Società Italiana di Fisiologia

The Italian Society of Physiology

SPERIMENTAZIONE ANIMALE

FROM PRECLINICAL STUDIES TO DRUG MARKETING

Identification of new compounds

- Modification of compounds known to act on selected targets
- Computer aided molecular design
- Synthesis of plant extracts
- Biological mainpulation
- High throughput screening of chemical/natural compounds in search of a particular activity

Supervising authorities for clinical trials

In **Italy**: Several public health authorities (AIFA; Istituto Superiore di Sanità; local Ethics Committees)

In **Europe**: from 1995 EMA coordinates and harmonizes the procedures in the countries belonging to the UE

In **USA**: FDA

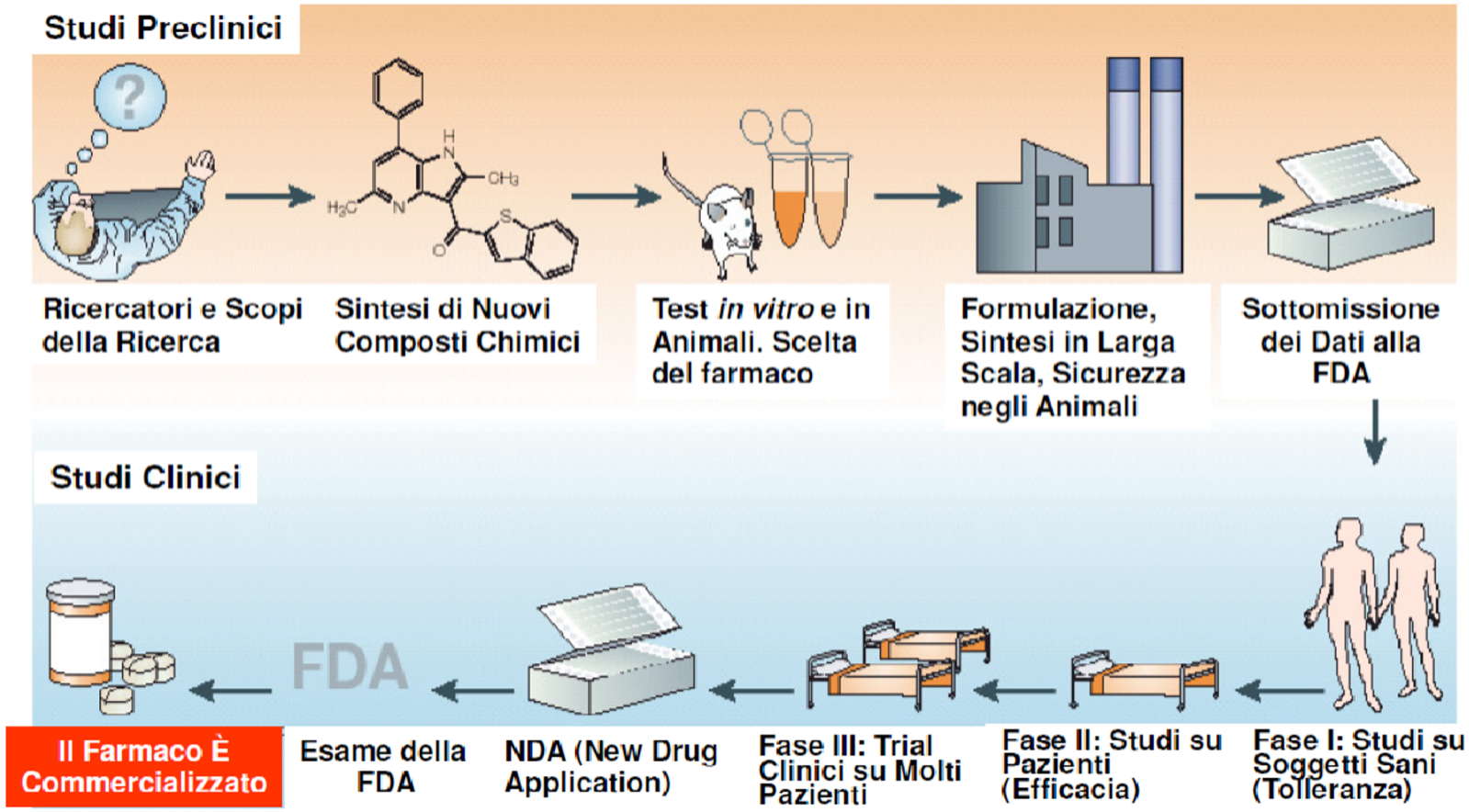
AIFA
AGENZIA ITALIANA DEL FARMACO

FDA
U.S Food and Drug Administration

ISTITVTO SVPERIORE DI SANITA'

