BIOENG-399
Immunoengineering

Lecture 12 Considerations in drug development

Dr. Yvan (Vanya) Loroch

L O R O C H
communication & training
in life sciences


What Pilots Can Teach Hospitals A
Hospitals Take Flight Lessons from Pilots to Avoid Government Penalties
In 2013, regulators will penalize 1,427 U.S. hospitals because many of their patients are readmitted to the hospital for these penalties
PALMD | PHYSICIAN | NOVEMBER 20, 2012
If pilots worked like doctors, the sky would rain planes
CLINICAL MEDICINE / ZENMED
5 things Physicians can learn from Pilots
by LUKAS ZINNAGL on Jan 11, 2011 • 9:42 pm
Why drug design is like airplane design.
By Wavefunction on Wednesday, December 07, 2011
Why do doctors kill more people than airline pilots?
By DR PHIL HAMMOND
UPDATED: 06:54 GMT, 5 August 2008
Clinical Pharmacology & Therapeutics
Commentary
Comparative regulation of drug and aircraft development: Lessons for regulatory reform?
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If we designed airplanes like we design drugs...
Perspective | Open access | Published: 03 December 2011 | 26,159–163 (2012)
Pilots Use Checklists. Doctors Don't. Why Not? By Maggie Mahar
TRENDING
Joseph Gordon-Levitt presents Don Jon | Arcade Fire | TIFF 2013
Why doctors should be treated more like airline pilots
DR. JAMES AW | 11/11/22 | Last Updated: 11/11/22 6:04 PM ET
More from Dr. James Aw
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Drug development is a long and complex journey

3.5 years
Discovery

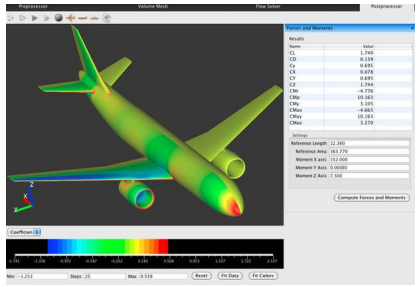
1.5 years
Phase 0
preclinical

1 year
Phase 1
First-in-human

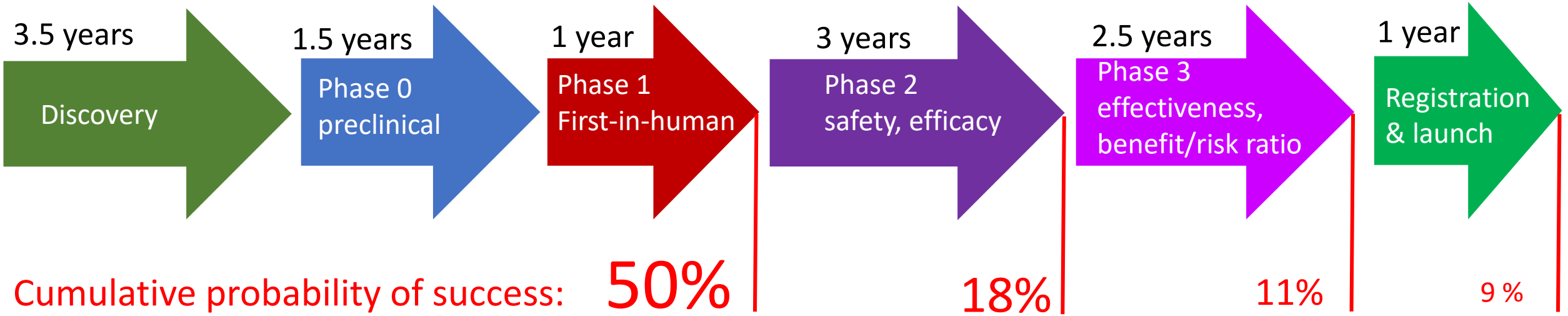
3 years
Phase 2
safety, efficacy

2.5 years
Phase 3
effectiveness,
benefit/risk ratio

1 year
Registration
& launch



Drug development is a high risk, expensive journey



Odds of winning the jackpot: 1 in 139 million
1 single combo ticket costs CHF 3.50
CHF 486 500 000 will buy all combinations
Record jackpot 210 million (in Switzerland)!

Ten times riskier than Euromillions…

FTLOSCIENCE		Average Time (Years)	Average Cost 2022 (US$ million)
Early Drug Discovery		2.5	353
Lead Optimization		2	562
Pre-Clinical Trials		1	340
Clinical Trials	Phase I	1.5	63
	Phase II	2.5	119
	Phase III	2.5	344
FDA Review and Approval		1.5	3
Total		> 13.5 Years	1784

But the Jackpot is much bigger and lives may be saved !

Drug development: how to improve the odds, reduce costs and go faster?

Learn to pilot the drug development journey using the best possible instruments

DC-3 (1930-s)

Few instruments
high risk

Boeing 747 (1970-s)

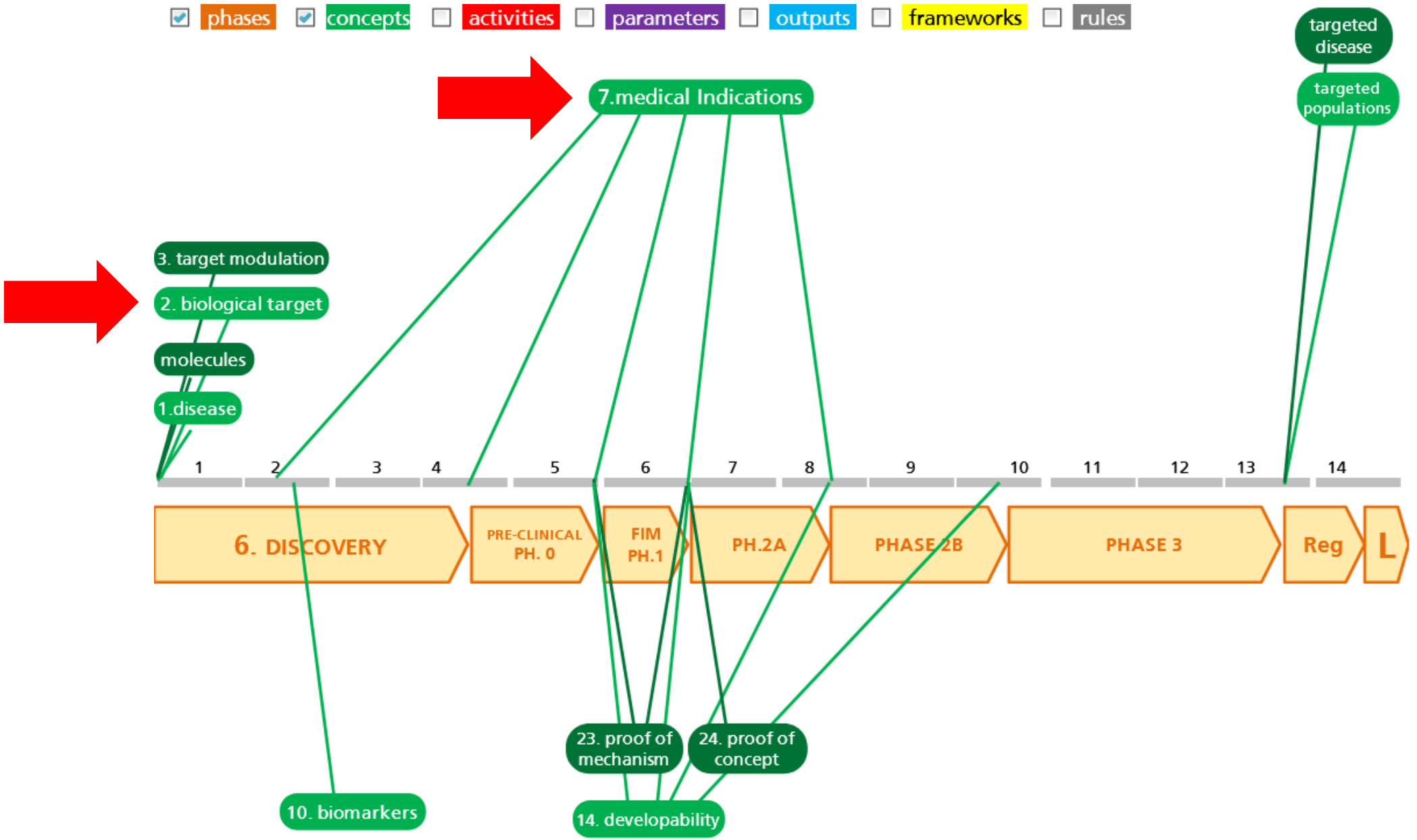
Many instruments
lower risk

Airbus A350 (2020-s)

