The views expressed in this presentation are the personal views of the speaker and may not be understood or quoted as being made on behalf of or reflecting the position of the EMA or one of its committees or working parties

Conflict of interest: none

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Outline

- Development of medicines for rare diseases: Where are the problems?

  - do we know enough?

  - why do we get "lost in translation"?

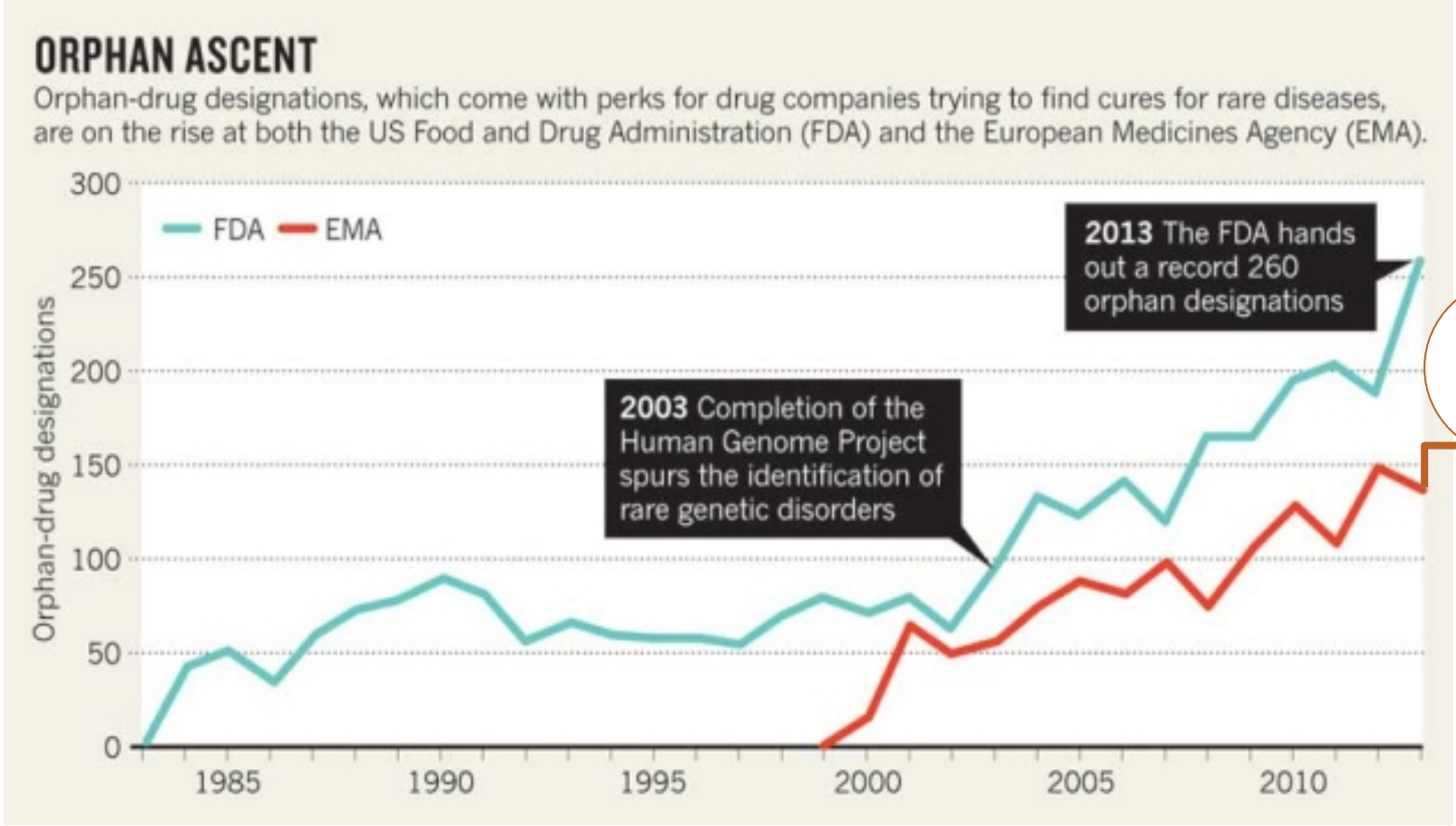
  - how do we know if trials REALLY fail?

- Regulatory pathway(s)
- Conclusions

What is RARE?

- working definition for public health/healthcare/regulatory
- Not more than 5 in 10,000 in the EU
- Not more than 200,000 in US
- includes diseases that could affect 1 or 250,000 people in the EU
- progeria: 25 patients
- cystic fibrosis: 40,000 (0.7 in 10,000)

How many medicines for rare diseases?



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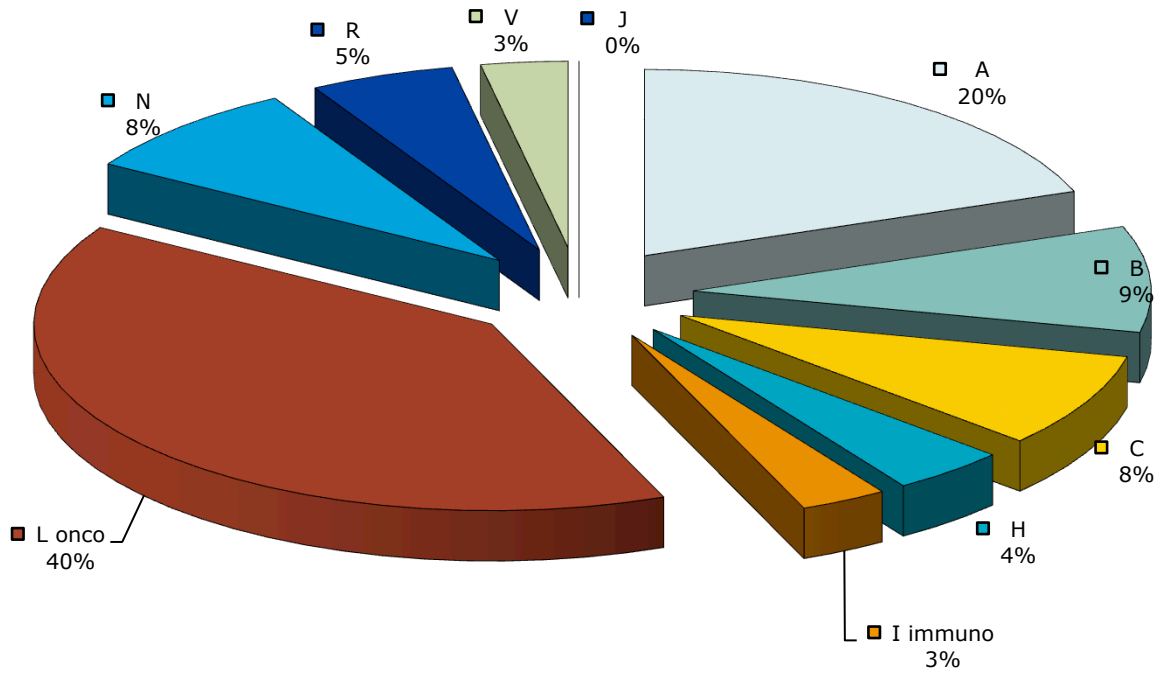
93 Orphan Medicines authorized in EU

A Alimentary tract and metabolism
B Haematology
C Cardiovascular
H Systemic hormonal;
J Anti-infective
I Immunology
L Antineoplastic;
N Nervous system
R Respiratory system
V Various