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Development of new drugs



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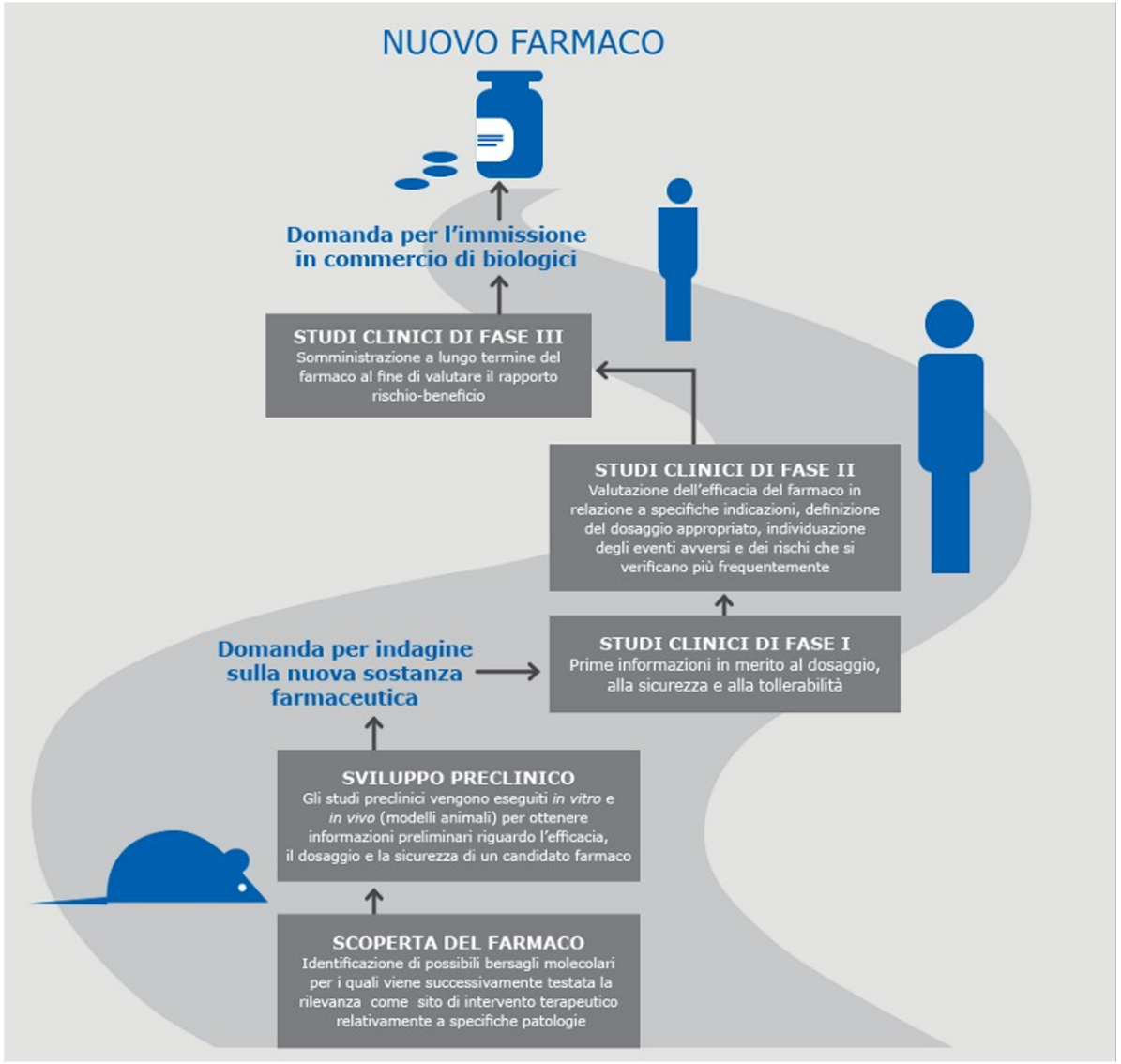

