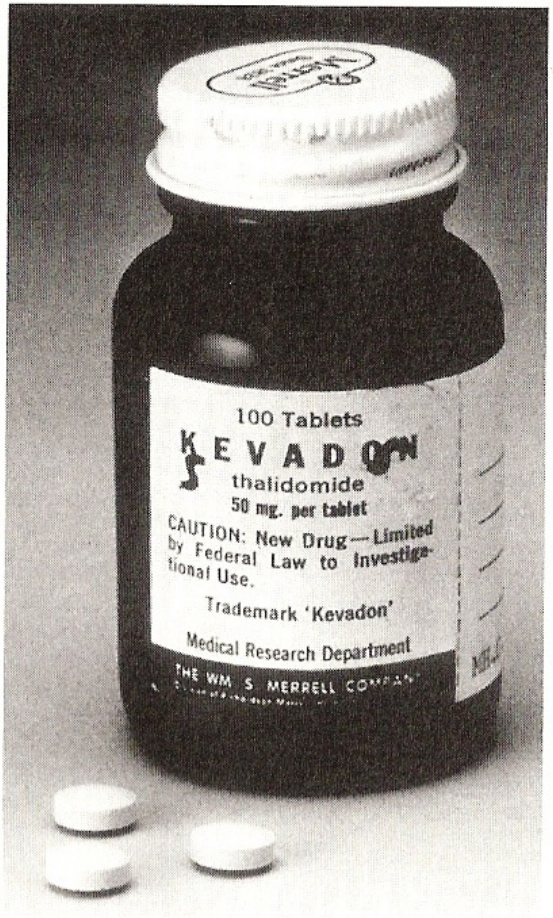
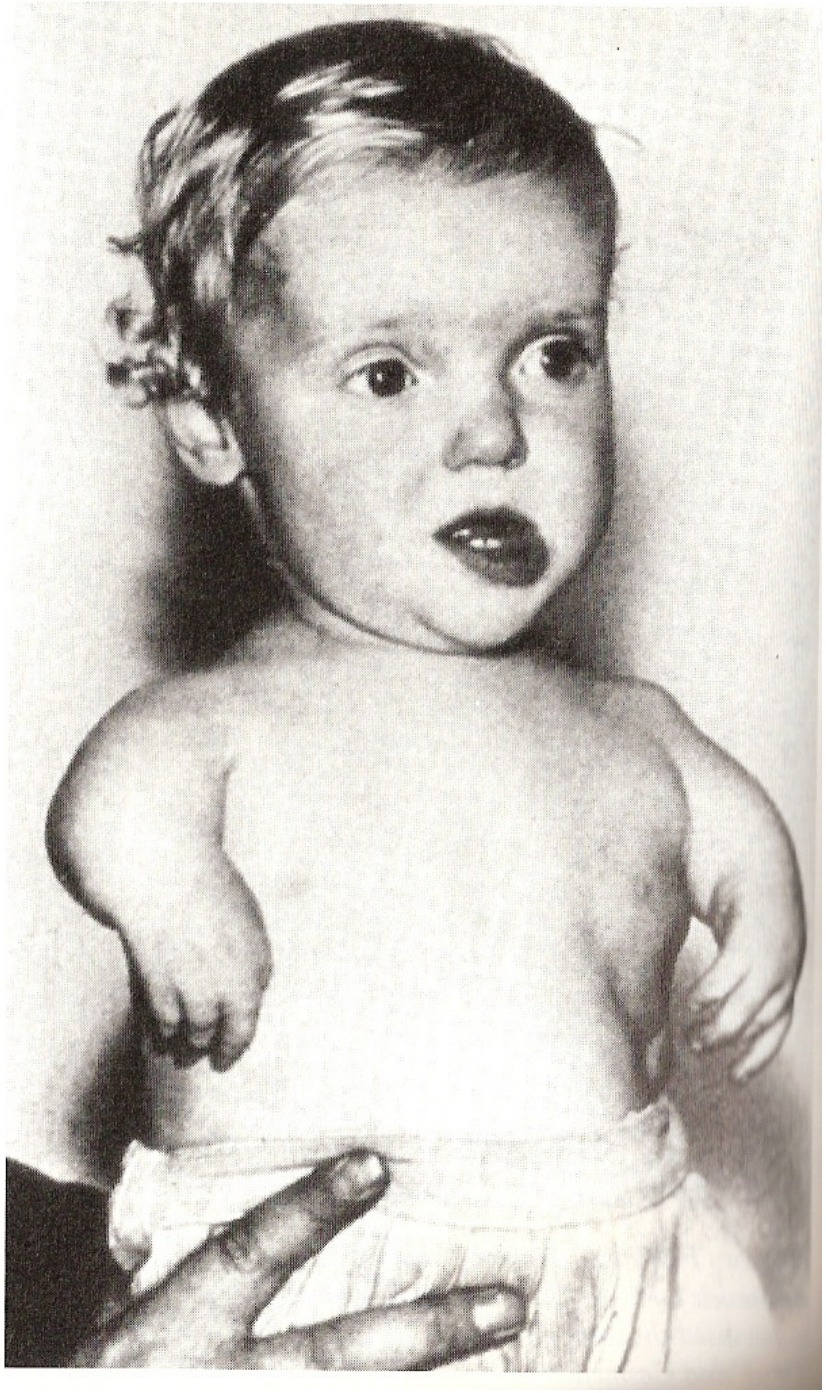
History: the teratogenic effects of thalidomide