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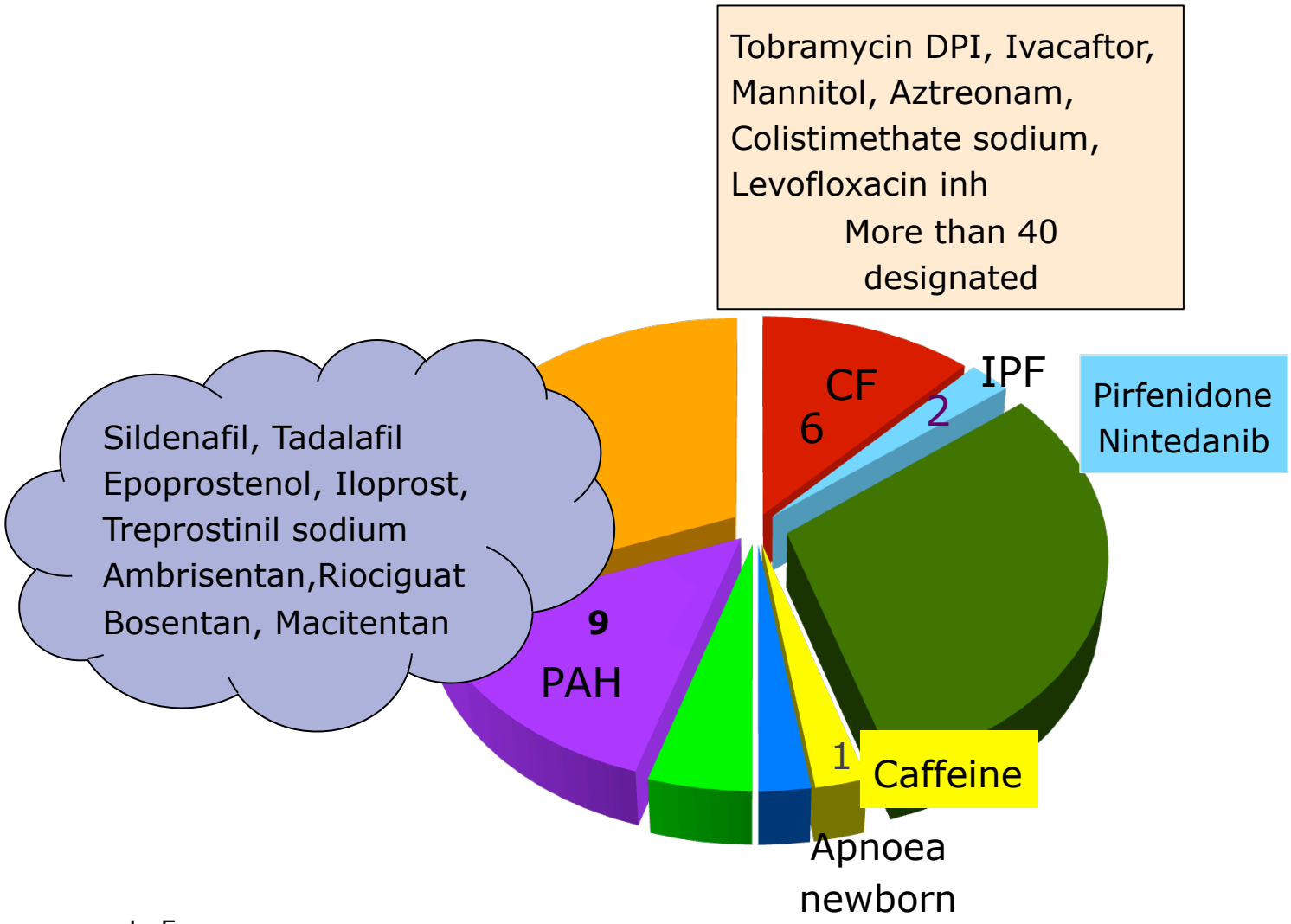
Rare Lung Diseases?



Alpha1 antitrypsin deficiency

Active substance	Disease / condition	Date of decision	Decision	Medicine name
Alpha-1 proteinase inhibitor (for inhalation use)	Treatment of congenital alpha-1 antitrypsin deficiency	03/06/2008	Positive	
Alpha-1 proteinase inhibitor	Treatment of emphysema secondary to congenital alpha-1 antitrypsin deficiency	15/02/2006	Positive	
Cyclo[L-alanyl-L-seryl-L-isoleucyl-L-prolyl-L-prolyl-L-glutaminyl-L-lysyl-L-tyrosyl-D-prolyl-L-prolyl-(2S)-2-aminodecanoyl-L-alpha-glutamyl-L-threonyl] acetate salt	Treatment of congenital alpha-1 antitrypsin deficiency	20/03/2013	Positive	
Recombinant adeno-associated viral vector containing human alpha-1 antitrypsin gene	Treatment of congenital alpha-1 antitrypsin deficiency	19/03/2007	Positive	

- Four products designated at centralized level in the EU; none authorized
- No recent designations

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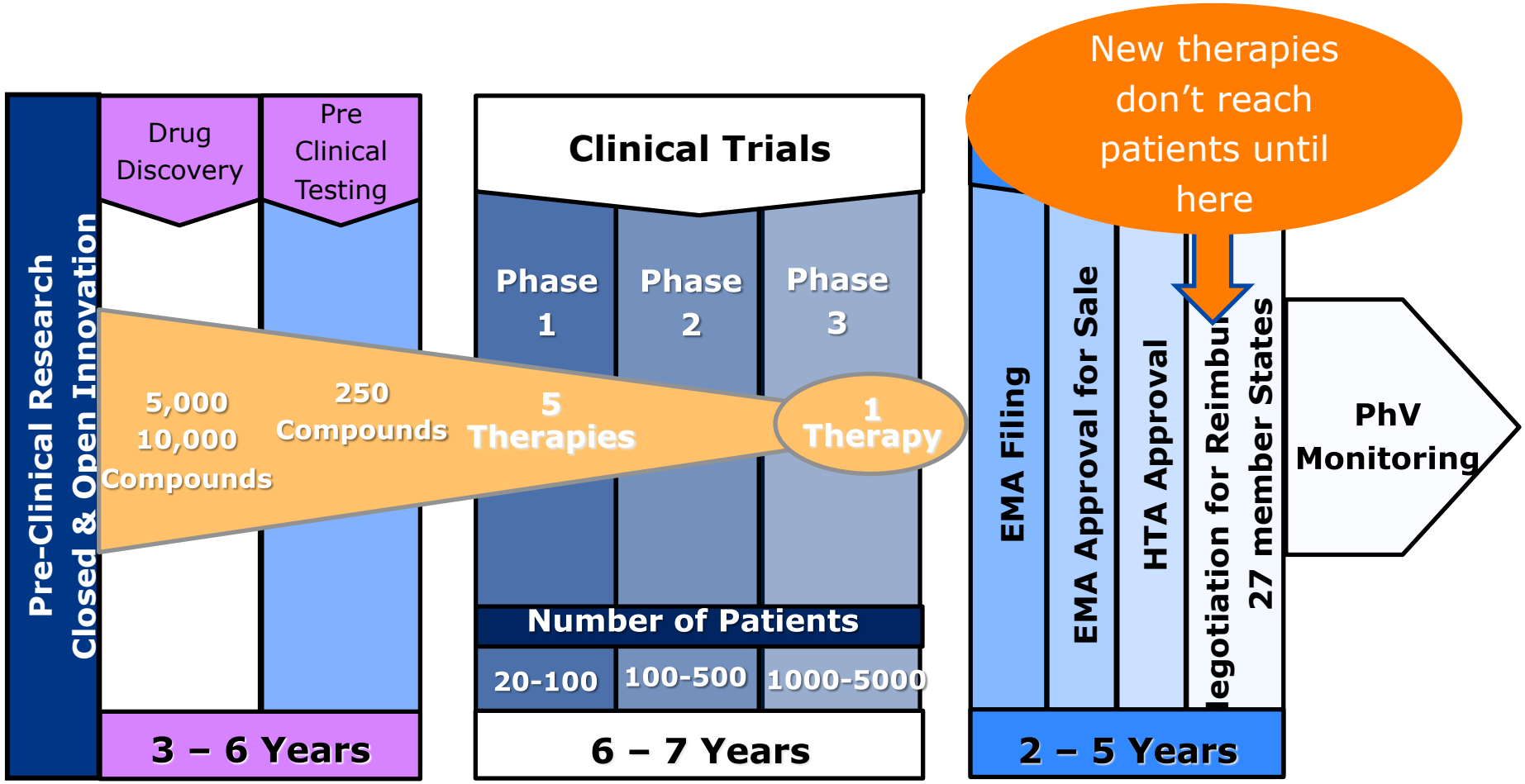
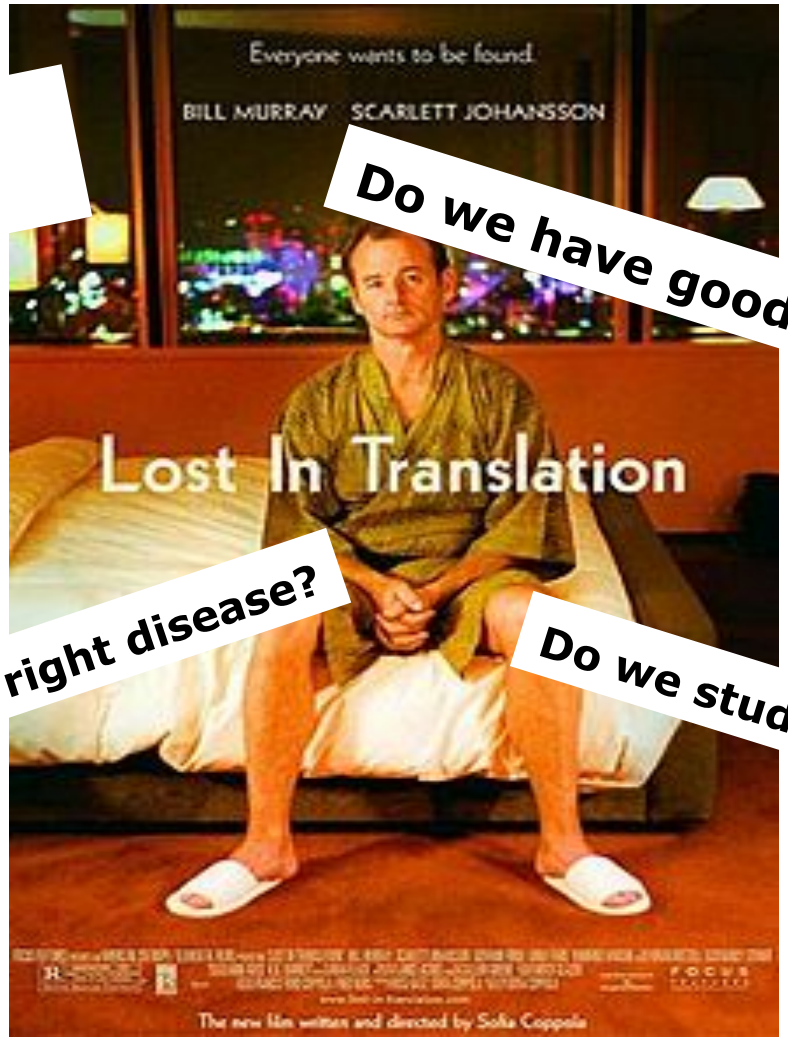
Development is **slow** and **expensive**