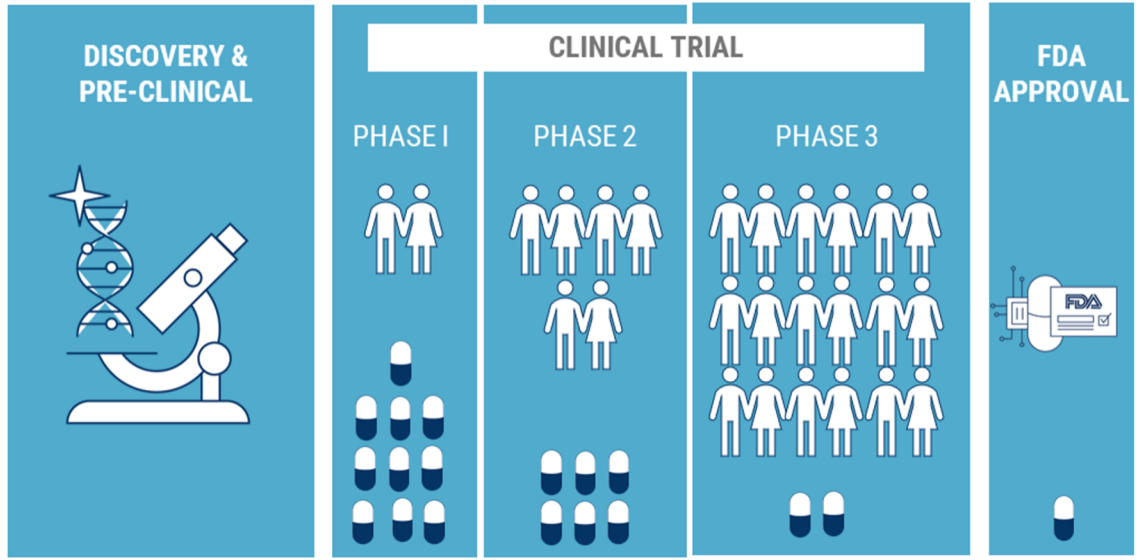

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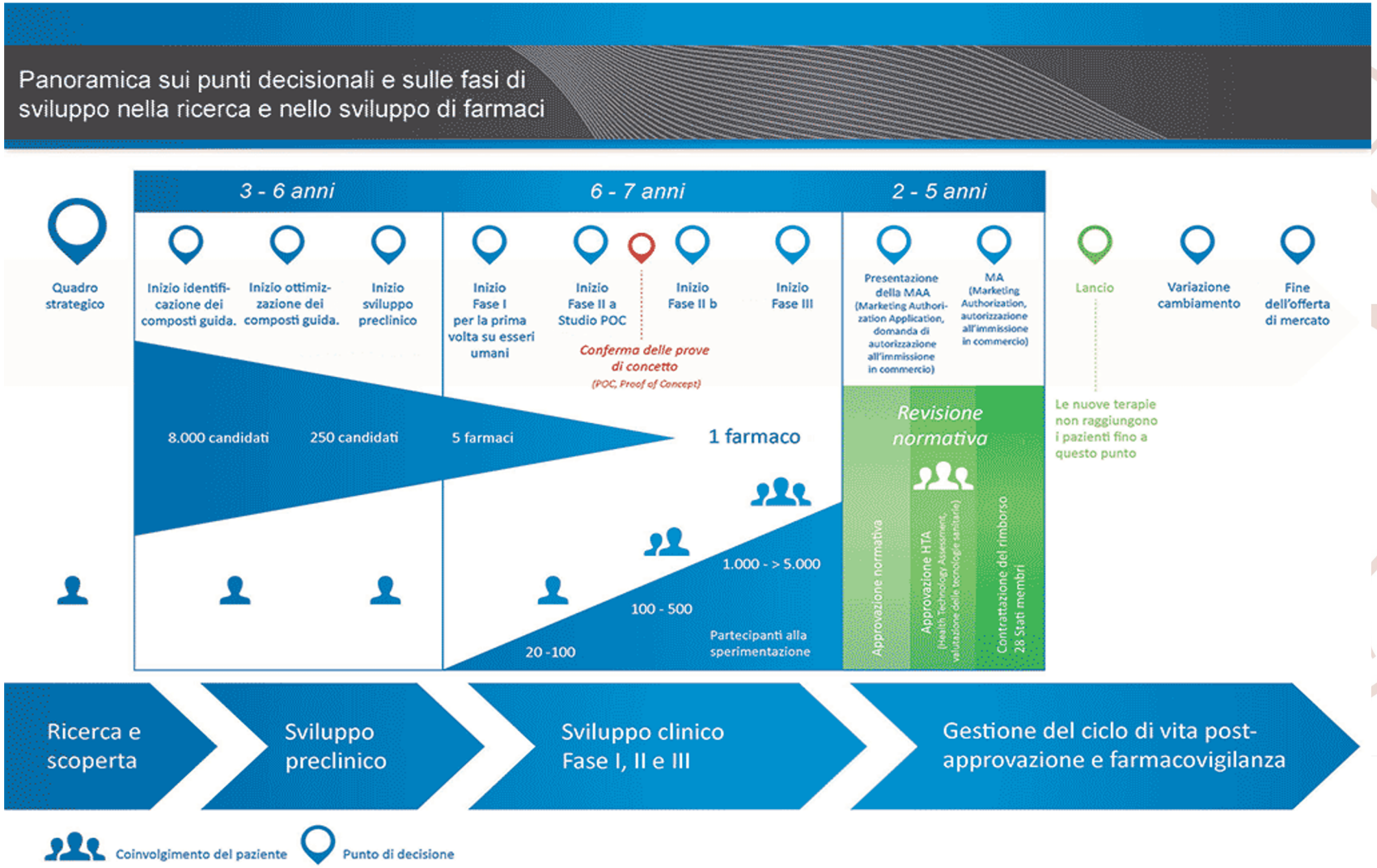


Goals of preclinical studies

Duration: 2-3 years

First phase

Pharmacodynamics
- Main effect
- Side effect
- Duration of the main effect

Acute toxicity
- Changes in vital signd
- DL50 determination

Chemical stability

Second phase

Pharmacokinetics
- Absorption
- Distribution
- Metabolism
- Excretion

Subacute and chronic toxicity
- Functional changes
- Anatomopathological changes
- Teratogenic effects
- Effects on fertility
- Effects on peri- and post-natal period
- Mutagenesis
- Cancerogenesis

Pharmaceutical technique
- Formulation
- Dosage

Extrapolation of the established dose in animals to humans

It is based on the knowledge of NOAEL (No Observable Adverse Effect Level) in the animal