Fewer instruments
lower risk
and more powerful

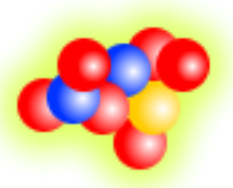
A simple simulation:
www.loroch.ch/dddd

Concepts: basic biological notions underlying the drug development process.



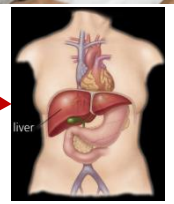
Who is the drug for?

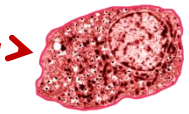
Idea !

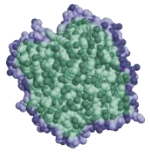


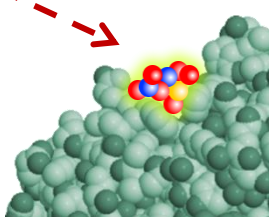
?

Drug









Implications for medicine.

In the good'ole days…

Symptoms
& clinical signs

↓

Today's
disease
taxonomy

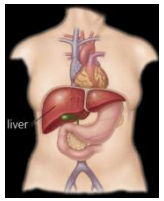
Implications for medicine.

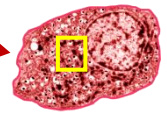
Today and tomorrow…

Precision medicine

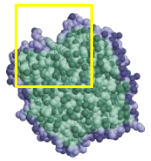
individual variations

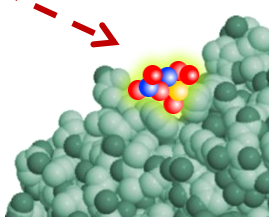
~~Symptoms & clinical signs – based disease taxonomy~~





mechanism–based disease taxonomy





Example: Hematological cancers

1950-s:	“Disease of the blood”	
1960-s:	Leukemia	Lymphoma
1970-s:	Chronic Leukemia Acute Leukemia **Preleukemia**	Indolent Lymphoma Aggressive Lymphoma

Current:

38 types of leukemias:

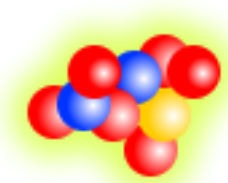
Acute myeloid leukemia (12 types)
Acute lymphoblastic leukemia (2 types)
Acute promyelocytic leukemia (2 types)
Acute monocytic leukemia (2 types)
Acute erythroid leukemia (2 types)
Acute megakaryoblastic leukemia
Acute myelomonocytic leukemia (2 types)
Chronic myeloid leukemia
Chronic myeloproliferative disorders (5 types)
Myelodysplastic syndromes (6 types)
Mixed myeloproliferative/myelodysplastic syndromes (3 types)

51 types of lymphomas:

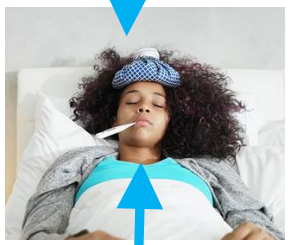
Mature B-cell lymphomas (14 types)
Mature T-cell lymphomas (15 types)
Plasma cell neoplasm (3 types)
Immature (precursor) lymphomas (2 types)
Hodgkin's lymphoma (5 types)
Immunodeficiency associated lymphomas (5 types)
Other hematolymphoid neoplasms (7 types)

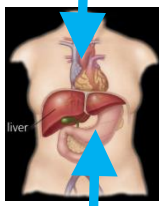
A single disease has become 89 different diseases in 70 years

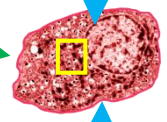
Implications for drug development

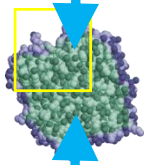


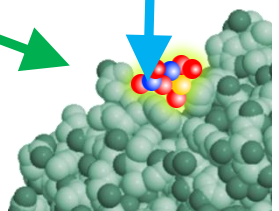
Translatability







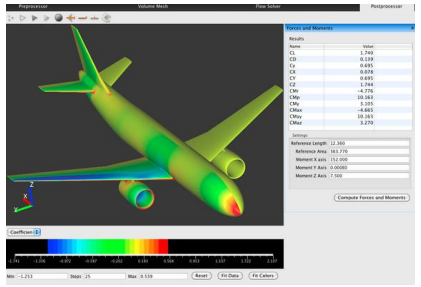




Drug mechanism of action is rooted in molecular biology

3.5 years

Discovery



Key questions:

Is the biological target identified?

Are there several drug candidates that bind to the target?

Does the chosen drug candidate work at a reasonable concentration?

Can it be manufactured in a reasonable way?

Is the chosen drug candidate believed to be safe?

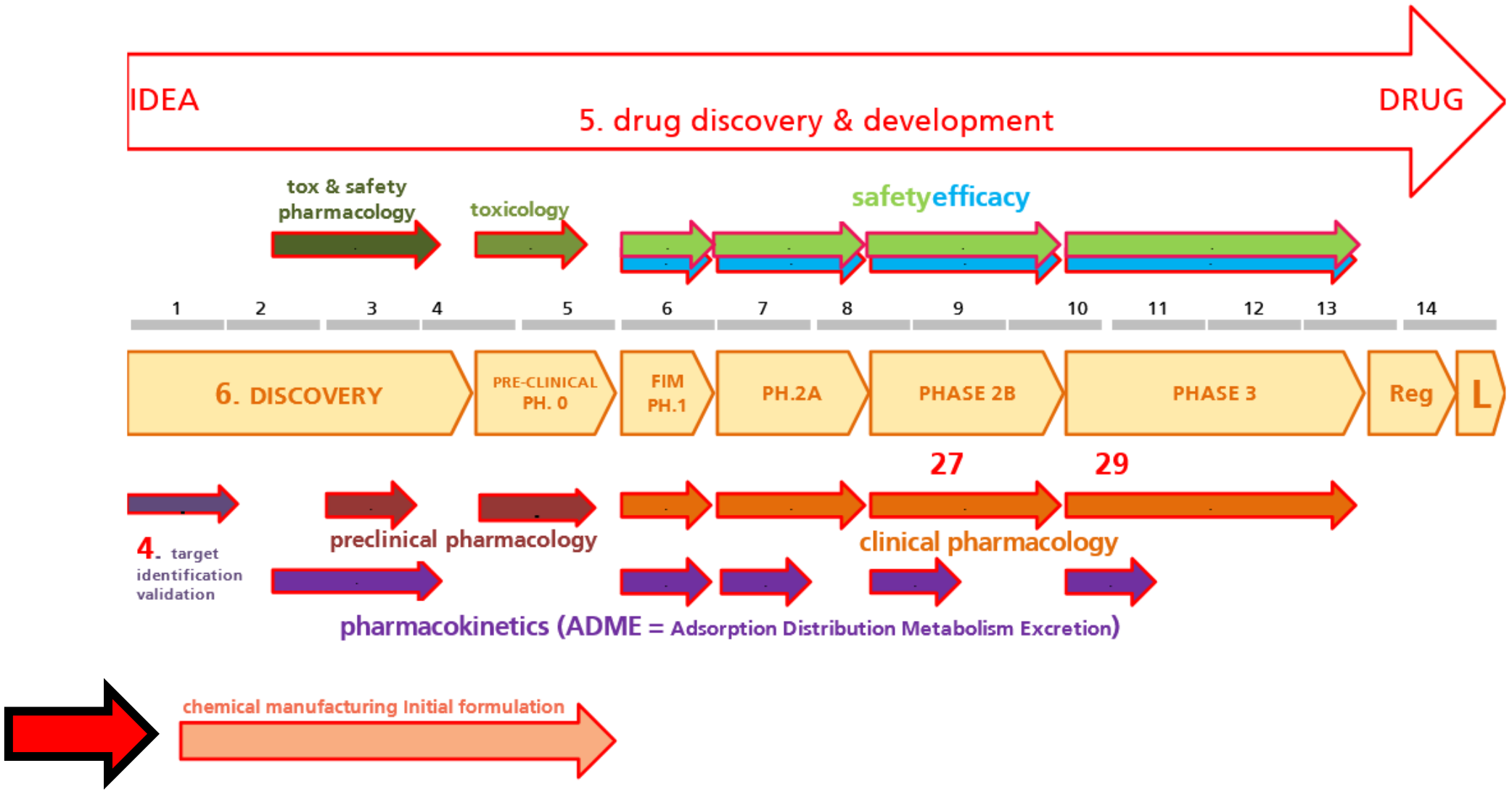
Can the drug candidate be patented?