Total Cost: → **$2 - $4 Billion USD**

Forbes, Matthew Herper, "The Truly Staggering Cost Of Inventing New Drugs", February 10, 2012

The problems?



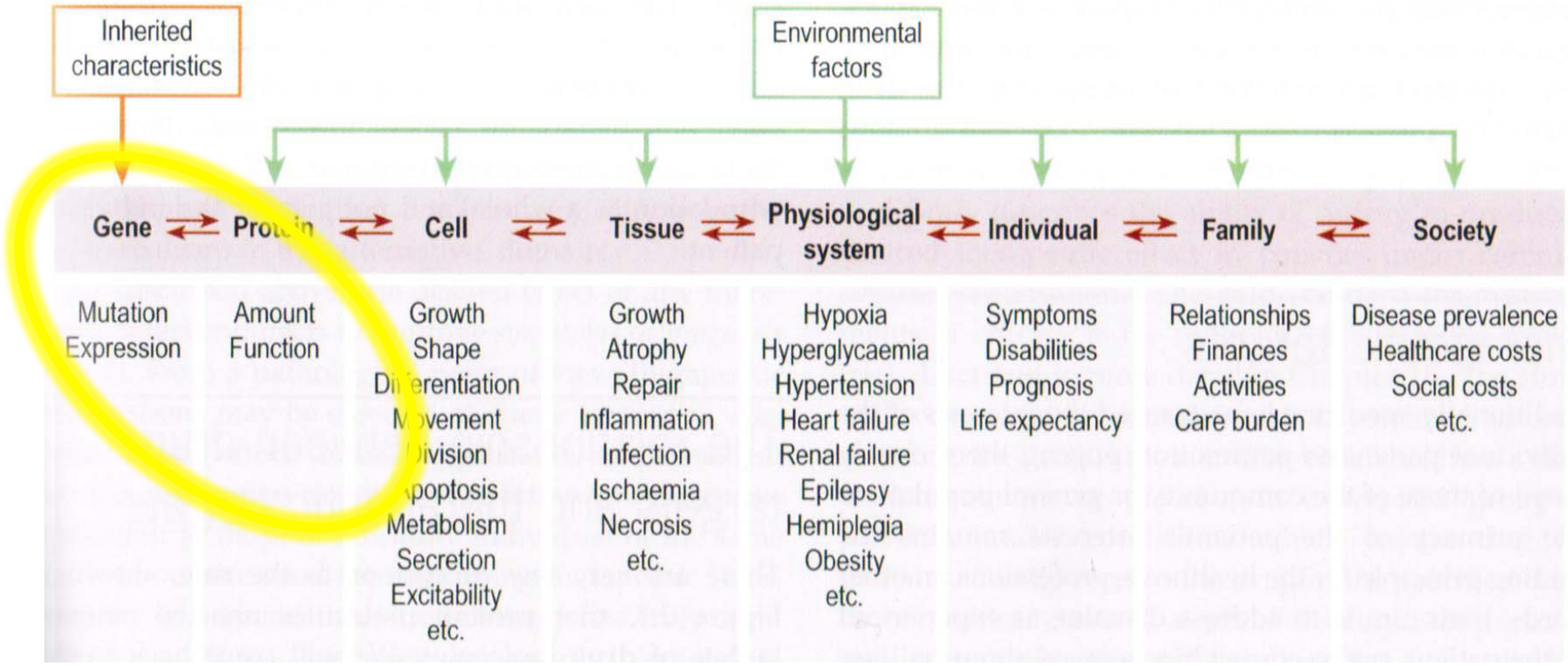
Do we know enough?

Do we have good preclinical models?

Are we looking at the right disease?

Do we study the right patients?

Do we know enough?



Drug Action

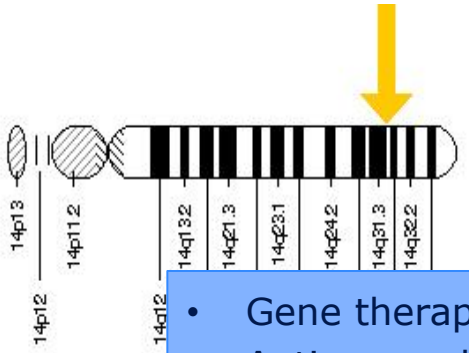
Therapeutic Aims

What do we know of AATD?

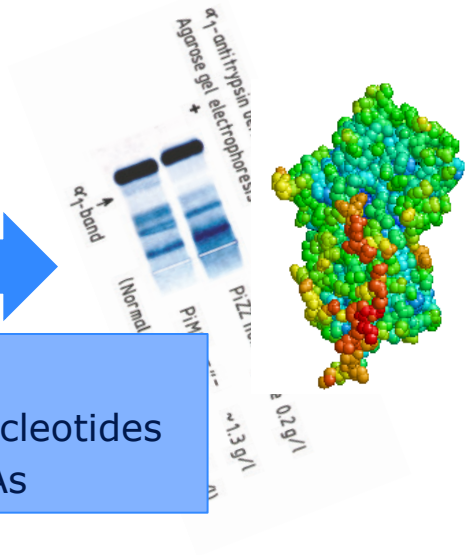
The genetic defect…

..its protein correlates..