Human Equivalent Dose (mg/kg) = Animal Dose (mg/kg) x Animal Km/Human Km

Km is a correction factor that reflects the relationship between body weight and body surface area

Km
Mouse = 3
Rat = 6
Guinea pig = 8
Rabbit = 12
Dog = 20
Human (adult) = 37

The **MRSD** (Maximum Recommended Starting Dose) used to start a clinical trial is the calculated HED divided by a safety factor (usually 10) in order to minimize the risk of toxicity

Clinical trial

Any form of planned experiment involving people, designed to clarify the most appropriate treatment for future patients with a given medical condition

Clinical trial: phase I

TARGETS

- Tolerability in humans
- Pharmacokinetics
- Dosage schedule for use in Phase II

SUBJECTS

- 20-100 healthy volunteers (or patients in case of highly toxic drugs)

DURATION

- 1-2 years

Clinical trial: phase II

TARGETS

- Efficacy and tolerability in patients
- Identification of the dose/effect relationship

SUBJECTS

- 100-500 patients

DURATION

- 1-2 years

Phase II is crucial in establishing whether or not to continue the trial.
The question is whether the result is so modest that it does not merit further study or good enough to justify the transition to Phase III.

Clinical trial: phase III

TARGETS

- Acquisition of efficacy and tolerability data on a large sample
- Verification of the clinical significance of predictable drug inetractions
- Final definition of the dose/effect relationship

SUBJECTS

- 1000-5000 patients

DURATION

- 3-4 years

Clinical trial: phase III

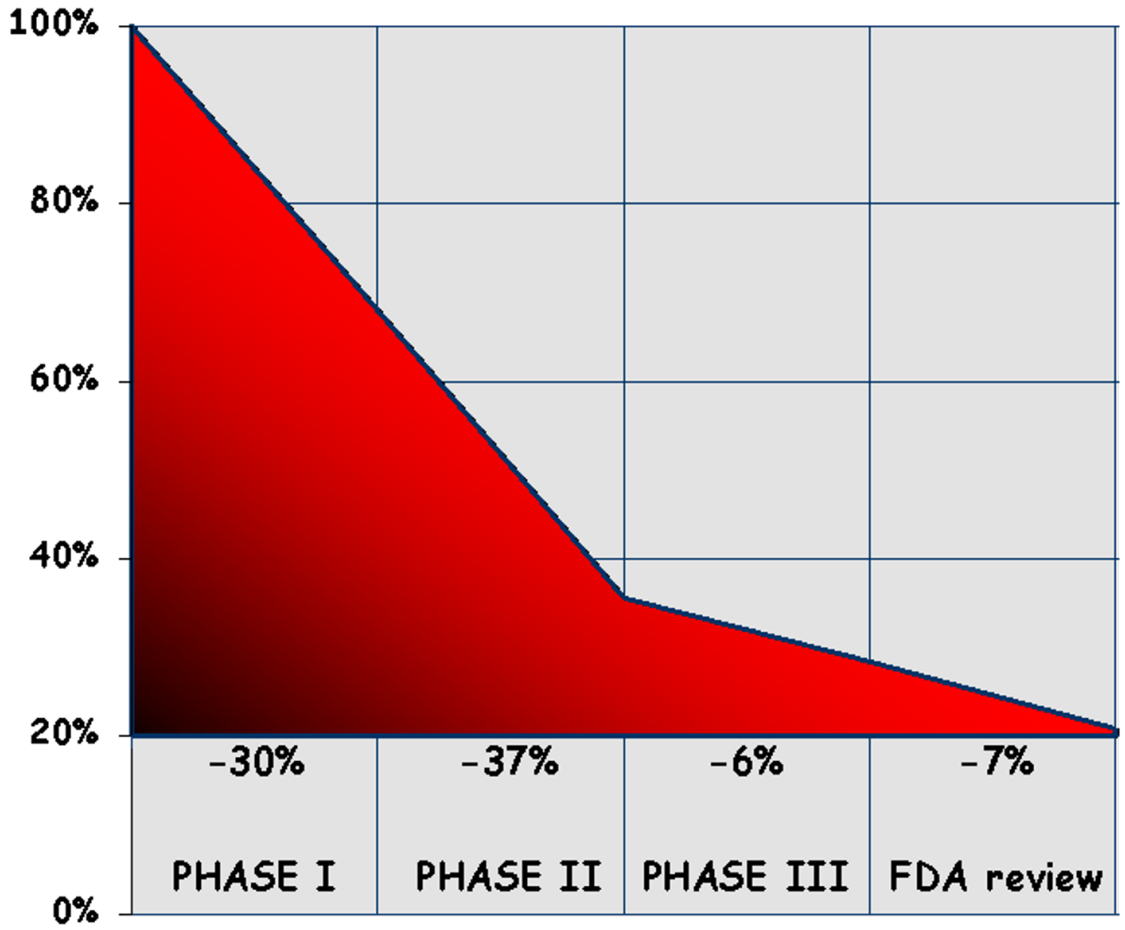
Different types of trials:

1. Uncontrolled trials

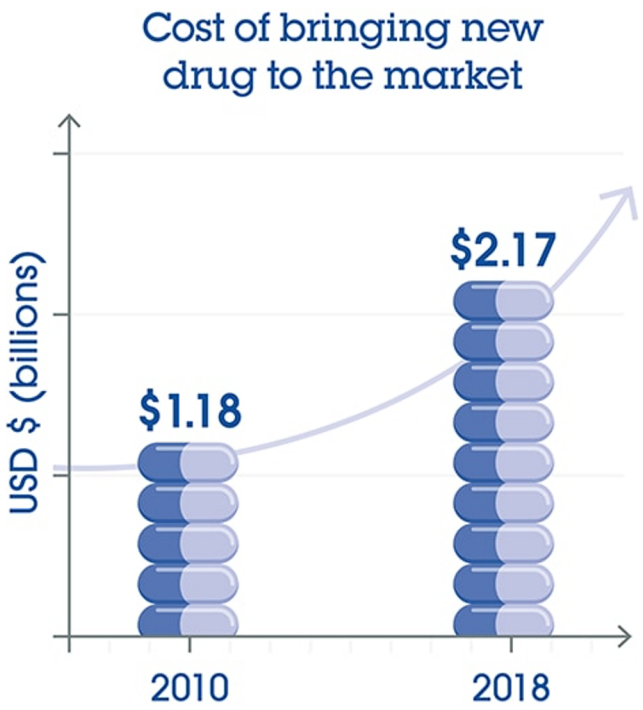
2. Non-randomized controlled trials
    - with parallel controls
    - with historical controls

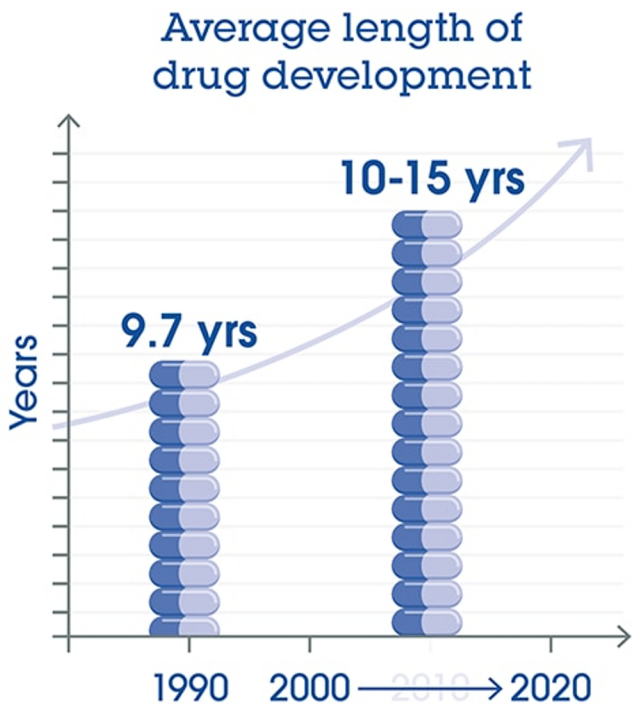
3. Randomized controlled trials

Dropout rate
(from the start of clinnical development)