Novel? Any prior art?

True invention, not obvious ?

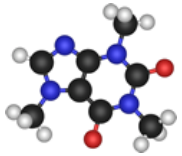
Not disclosed?

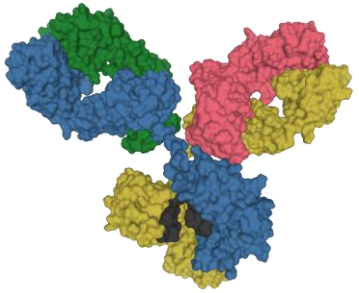
☑ phases ☐ concepts ☑ activities ☐ parameters ☐ outputs ☐ frameworks ☐ rules



What is a drug ?

API
Active Pharmaceutical Ingredient





Chemical or biological substance that modulates the activity of a **biological target**

+

Excipient(s)

Safe and effective API delivery to the **biological target**

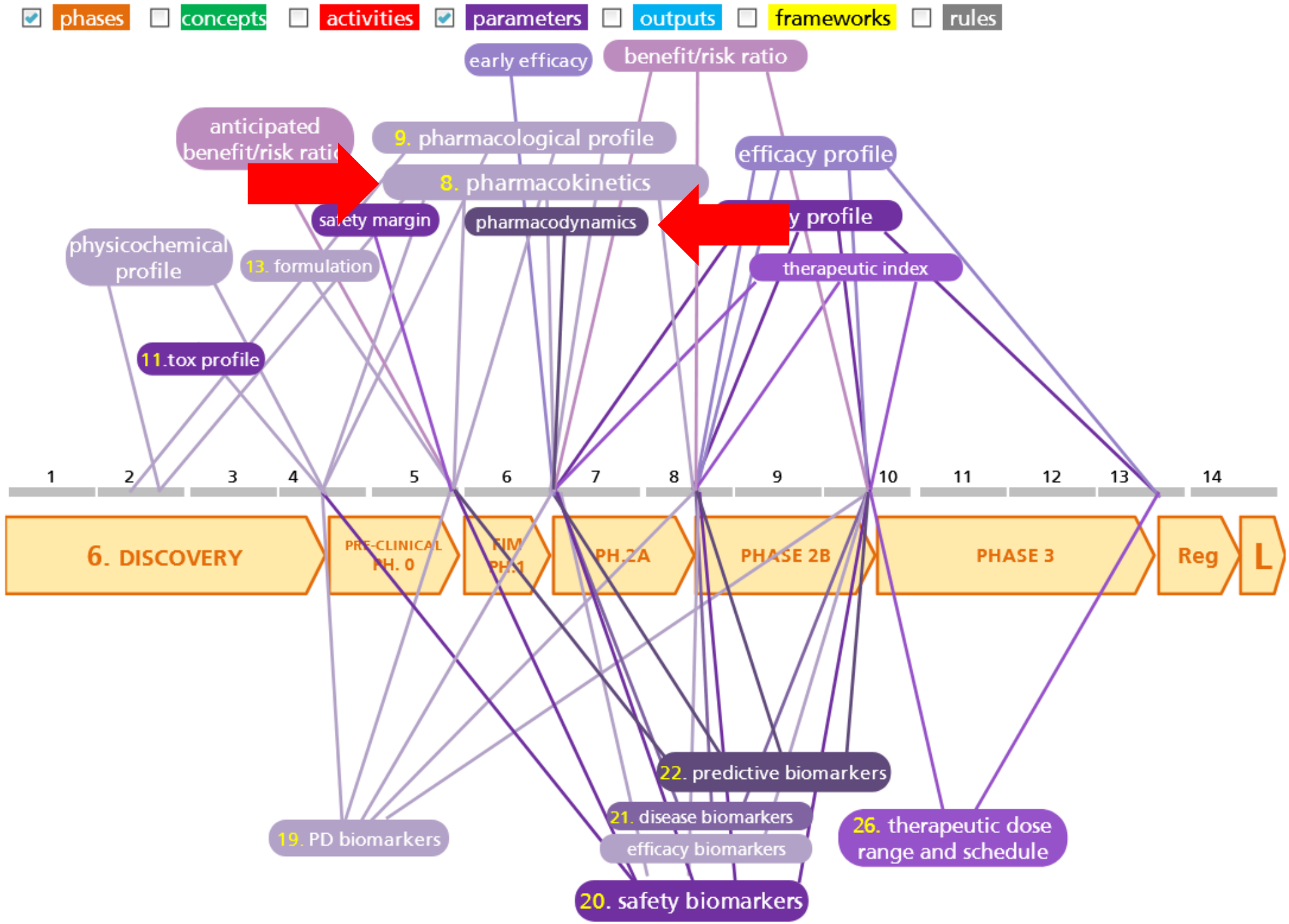
FORMULATION

Mode of administration

Don’t wait!

Different regulatory constraints

Formulation difficulties:
80% of all drug development projects
30% fail because formulations fail…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PH.2A
PHASE 2B
PHASE 3
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22. predictive biomarkers
21. disease biomarkers
efficacy biomarkers
19. PD biomarkers
26. therapeutic dose range and schedule
20. safety biomarkers

Pharmacokinetics (PK):
What happens to the drug inside the body?