Above: *Kevadon, also known as thalidomide. It was sold chiefly outside the United States as a sedative despite a lack of testing to determine if it was safe. It caused birth defects when taken in the early months of pregnancy, and led to thousands of cases of premature death and, most famously, a fetal disability in which limbs were stunted. The FDA refused to approve it without better safety data.*

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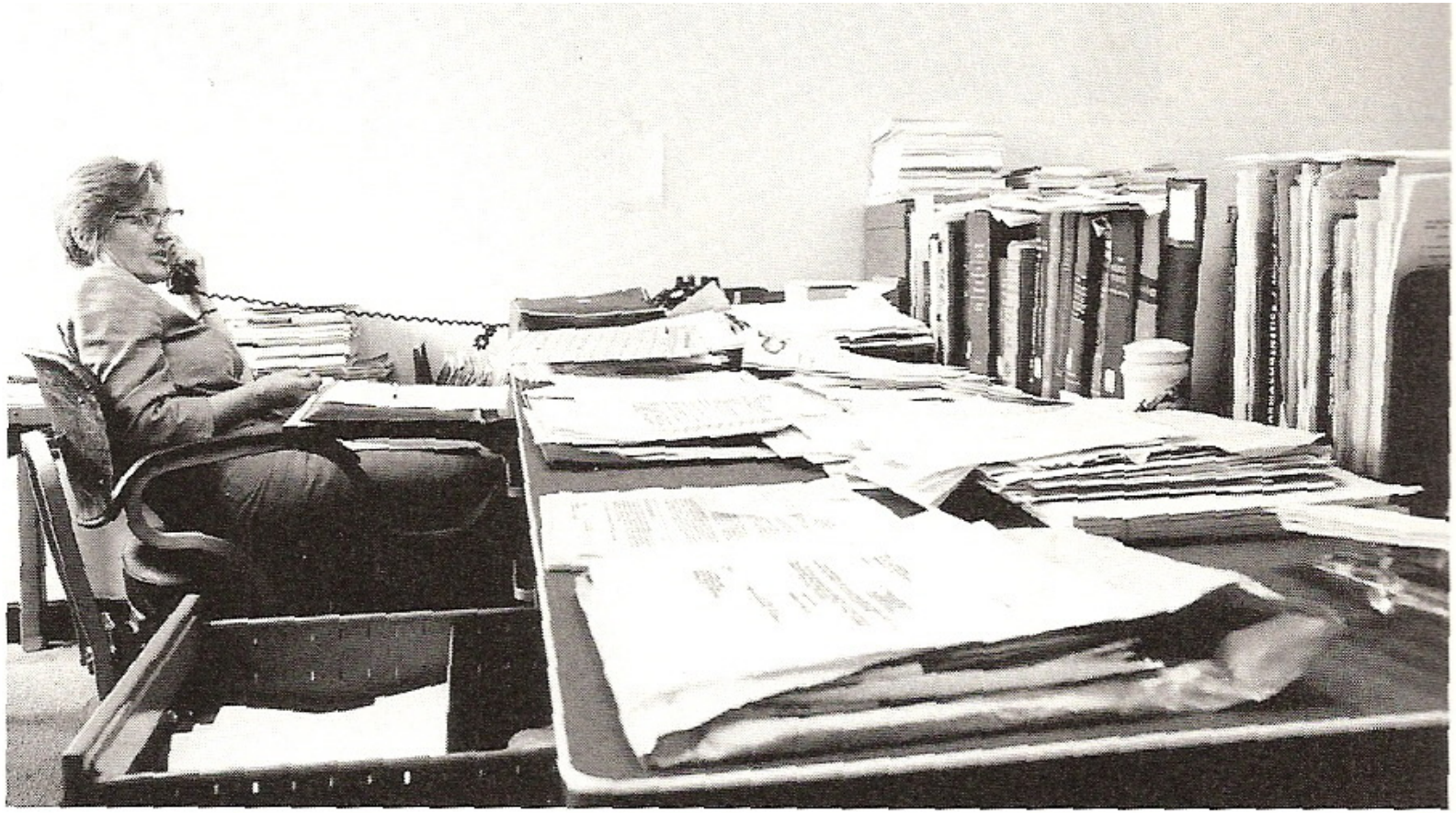
Frances Oldham Kelsey, 1962