Developing new drugs is expensive and time-consuming



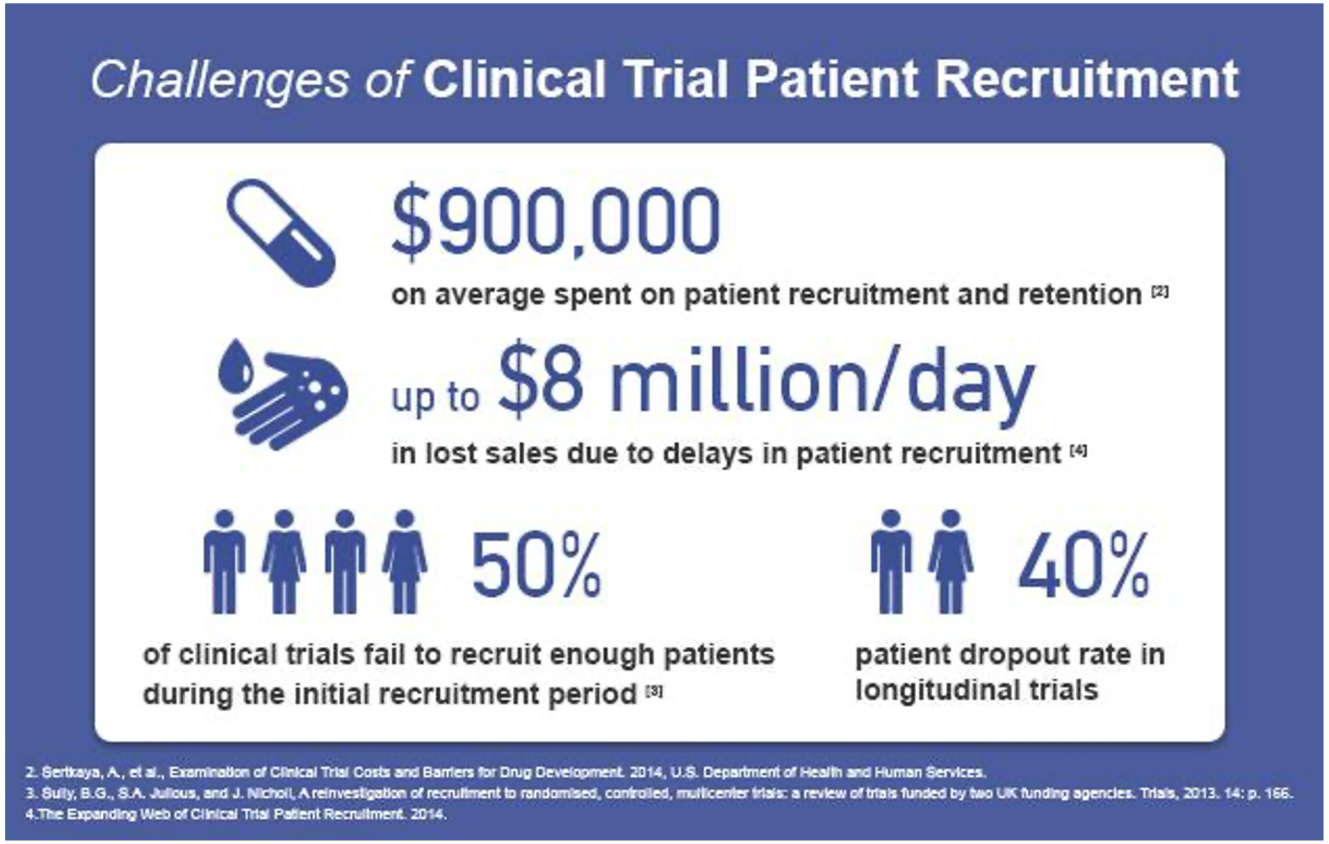


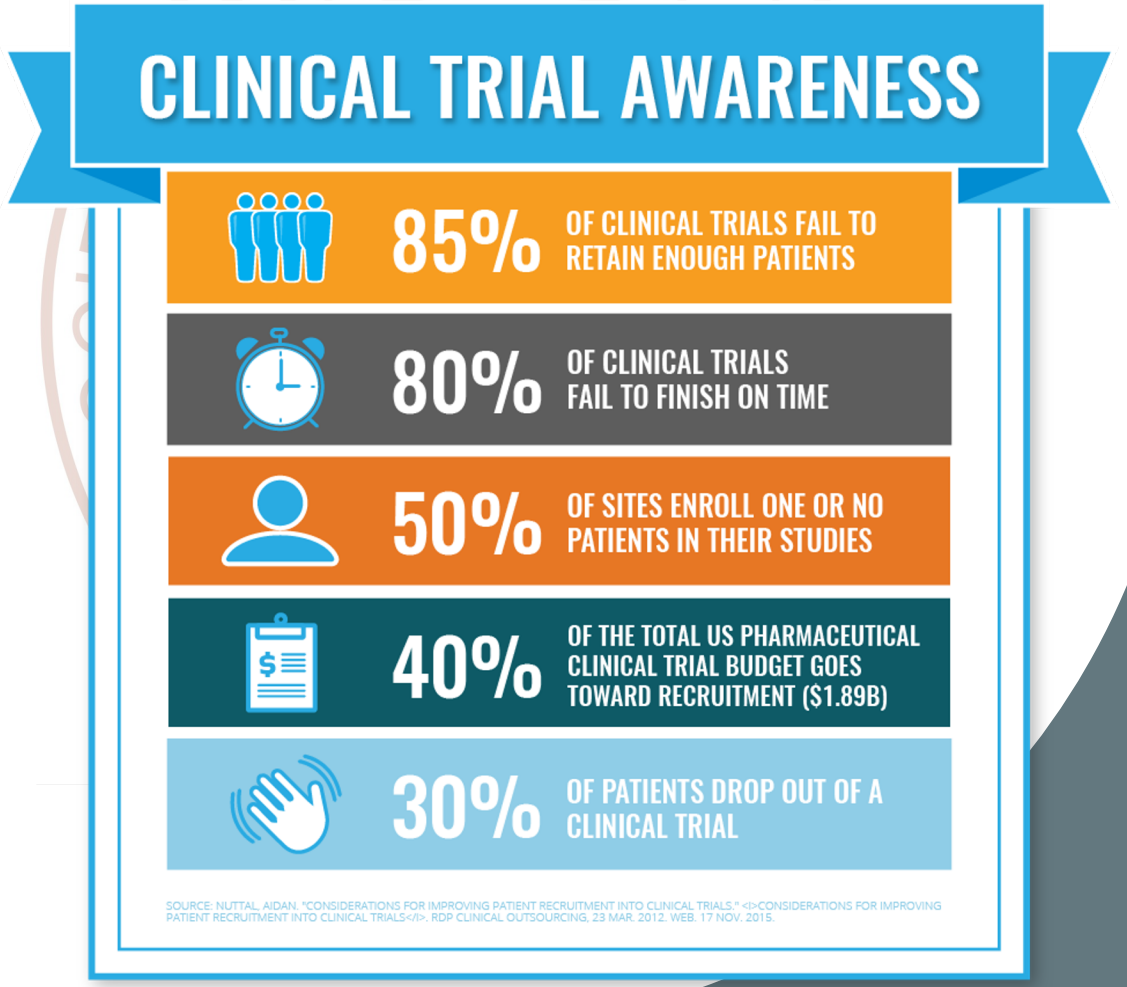
Average Cost of Drugs Approved by Year

Year	R&D (Billions)	Approved per year	Cost per Approved Drug (Millions)
1994	$13.4	22	$609.1
1995	$15.2	28	$542.9
1996	$16.9	53	$318.9
1997	$19.0	39	$487.2
1998	$21.1	30	$703.3
1999	$22.7	35	$648.6
2000	$26.0	27	$963.0
2001	$29.8	24	$1,241.7
2002	$31.0	17	$1,823.5
2003	$34.5	21	$1,642.9
2004	$37.0	36	$1,027.8
2005	$39.9	20	$1,995.0
2006	$43.4	22	$1,972.7
2007	$47.9	18	$2,661.1
2008	$47.4	24	$1,975.0
2009	$46.4	26	$1,784.6
2010	$50.7	21	$2,414.3