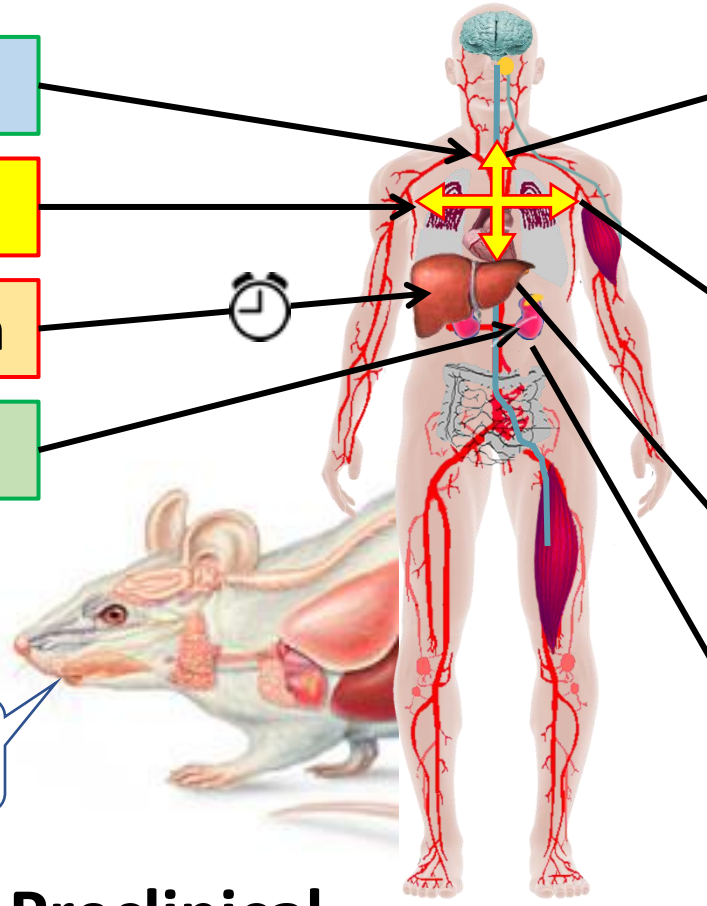
Absorption

Distribution

Metabolism

Excretion

ADME

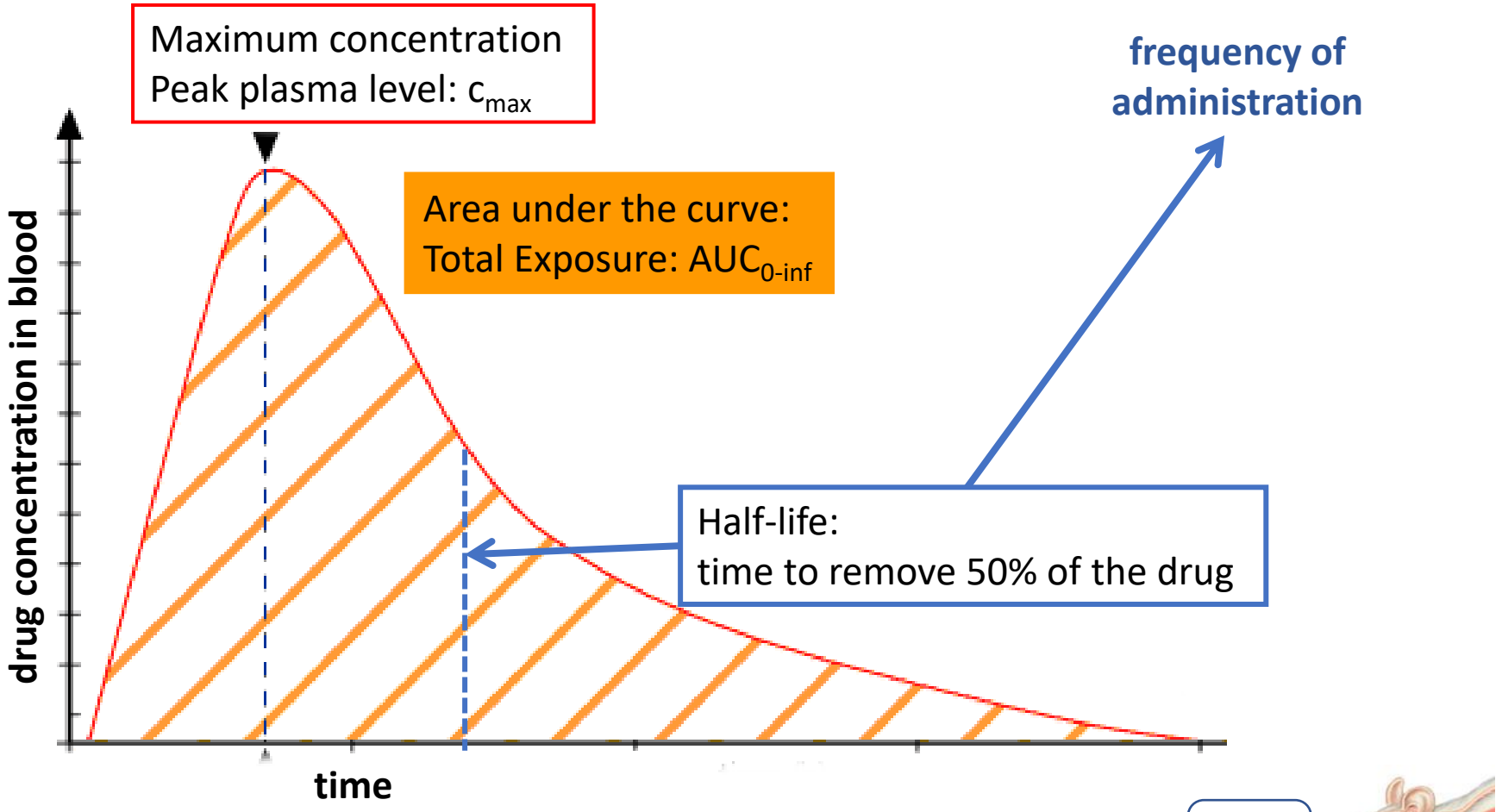


Why me?

Preclinical

What is Absorption?

(aka how does the drug travel into the bloodstream?)



What is Distribution?

(aka how does the drug travel into different locations of the body ?)

Factors Affecting Distribution of Drugs

Factors Related to Drug	Factors Related to Body
Lipid solubility	Vascularity
Molecular size	Transport Mechanisms
Degree of Ionization	Blood Barriers
Cellular binding	Placental Barriers
Duration of Action	Plasma Binding Proteins
Therapeutic effects	Free and Bound forms of Drugs
Toxic effects	Drug Interactions
	Disease States
	Drug Reservoirs
	Volume of Distribution

What is Metabolism?

(aka what can happen to molecules inside the body?)

Binding

Molecules can bind other molecules.