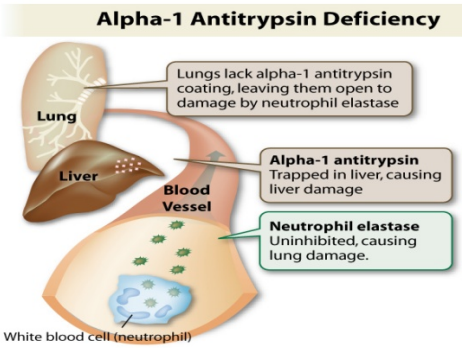
..how the deficiency acts in the body



- Gene therapy
- Antisense oligonucleotides
- siRNAs, microRNAs

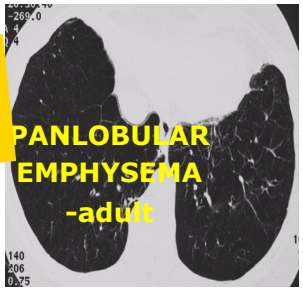


- Autophagy enhancing molecules (carbamazepine, fluphenazine)
- Prevention of polymerization (small peptides, molecular chaperones)
- Replacement therapy

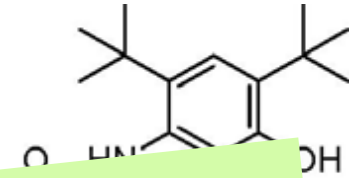


…and its clinical manifestations

- Stem cells
- Alveolar regeneration



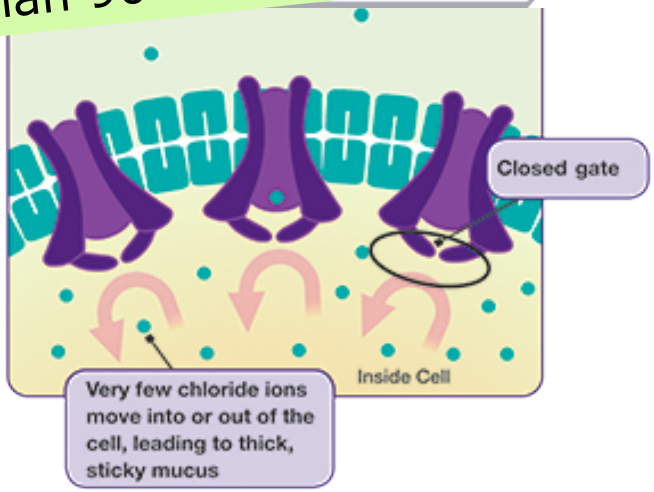
Genotype-phenotype correlation: Ivacaftor and G551D Cystic fibrosis

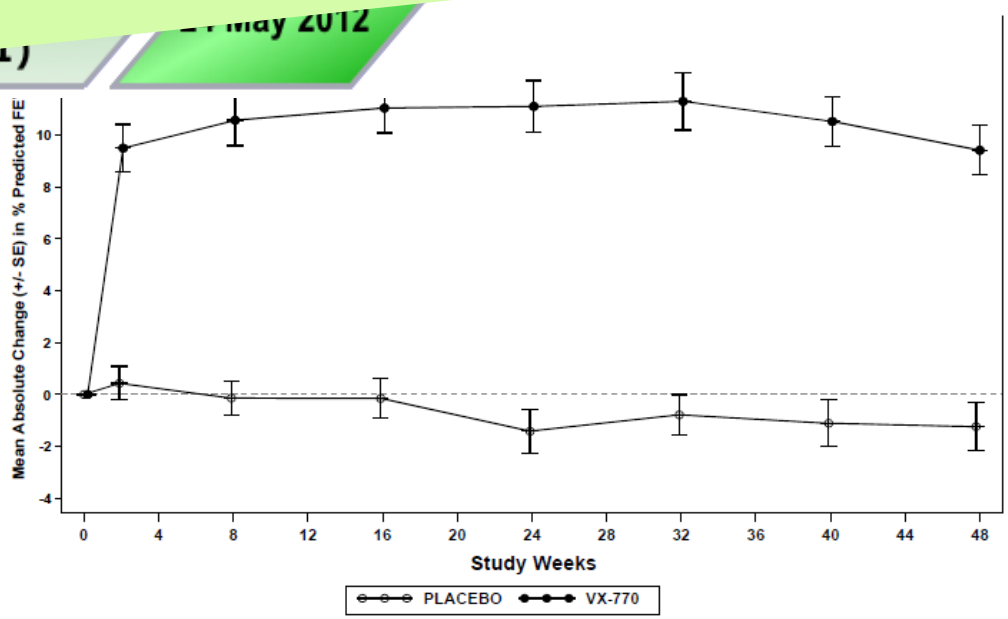


Discovery/Manufacture

Pre-clinical development

In spite of good ***in vitro*** data on different mutations, Ivacaftor alone works only on G551D (4% of CF patients) and not on F508Del (more than 90% of CF patients)





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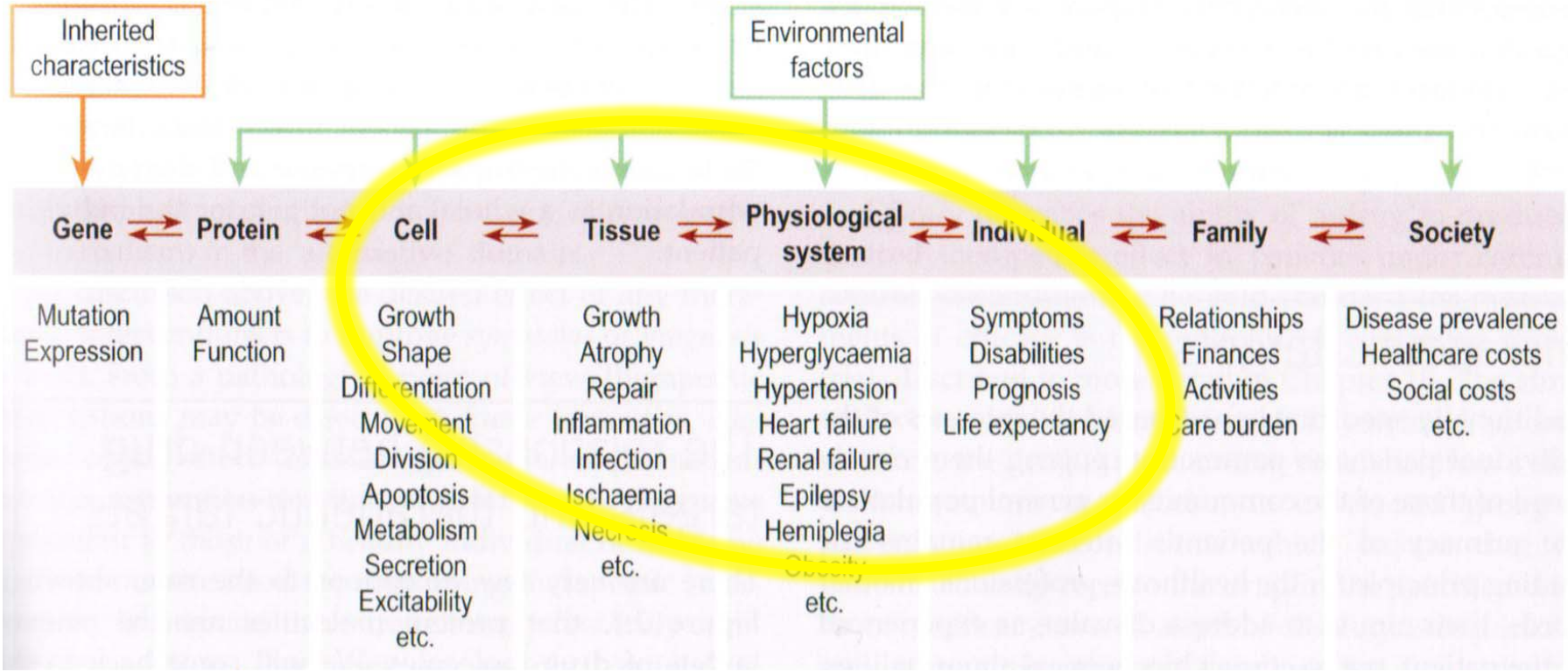
Why (When, and Where) do we get lost in translation?