Frances O. Kelsey, the FDA medical officer who stopped thalidomide from reaching the American market in 1962. The drug was approved for marketing in Germany, England, and other countries, but Dr. Kelsey noticed that the safety data was defective, and she asked the manufacturer to provide more information. That pause for questions was itself enough to avoid many thousands of deaths and deformities in the United States.

Signature of the Kefauver-Harris Amendments to FDC Act; 1962

President Kennedy signs the 1962 Kefauver-Harris Amendments to the U.S. Food, Drug and Cosmetic Act. In the group behind him are Dr. Frances Kelsey (second from left) and Sen. Estes Kefauver (behind Kennedy, with his hand on Kennedy's chair). The amendments set higher scientific standards for safety and effectiveness that all new drugs must now meet.

Requirement for drug manufacturers to provide proof of the effectiveness and safety of their drugs before approval.

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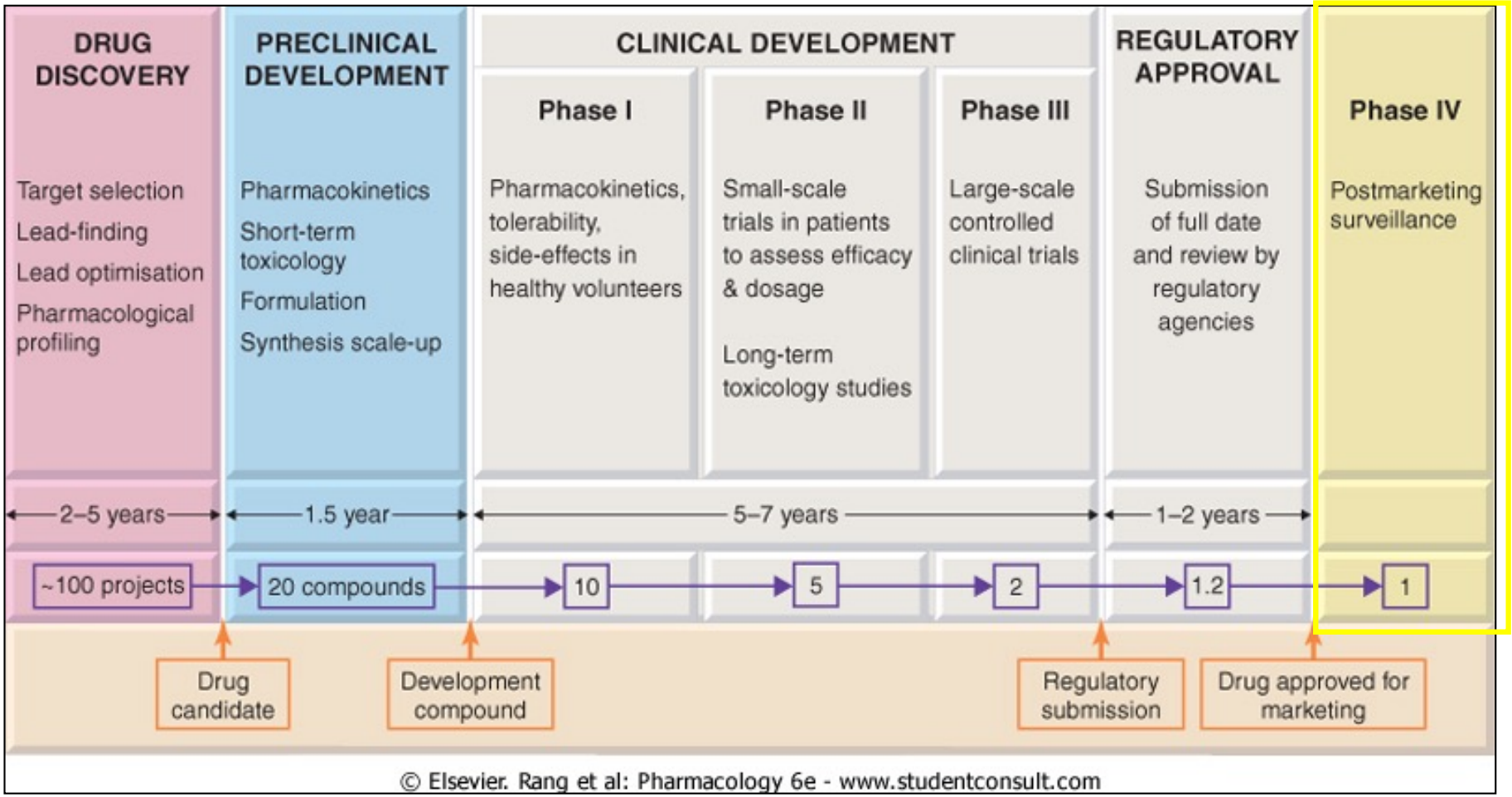
Clinical development : phase IV



Postmarketing surveillance

- Verify the adequacy of the treatment with respect to the indications
- Record the side effects
- Record the drug interactions