Signaling

Breaking living matter

CATABOLISM

Making living matter

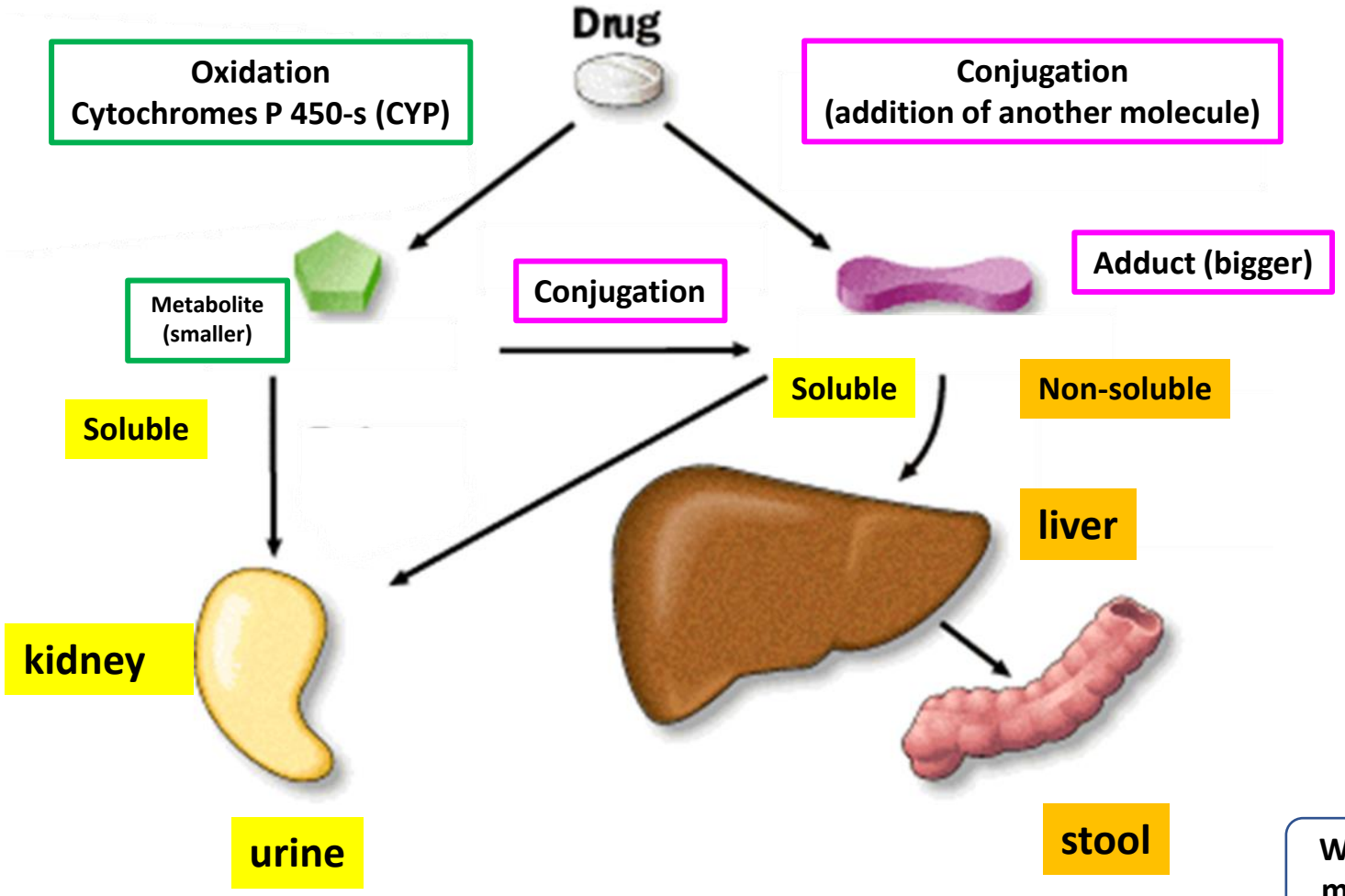
ANABOLISM

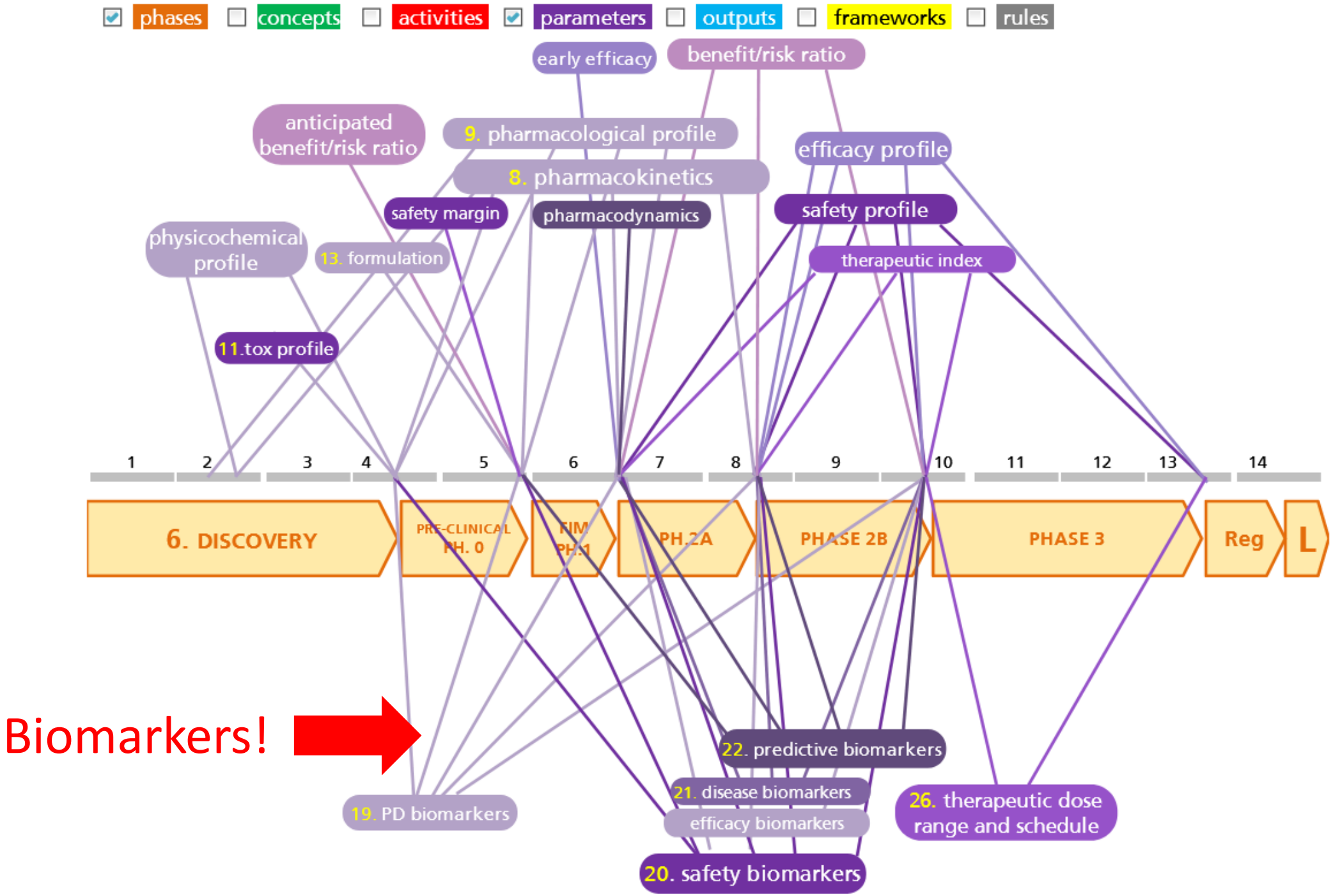
BALANCED

METABOLISM

What is Excretion?

(aka how does the drug or what's left of it leave the body?