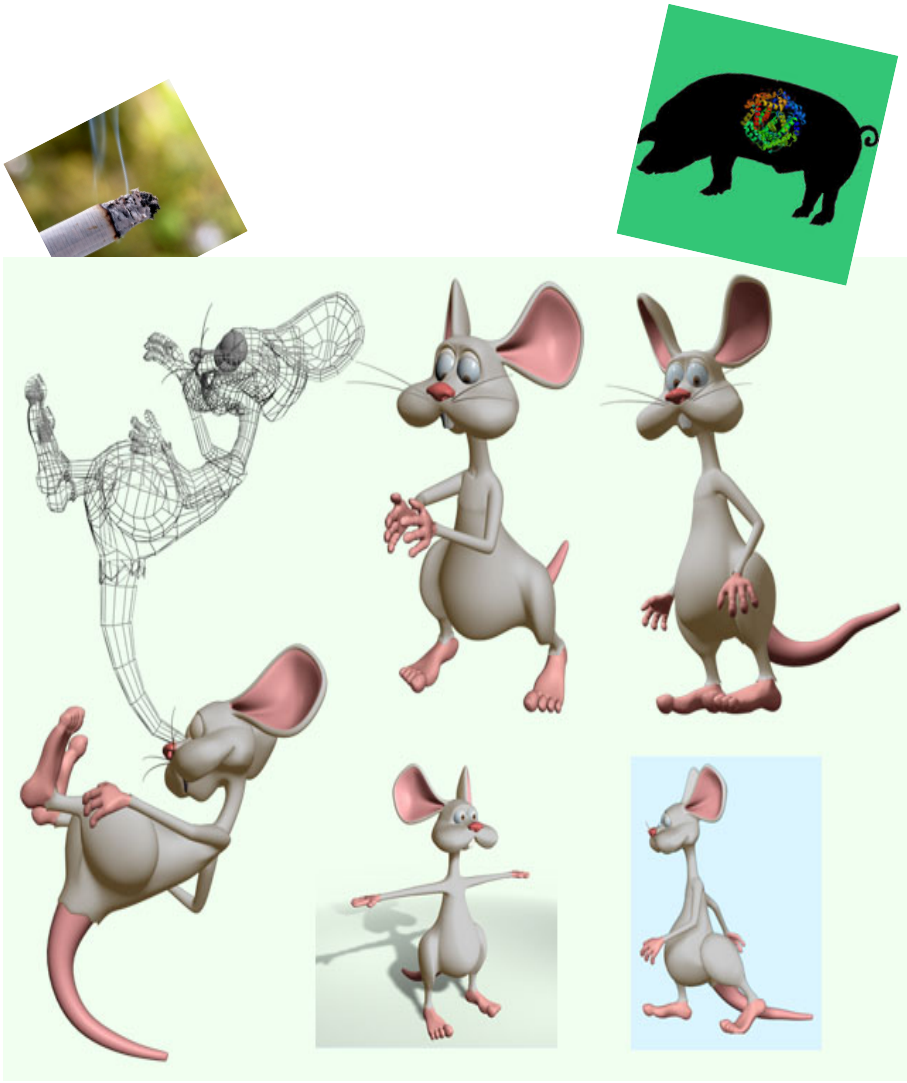


"*Failure of efficacy to translate from pre-clinical models to the clinical setting combined with the emergence of adverse events not predicted from the pre-clinical models remain at the core of late stage attrition*" (IMI2 Strategic Research Agenda)

Which model?

Lung disease models

- Cigarette smoking expensive, cumbersome (months, high exposure), variability of damage, mild emphysema, comorbidities
- Tissue-degrading approaches (PPE, human neutrophilic elastase, papain) and serine/cysteine proteases): lower costs, higher homogeneity of the damage, dose-response, panacinar emphysema
- "Natural models": e.g. tight skin, pallid mice. Defect and its consequences natural, no evidence of good translation



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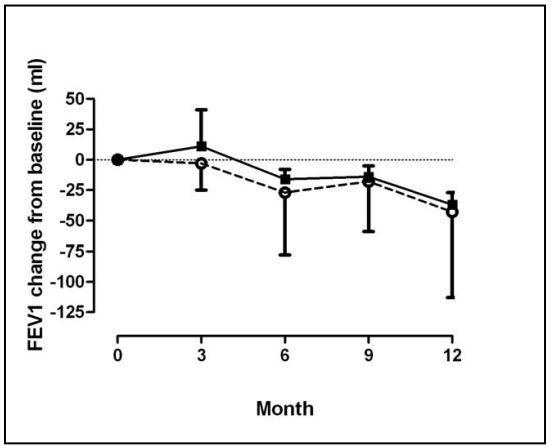
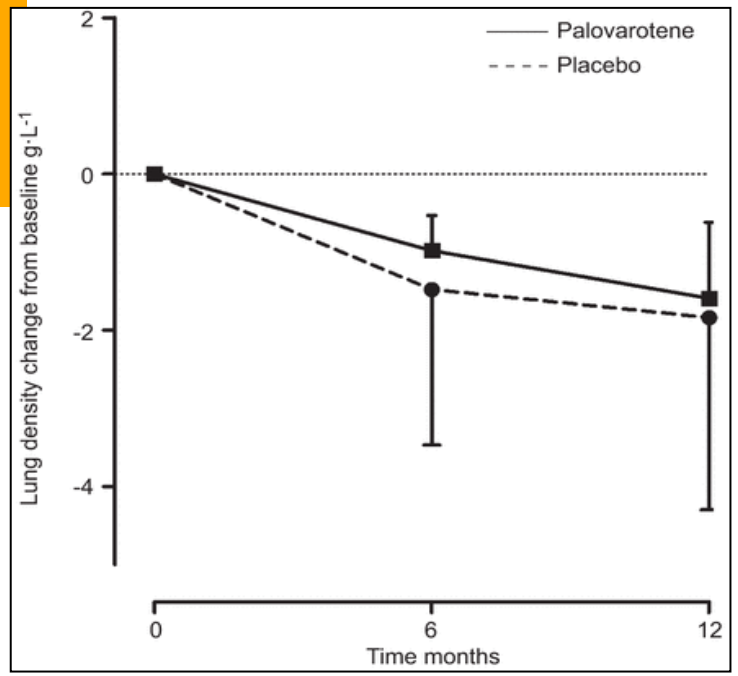
Poor translation of good results of an elastase challenge rat model

RAT Elast. RARα RARβ RARγ

Lung Veh

*** 2 U/g Elastase +/- 0.5 mg/ Kg retinoid**





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Stolk J et al, Eur Respir J 2012; 40: 306–312

How do we know if those trials REALLY failed?

Outcome

What the trial is measuring
(e.g. lung function)

Endpoint

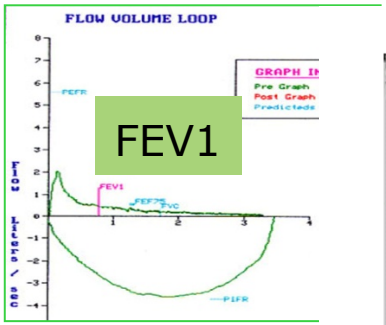
How it is measured
(e.g. FEV1)

- *"Ideally a trial would have an objective or 'hard' endpoint such as mortality, the complete disappearance of a tumor or no trace of infection in a sample"*
- To detect a 40% reduction in mortality in 5 years, **684** α1-antitrypsin deficient individuals with FEV1 35%–49% predicted would need to be recruited **over a 2-year** period *(Schluchter MD, Am J Respir Crit Care Med. 2000)*
- Surrogate endpoints are those that measure e.g. function, QoL, etc.
- Important that the surrogate endpoints reflect the disease and its natural history

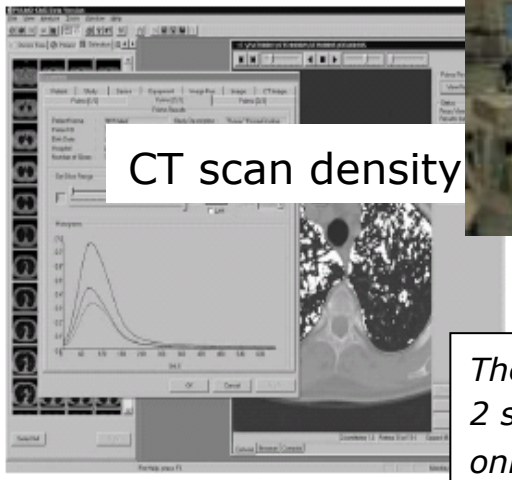
Drug	Trial acronym	Year	Study duration weeks	Subjects n	Primary end-point	Result
Interferon-γ		2004	58	330	PFS	No effect [28]
Pirfenidone		2005	36	107	Change in lowest 6MWD SpO_2	Reduced acute exacerbations [27]
Warfarin		2005	57#	56	Survival time	Improved survival [30]
***N*-acetylcysteine**					Change in VC	Reduced progression [29]
Bosentan					Change in 6MWD	No effect [35]
Etanercept					Change in FVC and *D*LCO	No effect [31]
Interferon-γ					Survival time	No effect [32]
Pirfenidone					Change in VC	Reduced progression [34]
Imatinib					Time to disease progression	No effect [33]
Sildenafil					>20% increase in 6MWD	No effect [46]
Bosentan					Time to IPF worsening	No effect [47]
Pirfenidone					Change in % pred FVC	Reduced progression [36]
Nintedanib (BIBF1120)					Rate of FVC decline	Trend to reduced progression [48]
Prednisolone+ azathioprine					Change in FVC	Increased mortality [49]
Warfarin					PFS	Increased adverse events [50]
Thalidomide		2012	24	24	Cough questionnaire	Reduced cough [51]
Ambrisentan	ARTEMIS	2013	35#	492	Time to disease progression	No effect [52]
Septrin	TUPAC	2013	52	118	Change in FVC	No effect [53]

PFS: progression-free survival; 6MWD: 6-min walking distance; SpO_2: arterial oxygen saturation measured by pulse oximetry; VC: vital capacity; FVC: forced vital capacity; *D*LCO: diffusing capacity of the lung for carbon monoxide. #: median follow-up.