It happens regularly that drugs are withdrawn after having been on the market for a few years (ex. COX-2 inhibitors, see class on non-steroidal anti-inflammatory drugs).

Diese Information erfolgt in Absprache mit Swissmedic. Cette information a été rédigée en accord avec Swissmedic.

Avis important relatif à la sécurité **Vernier, 2013**

Efient® (prasugrel), Comprimé pelliculé à 5 mg et 10 mg

Risque accru de saignements chez les patients avec un NSTEMI qui subissent une intervention coronarienne percutanée (ICP), si EFIENT est administré avant l'angiographie coronarienne.

Docteur,

D'entente avec Swissmedic (Suisse) S.A. et Daiichi Sankyo AG souhaitent vous faire part mation importante relative à d'EFIENT (prasugrel):

EFIENT (prasugrel) est un in l'agrégation plaquettaire qui pour le traitement des patie d'un syndrome coronarien aig subissent une intervention c percutanée (ICP).

→ Dans une étude clinique achevée1, dans laquelle avec un NSTEMI ont reç de charge initiale de 30 m grel avant (en moyenne l'angiographie coronari gnostique et une nouve 30 mg au moment de l'I gnements péri-procédura et légers ont été augm autres bénéfices additionnels, par rapport à l'administration d'une dose unique de 60 mg de prasugrel au moment de l'intervention coronarienne.