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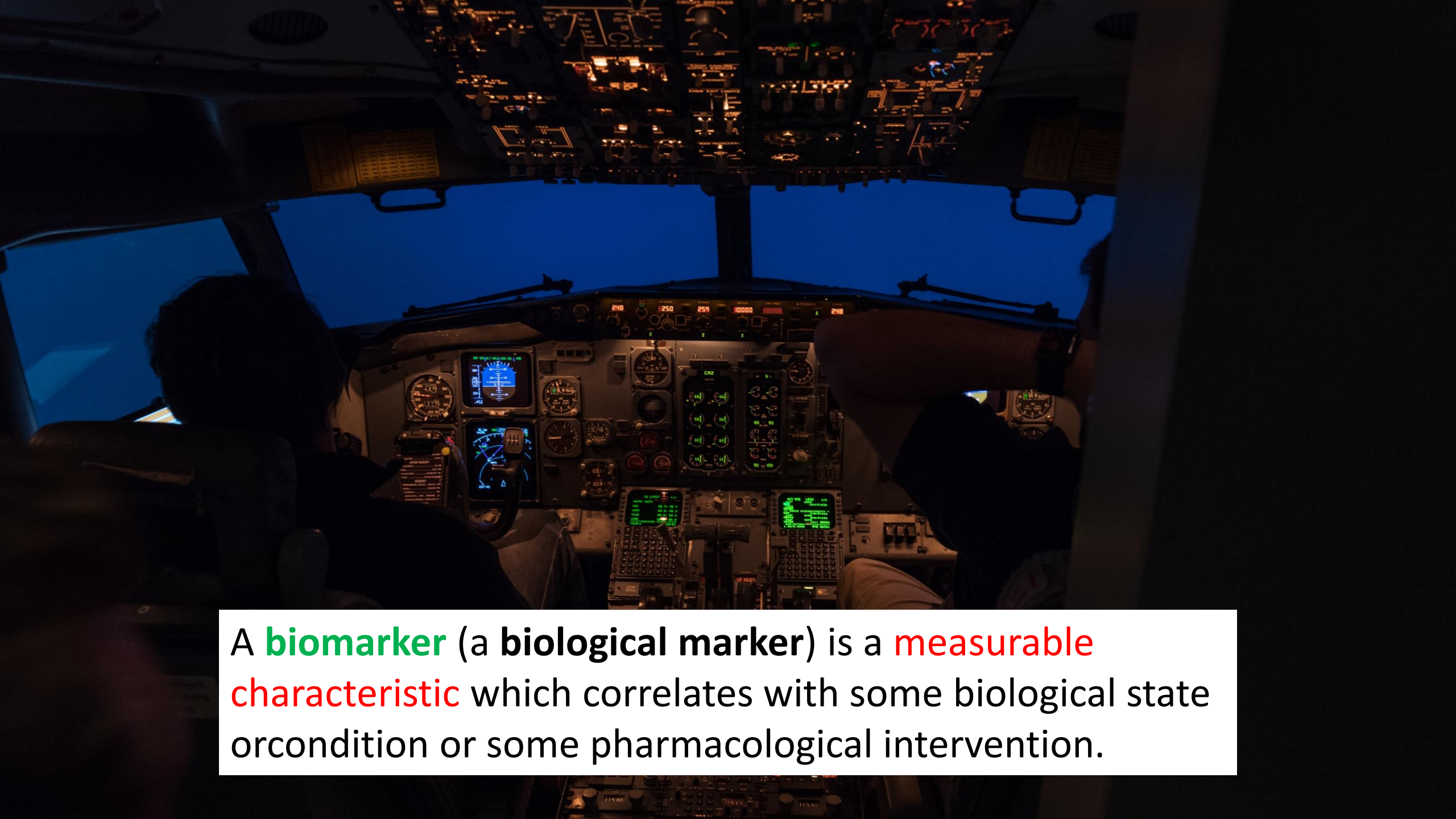


A **biomarker** (a **biological marker**) is a measurable characteristic which correlates with some biological state orcondition or some pharmacological intervention.

What are the different kinds of biomarkers ?
(aka what can we see in the invisible world?)

Pharmacodynamic (PD) biomarkers

correlate with a pharmacological response (e.g. limb diameter in arthritic rats)

Efficacy biomarkers

correlate with desired clinical outcomes

Safety biomarkers

may support safety-related decisions during drug development

Disease biomarkers

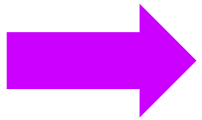
correlate with disease processes

Predictive biomarkers

predict response to a particular treatment

Stratification biomarkers

predict patient groups that will respond to a particular treatemnt



Precision medicine

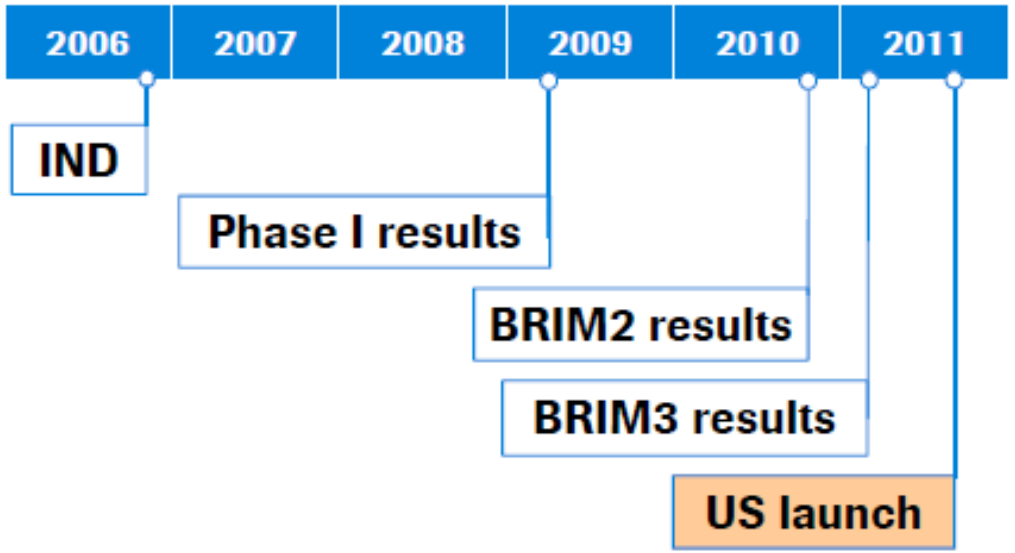
Zelboraf:
Melanoma Drug + Companion diagnostics (stratification biomarker)

The drug:
Binds and inhibits a specific mutant of BRAF, a signaling kinase in melanoma (v600 mutation)

Companion diagnostics:
detect the BRAF v600 mutation by PCR

Zelboraf

US approval and launch in record time



Less than 5 years from IND to first launch

- Fastest development program (<5 years from IND to FDA approval)
- Fastest initiation of a global Expanded Access Program
- Fastest approval in Roche portfolio (3.5 months after submission)
- Five days from approval to launch
- 5 weeks after launch: sales of CHF 11 m

Zelboraf: Interesting aspects

Science

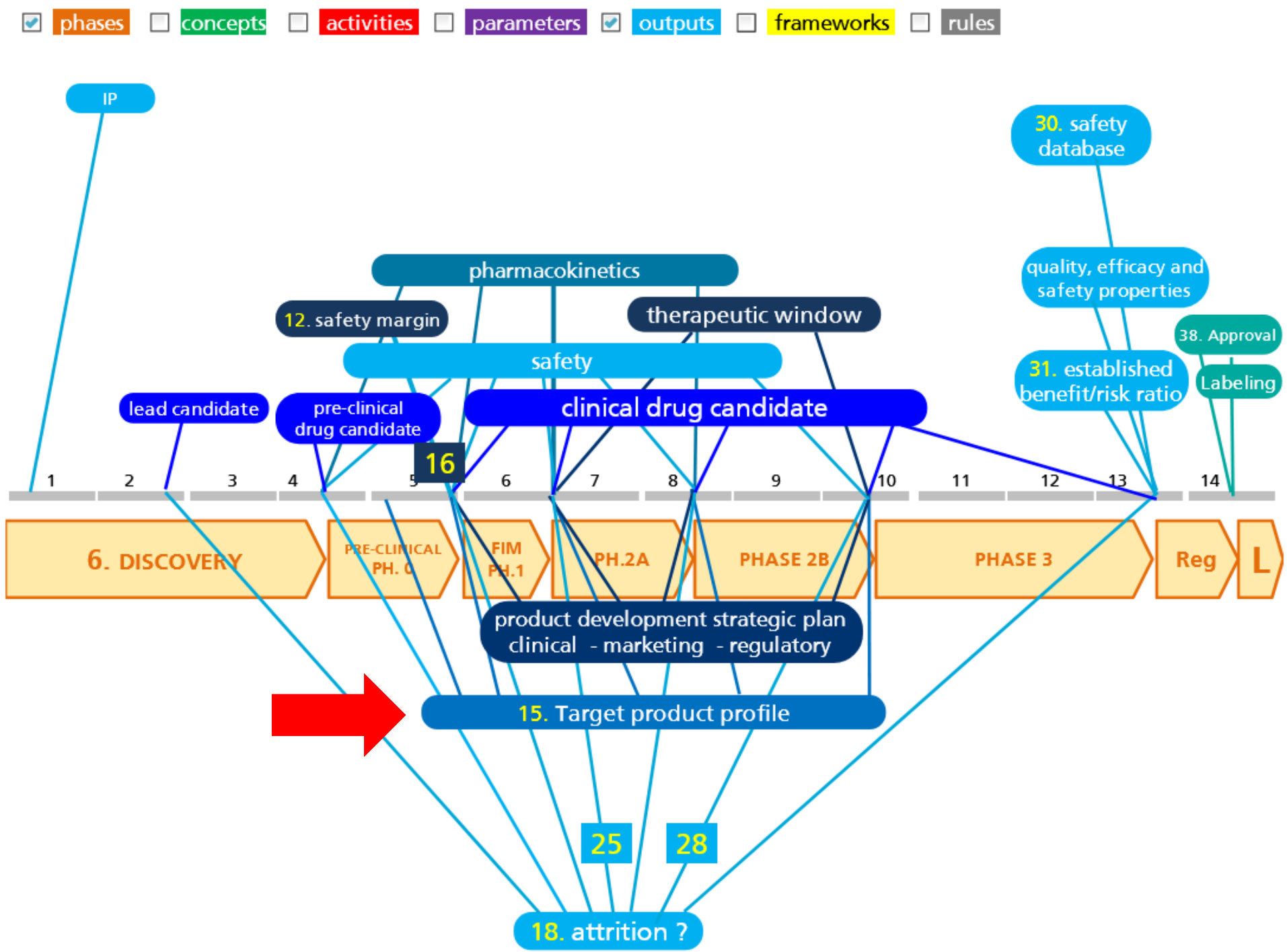
1. **Highly personalized:**
   Works against *BRAF*V600E and V600K variants
   one of the side effects (squamous cell carcinoma) is markedly reduced when BRAF inhibition is combined with MEK inhibition (rationale for combination therapies)