Which endpoints for AATD?



FEV1



CT scan density

TLCO, Ventilation inhomogeneity

AAT levels (e.g. gene therapy)

6MWT

Exacerbations?

SGRQ

Other PROs?

Mortality?

The overall results of the combined analysis of 2 separate trials of comparable design, and the only 2 controlled clinical trials completed to date, has confirmed that IV AAT augmentation therapy significantly reduces the decline in lung density (Stockley RA et al, 2010)

Cochrane review from 2010 conclude on no certainty on efficacy

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Trial designs

- Replacement therapy IV 60 mg/kg/week based on "protective" threshold of 80 mg/dL (patients with heterozygous phenotypes whose levels of α1-antitrypsin exceed this level do not usually develop lung disease.

  ⇨ How do we know if this is really the protective dose?

- Slow decliners/worsening vs. fast decliners/ worsening:

  ⇨ How do we know which ones we are studying?

- Lack of significant changes at CT scan in most studies

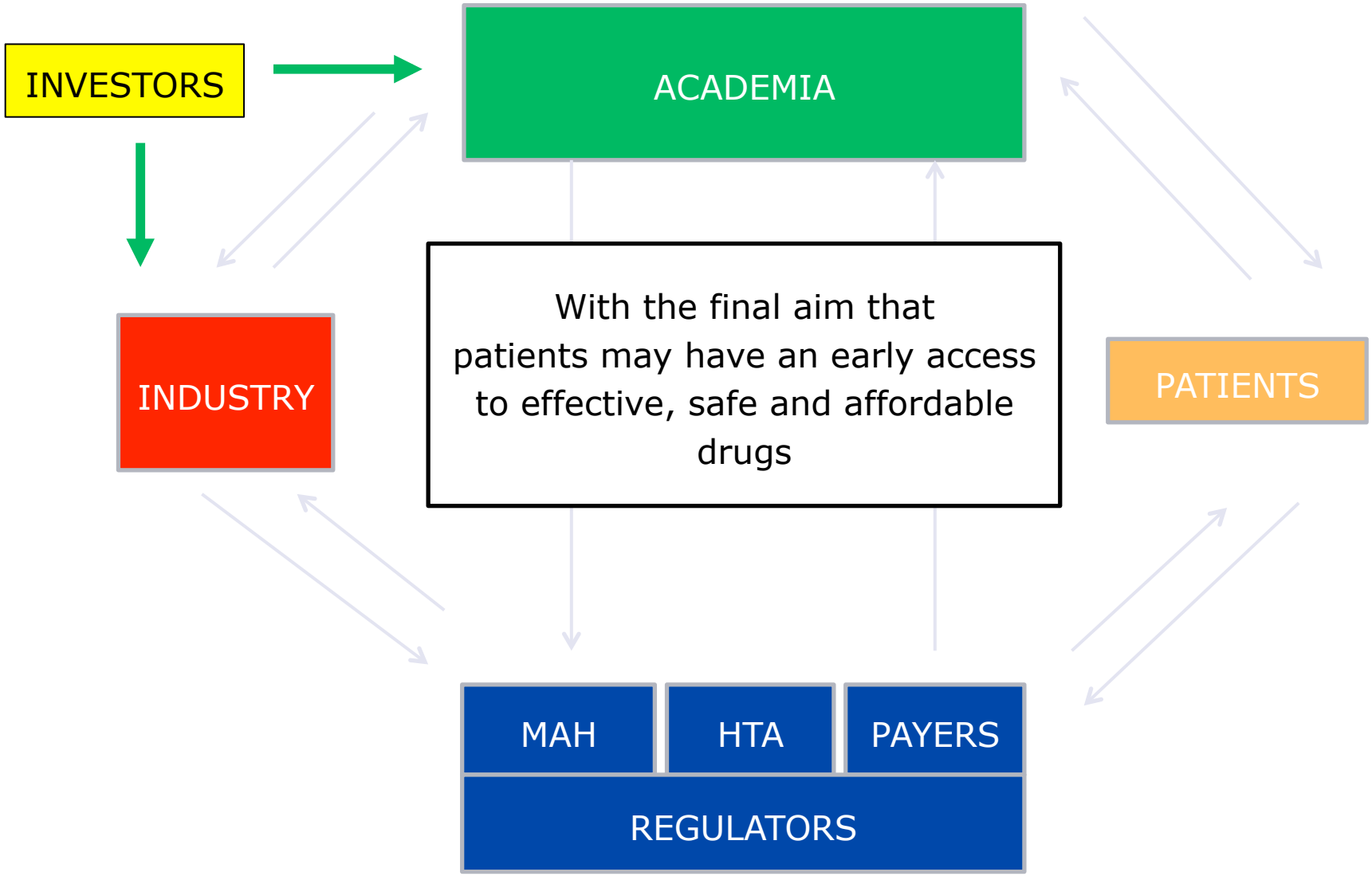
  ⇨ Observation period: how long is long enough?

- Which endpoint and design for which therapeutic indication/product? (e.g. gene therapy, regeneration/stem cells)

The regulatory pathway in the EU

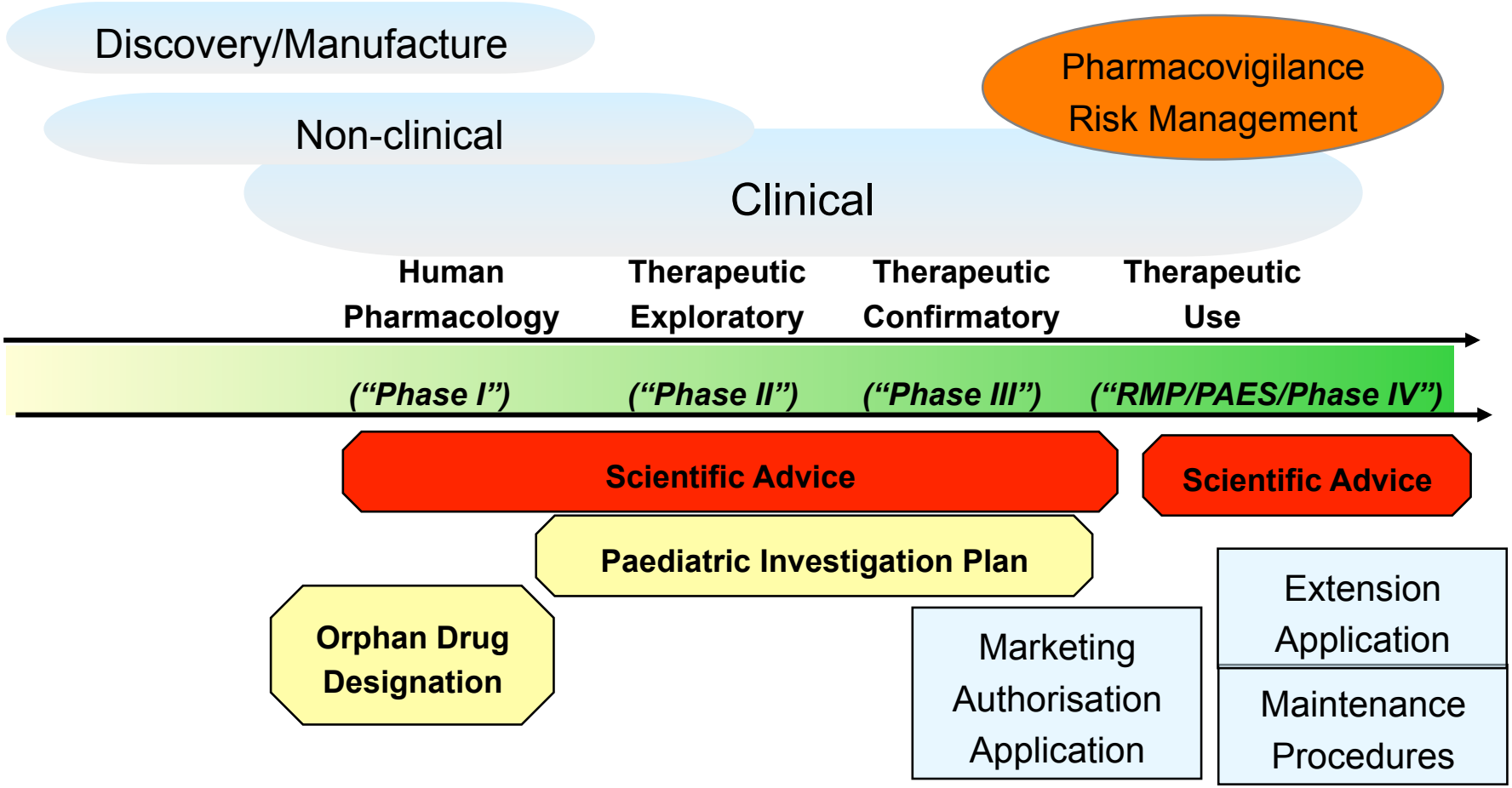
"The areas of science used in the assessment of quality, safety and efficacy of human and veterinary medicines throughout their life-span"