2011	$48.6	30	$1,620.0
2012	$49.6	39	$1,271.8
2013	$51.1	27	$1,892.6
Total	**$691.6**	**559**	**$27,596.0**

Source: PhRMA, FDA

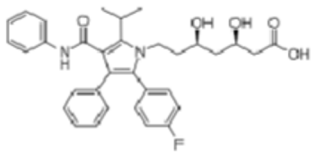
Enrolling patients is expensive, time-consuming and often challenging



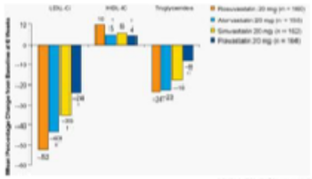


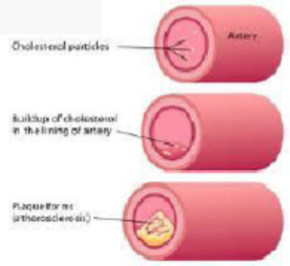
Stratified Medical – Deep Learning in Drug Discovery

~1,500 drugs
~1,000,000,000,000,000,000,000 drug-like molecules

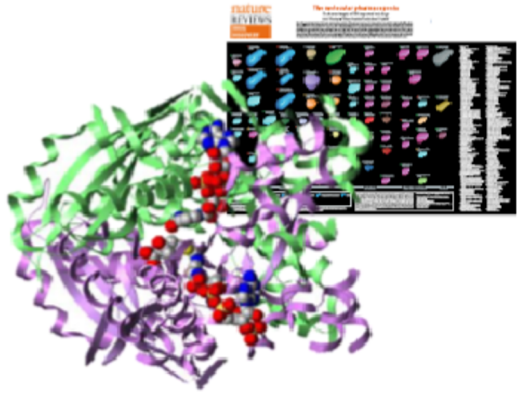


Drug





Disease — Target

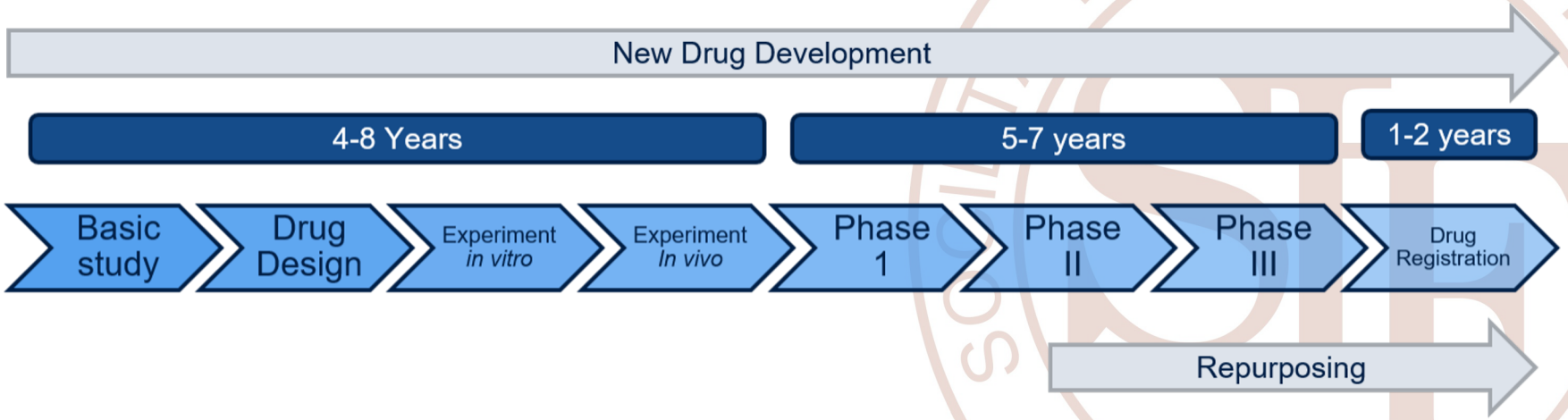


~5,000 'treated' diseases
~14,400 diseases (~7,000 rare diseases)