2. Companion diagnostics is also important **to prevent a negative impact** on (some) patients: Zelboraf stimulates wild-type BRAF and may promote tumor growth in such cases.

3. **Without prior screening of patients for clinical trials, the drug candidate would have never obtained its marketing authorization**

Business

1. The cost of the CDx is very low and the cost of the Drug is very high. But the drug is reimbursed (because of high efficacy and of course the disease area). The low cost of the Dx has to do with having an in-house Developer (Roche diagnostics).
2. Revenue: roughly $400 million in Zelboraf sales worldwide in 2013, a bit less today because of competition.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PHASE 2B
PHASE 3
Reg
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product development strategic plan
clinical - marketing - regulatory
15. Target product profile
25
28
18. attrition ?

What is a Target Product Profile (TPP)?

A summary of a drug development program described in terms of labelling concepts

says the FDA…

What is a Target Product Profile (TPP)?

Guide for development

Internal
Development teams

External
Regulatory

FDA members on a tour in Idaho!

What is a Target Product Profile (TPP)?

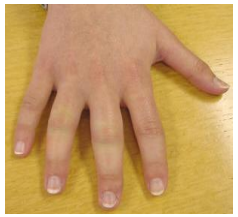
Flight plan…

Product labelling (PL)

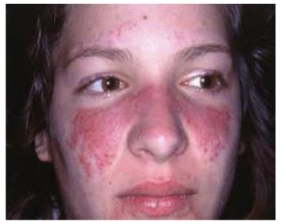
NYC JFK

PI3KD - An example of TPP- Guide

Targeted indication :
Systemic lupus erythematosus (SLE)