"..basic and applied biomedical sciences (genetics, pharmacology, biostatistics, …), social sciences such as decision sciences, risk assessment and communication sciences…"


INVESTORS
ACADEMIA
INDUSTRY
With the final aim that patients may have an early access to effective, safe and affordable drugs
PATIENTS
MAH
HTA
PAYERS
REGULATORS

EUROPEAN MEDICINES AGENCY

Drug development in the centralized EU regulatory system



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The Committee for Orphan Medicinal products (COMP)

- 1 member per each of 28 Member States
- 3 members representing patients' organisations
- 3 members nominated by the European Commission
- 1 member nominated by Iceland and one by Norway.

- Decides on orphan status at early development stage and on its confirmation when a medicine reaches marketing authorization
- Patients inputs in e.g. deciding on advantages of new formulations and administration routes, among others

Orphan Status

Early development phases

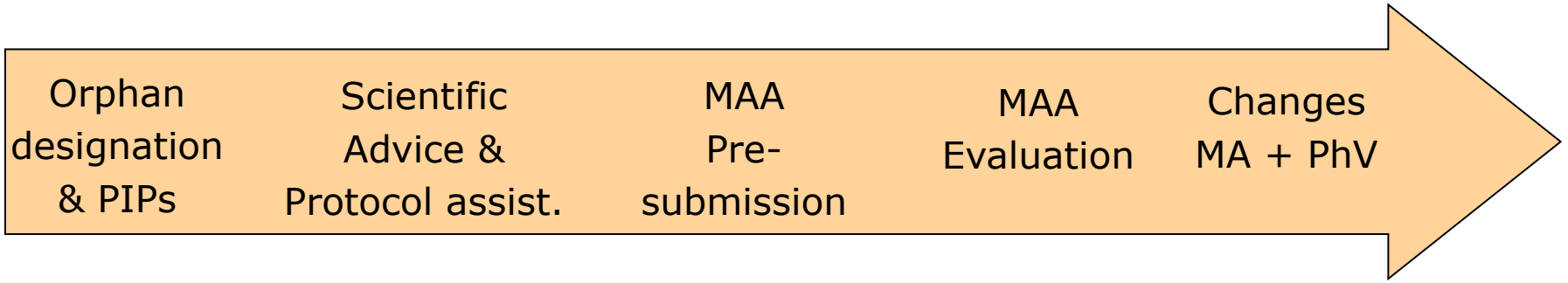
- Proof of concept
- Prevalence criterion
- Serious (life-threatening and or chronically debilitating)
- Significant benefit (EMA only)

Gives access to incentives

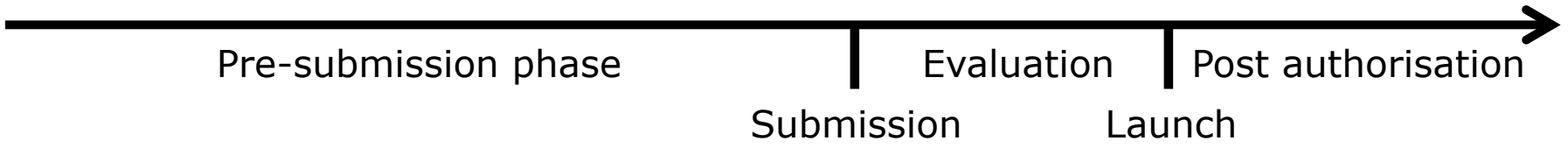
- 10 years market exclusivity
- EU and national funding
- Data protection

Can be granted to companies or private citizens

EMA Committees (Human products)



Orphan designation & PIPs	Scientific Advice & Protocol assist.	MAA Pre-submission	MAA Evaluation	Changes MA + PhV
COMP	SAWP /CHMP	CHMP	CHMP	CHMP
PDCO	CAT	PDCO	CAT	PRAC
	HMPC		PDCO	CAT
			PRAC	COMP
			COMP	PDCO

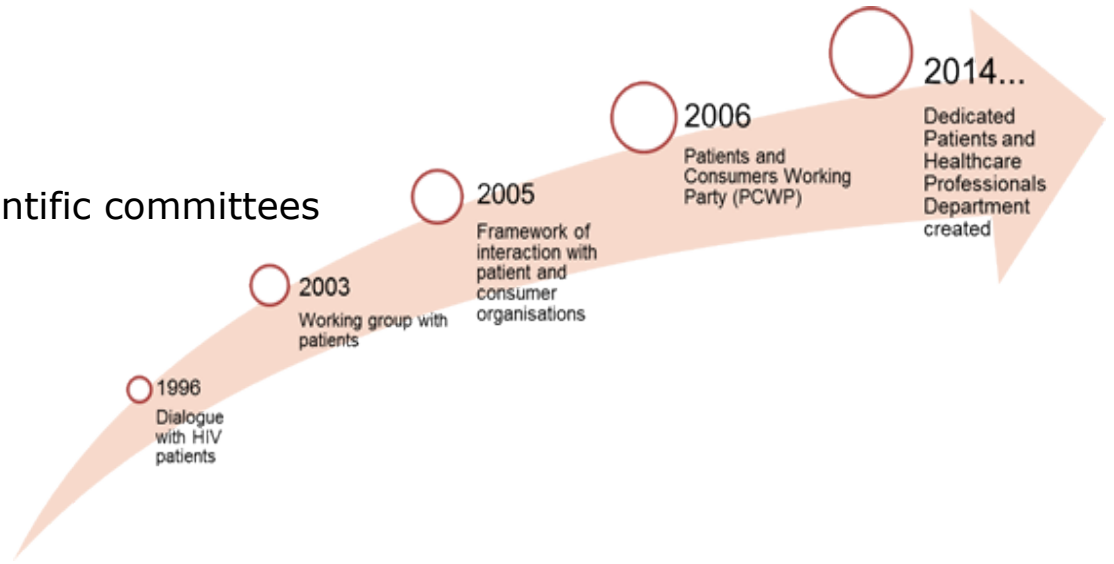


PCWP

Since 2006, the Agency has had a permanent Patients' and Consumers' Working Party (PCWP) in place, to provide advice to the Agency and its scientific committees on matters of direct and indirect interest to patients in relation to medicines

Three main areas:

- transparency and communication;
- safety of medicines;
- involvement with EMA and its scientific committees regarding medicines evaluation



How do we assess medicines?

QSE
Quality
Safety
Efficacy

- Clinical Evaluation
- Non-clinical Evaluation
- Quality Evaluation

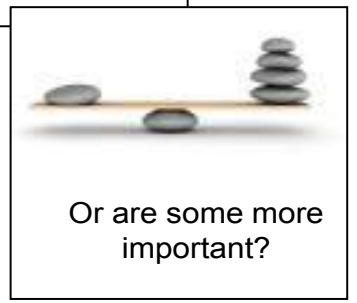
Decision on benefit-risk balance

- Regulatory Decision – Market approval and post-market commitments

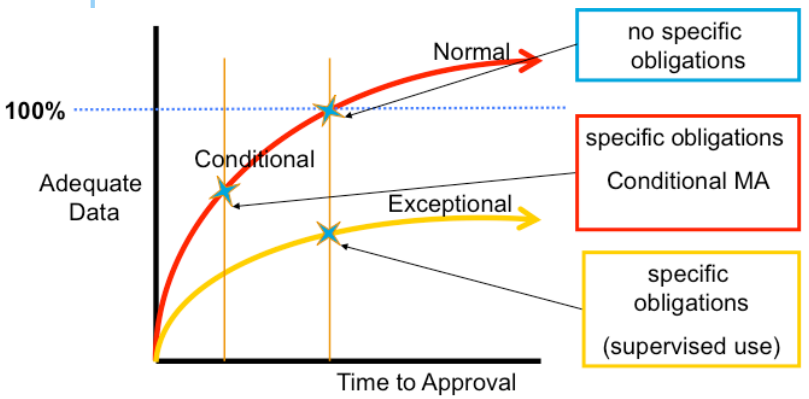
Benefit-risk assessment

- Evaluator's recommendation
- Peer review
- Expert opinions/ Consultations
- Medical / Scientific Advisory
- Dialogues with applicants