En clinique, les utilisateurs devraient tenir

Modification de l'information professionnelle du médicament

Les informations suivantes ont été incluses dans les chapitres «Mises en garde

→ Dans une étude clinique récemment achevée1, dans laquelle des patients avec un NSTEMI ont reçu une dose de charge initiale de 30 mg de prasugrel avant (en moyenne 4 heures) l'angiographie coronarienne diagnostique et une nouvelle dose de 30 mg au moment de l'ICP, les saignements péri-procéduraux sévères et légers ont été augmentés, sans autres bénéfices additionnels, par rapport à l'administration d'une dose unique de 60 mg de prasugrel au moment de l'intervention coronarienne.

NSTEMI=infarctus myocardique sans élévation ST

gnostique, a entraîné une augmentation du risque de saignements péri-procéduraux sévères et légers par rapport à une dose de charge administrée directement au moment de l'ICP. C'est pourquoi, chez les patients avec un NSTEMI, la dose de

Annonces d'effets indésirables

Nous vous prions de bien vouloir annoncer les effets indésirables, sur le formulaire prévu à cet effet, au centre de pharce régional. Le formulaire usmentionné est disponible le Swissmedic (www.swiss-Directement sur → Annonces ésirables → Pharmacovigiut être commandé auprès de (tél. 031 322 02 23).
ation professionnelle actuaée sur le site web de Swissesse www.swissmedicinfo.ch.

haitez de plus amples infor- si vous avez des questions e présent courrier, veuillez r à notre Département d'inédicale, au numéro de télé-2 417 7095 ou par e-mail à: o_lilly_medinfo@lilly.com

er, Docteur, l'expression de nts les meilleurs,

isse) S.A.
Dr méd. Corinne Wijkström
Medical Director

DAIICHI SANKYO (Schweiz) AG
Dr méd. vét. Daniel Staub
Medical Director

28 ... or it happens that the information on the use of a drug has to be updated

Example phase IV: COX-2 inhibitors

- The cyclo-oxygenase (cox) is an enzyme that is the target of anti-inflammatory and analgesic drugs, such as Aspirin
- The isoform cox-2 is mainly involved in the inflammatory response
- → selective targeting of cox-2 may reduce some of the side effects (gastrointestinal toxicity)
- The cox-2-specific inhibitors celecoxib and rofecoxib were developed and found to have on animals the expected anti-inflammatory effect, without gastric toxicity
- In May 1999, on the basis of large-scale (phase III) trials, Merck received approval from the FDA to market rofecoxib as Vioxx® for rheumatoid arthritis pain and inflammation
- Became very popular
- Several clinical studies, whose results were published in 2000-2005, indicated a higher incidence of thrombotic events or myocardial infarction in patients having taken rofecoxib.
- September 2004: rofecoxib withdrawn from market. More than 80 million patients had taken the drug, accounting for annual sales revenues of > 2.5 billion US$

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The legislation

WHO Constitution (WHO1946):

'the possession of the highest attainable standard of health constitutes one of the fundamental rights of every human being'

Access to health is a fundamental right

Switzerland:

Loi fédérale sur les médicaments et les dispositifs médicaux – (Loi sur les produits thérapeutiques – LPTh ; 1er janvier 2002)

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Swissmedic guarantees that only high-quality, safe and effective therapeutic products are offered for sale in Switzerland.

Principal activities of Swissmedic

- Monitoring of clinical studies
- Delivering marketing authorization for drugs
- Monitoring of drugs that are on the market
- Delivering license for manufacturing and wholesale trade; inspections.

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OFSP : commission fédérale des médicaments

(ofsp=Office fédéral de la santé publique)

Objective: promote health rather than to fight disease

Activities related to medicinal products

•Registration of medicinal products in the list of pharmaceutical specialties (LS list) Medicines on the LS list are reimbursable by the health insurance (38% of drugs registered by Swissmedic). The health insurances finance ~80% of the CH drug market

Conditions for acceptance in the LS list: efficacy, therapeutic value (usefulness, adverse effects, risk of misuse, etc.) and economics of the drug (pharmaco-economic evaluation of drugs: cost-benefit ratio)

Example: cancer drug

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