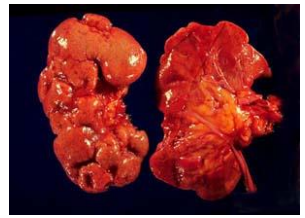


Targeted population :
SLE patients refractory to existing treatments



Rash

Efficacy profile :
Prevention of lupus signs, renal damage and joint damage

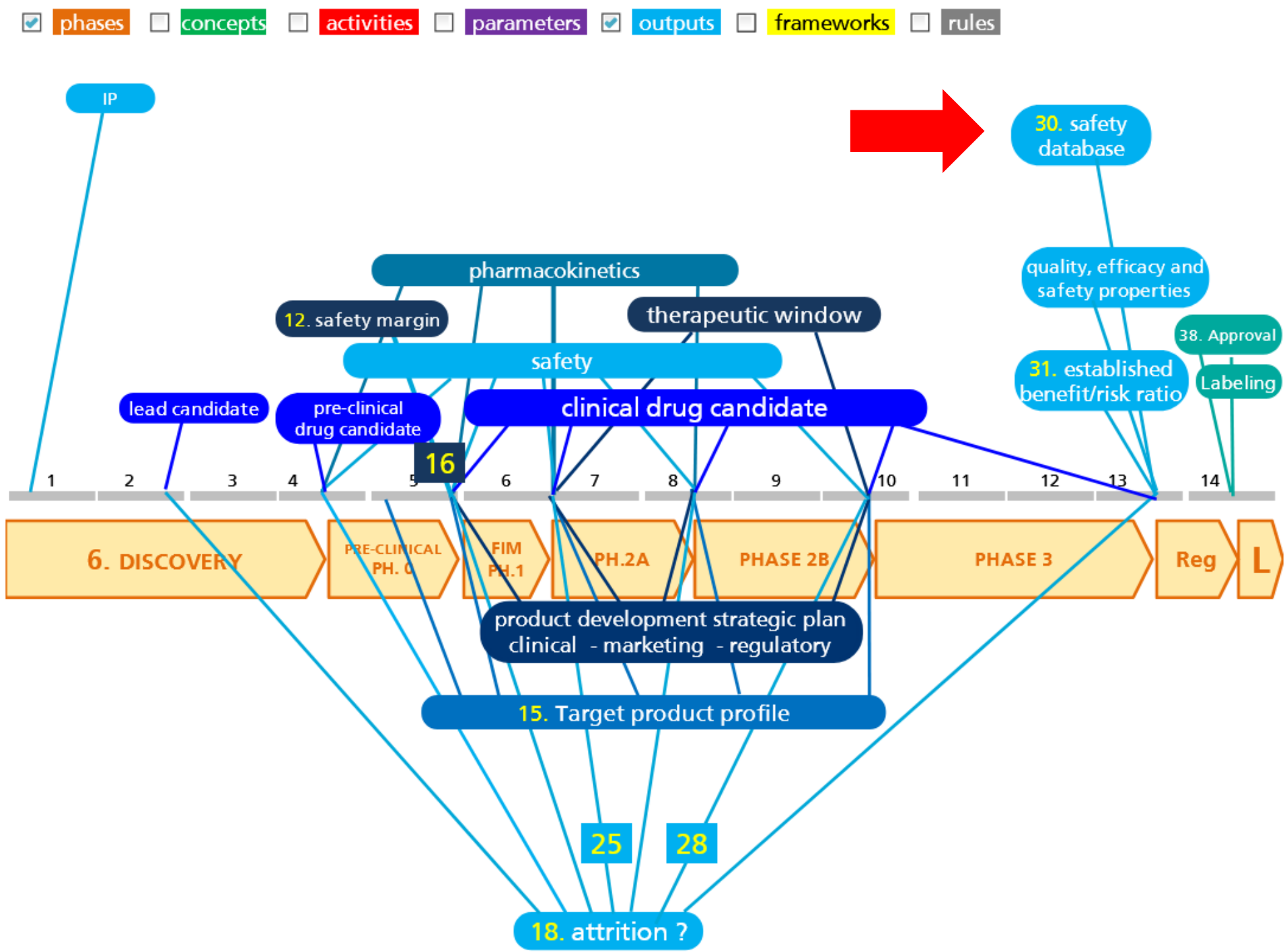


Nephritis

Safety profile :
favorable

Convenience :
one oral intake per day

Positioning versus existing treatments :
Superior benefit-risk ratio to Orals or Biologics
Reduces dose of cortisone
Reduces risk of cardio-vascular events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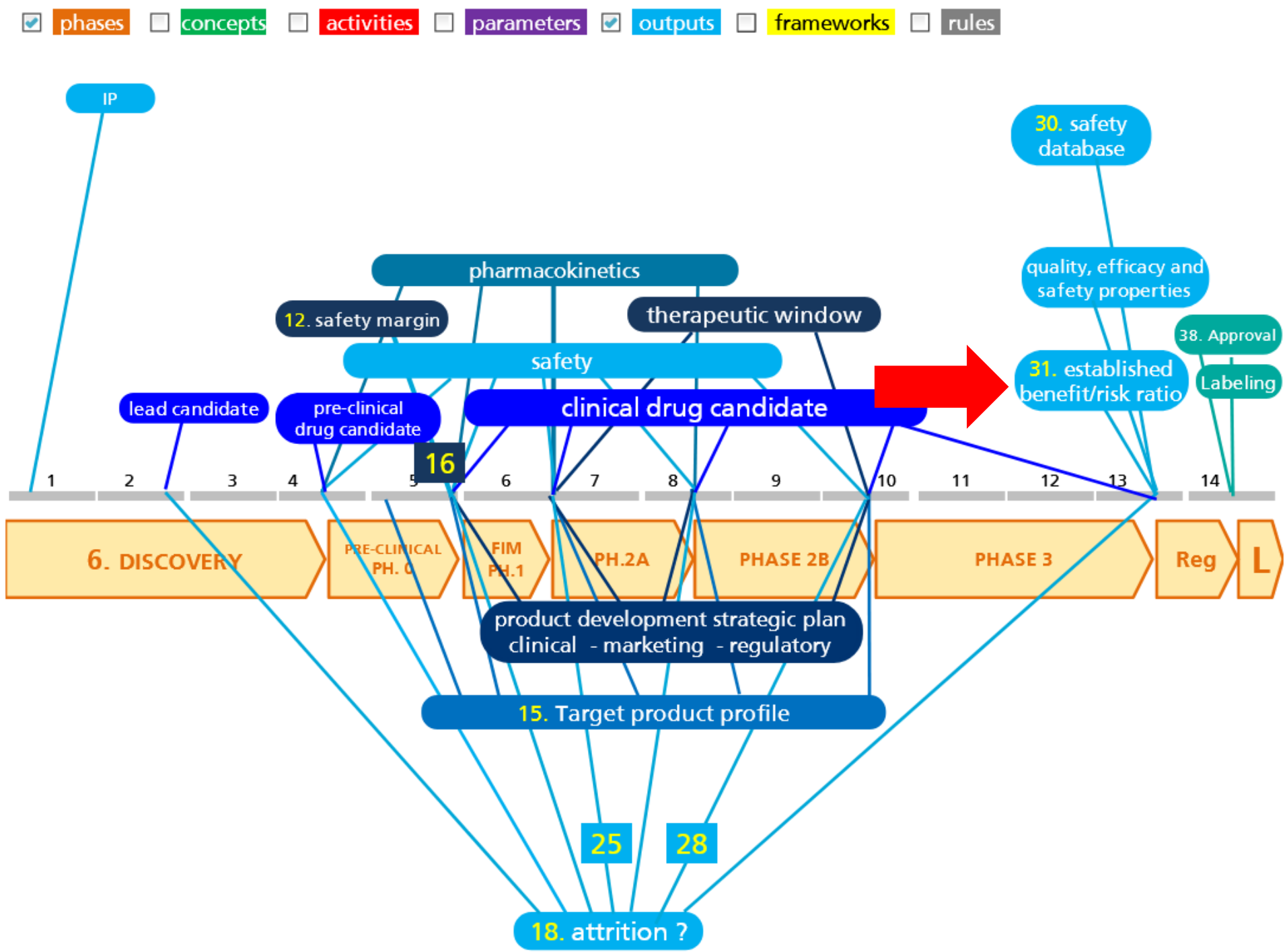
18. attrition ?

Required safety database

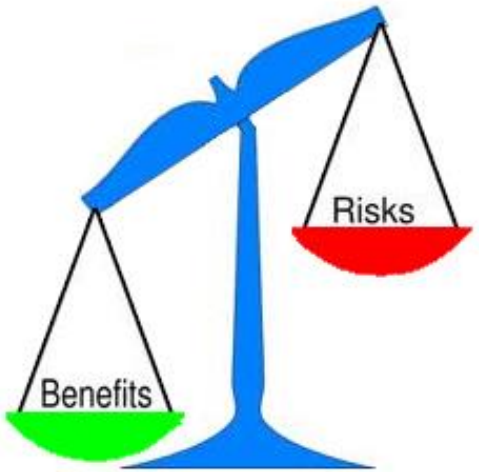
Safety data collected and stored from 3500-5000 patients exposed to the drug during all phases of drug development

data

storage of all flight data


phases
concepts
activities
parameters
outputs
frameworks
rules
IP
30. safety database
quality, efficacy and safety properties
pharmacokinetics
12. safety margin
therapeutic window
38. Approval
safety
31. established benefit/risk ratio
Labeling
lead candidate
pre-clinical drug candidate
clinical drug candidate
16
1
2
3
4
5
6
7
8
9
10
11
12
13
14
6. DISCOVERY
PRE-CLINICAL PH. 0
FIM PH.1
PH.2A
PHASE 2B
PHASE 3
Reg
L
product development strategic plan
clinical - marketing - regulatory
15. Target product profile
25
28
18. attrition ?

Established benefit-risk ratio



therapeutic efficacy

improvement of quality of life

pharmacoeconomics

sum of all adverse effects

potential risk of unobserved adverse effects anticipated on the basis of the mechanism of action.

Approval Criteria

1. Product is safe and effective:
   trial data support and demonstrate claims

2. Patients' rights and well-being are protected

3. Proposed labeling is appropriate

4. Product manufacturing follows strict regulations and are adequate to assure identity, purity, potency, and stability

There may be special conditions for approval and/or post approval commitments

Special Regulatory Situations

1. Orphan designation for "orphan drugs”

- Rare diseases affecting small numbers of people
- Companies may incur a financial loss
- Public interest to provide financial incentives
- Key Incentives include
  - ✓ Study design assistance from HAs
  - ✓ Tax incentives for clinical research
  - ✓ Seven years of marketing exclusivity after the approval of the drug or biological product

Rare diseases are rare, but patients are many !

5954 diseases!!!

Special Regulatory Situations

2. Fast Track

- Process designed to facilitate the development, and expedite the review of drugs
  - ✓ Treat serious diseases and
  - ✓ Fill an unmet medical need
- Purpose: to get important new drugs to the patient earlier
- Designation allows eligibility for Accelerated Approval

Special Regulatory Situations

3. Priority Review

- Products that offer major advances in treatment or provide a treatment where no adequate therapy exists
- FDA reduces time to review a new drug application
  Goal : 6 months
- Can apply both to drugs that are used to treat serious diseases and to drugs for less serious illnesses

Special Regulatory Situations

4. Accelerated Approval

- Earlier approval of drugs to treat serious diseases and that fill an unmet medical need based on a surrogate endpoint.
  - ✓ A surrogate endpoint is a marker that is used in clinical trials as an indirect or substitute measurement that represents a clinically meaningful outcome (eg survival or symptom improvement).

- Condition: post marketing clinical studies should verify the anticipated clinical benefit.

The final problem

"I found the secret to happiness, but the FDA won't let me release it."