~400 drug targets
~19,000 genes in human genome

Drug repurposing/drug rescue reduce the drug discovery timeline (as well as costs)

Drug Repurposing: finding a new clinical use for an approved drug
Drug rescue: finding a clinical use for a stalled clinical development stage compiound (phase II or beyond – established PK and tolerability, maybe safety and usually a known chemical structure)



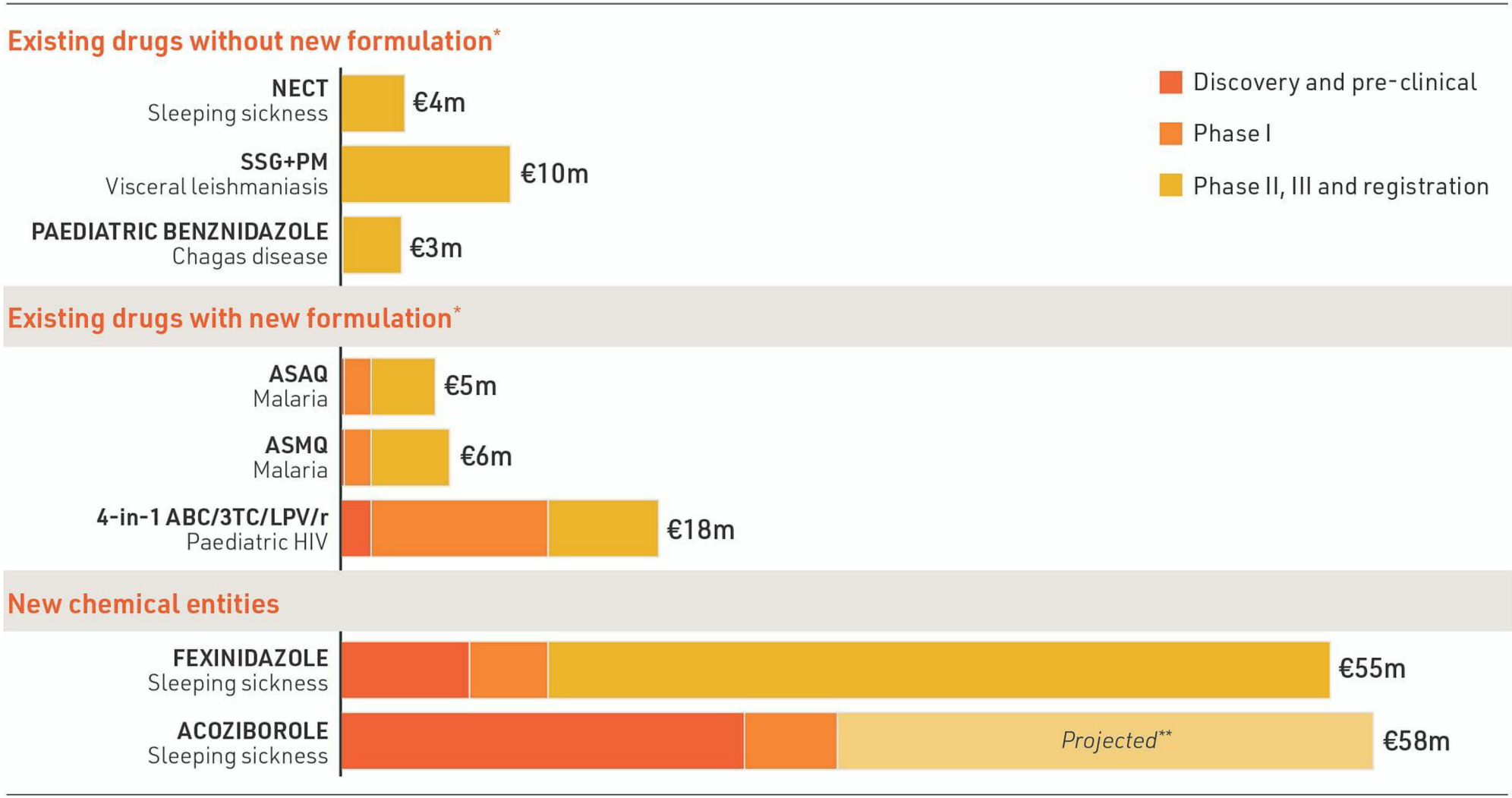
Drug Repurposing on target:

- Finding new uses of a drug acting through the originally known target
- Literature, omics experiments, …
- Positive feature is that it is likely to be compatible with dosing of original drug

Drug repurposing off target:

- Finding new uses of a drug acting through a novel or unanticipated target
- Docking, fingerprint methods, …
- Drug was not originally optimised for that target, so need to be watchful of dosing

Some examples of repurposed drugs



* Combinations (as loose or fixed-dose combinations) or repurposing of existing drugs
** Acoziborole is still under development. Late-stage costs are projections.