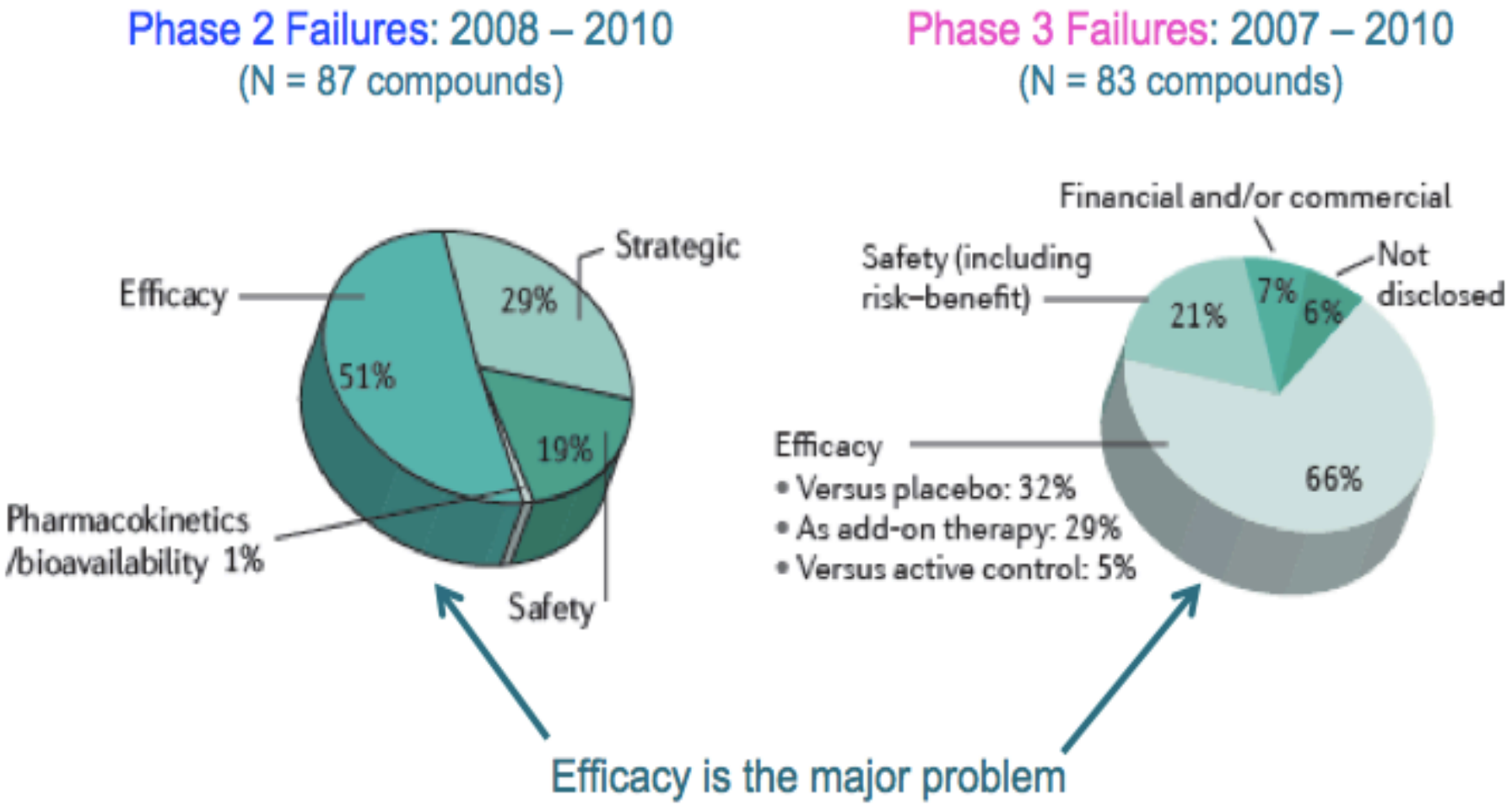
Is everything equal?



Or are some more important?

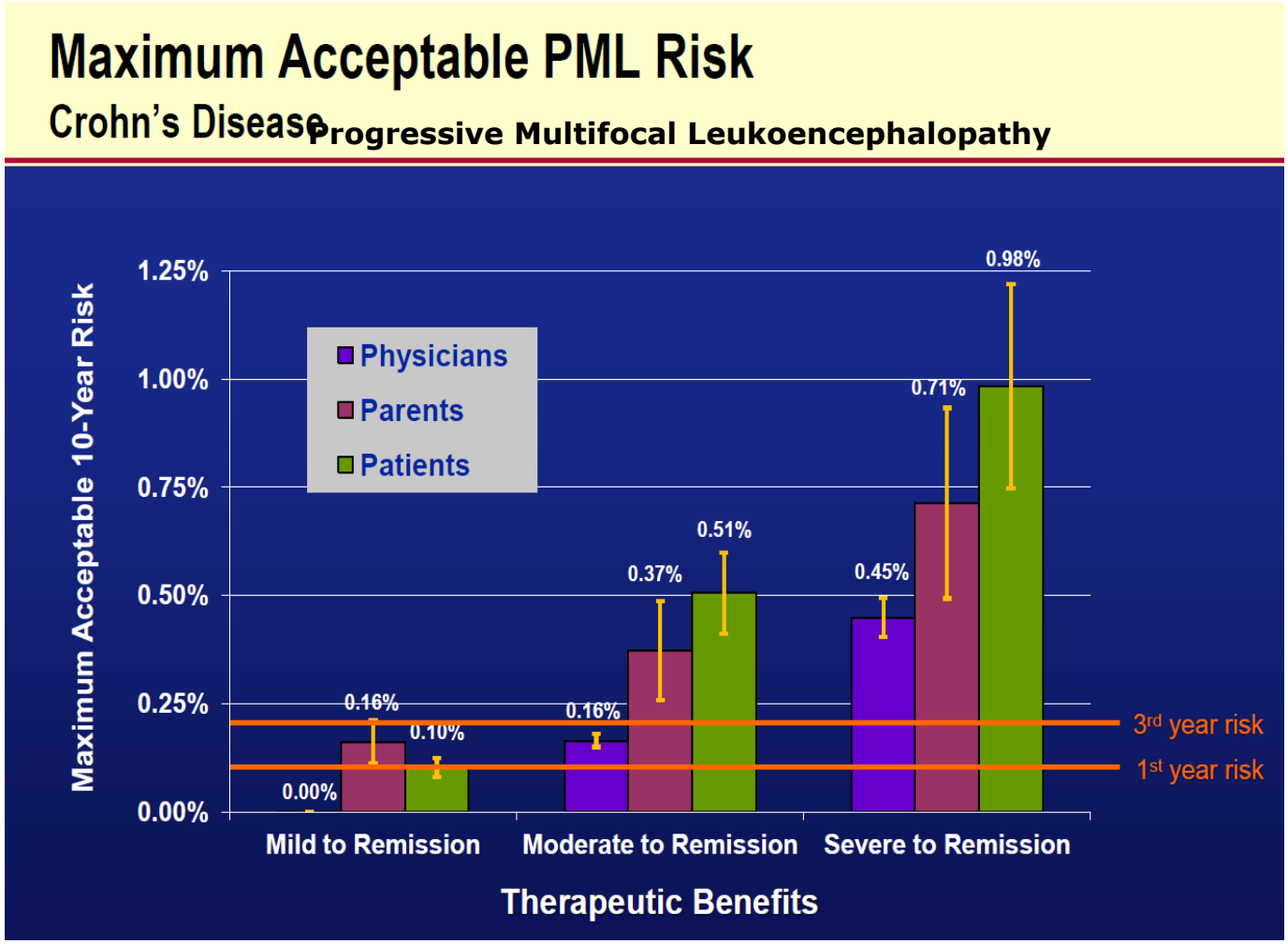


Areas of failure



Arrowsmith J. Nat Rev Drug Discov 2011;10:82 and 328

The patient's voice on benefit/risk



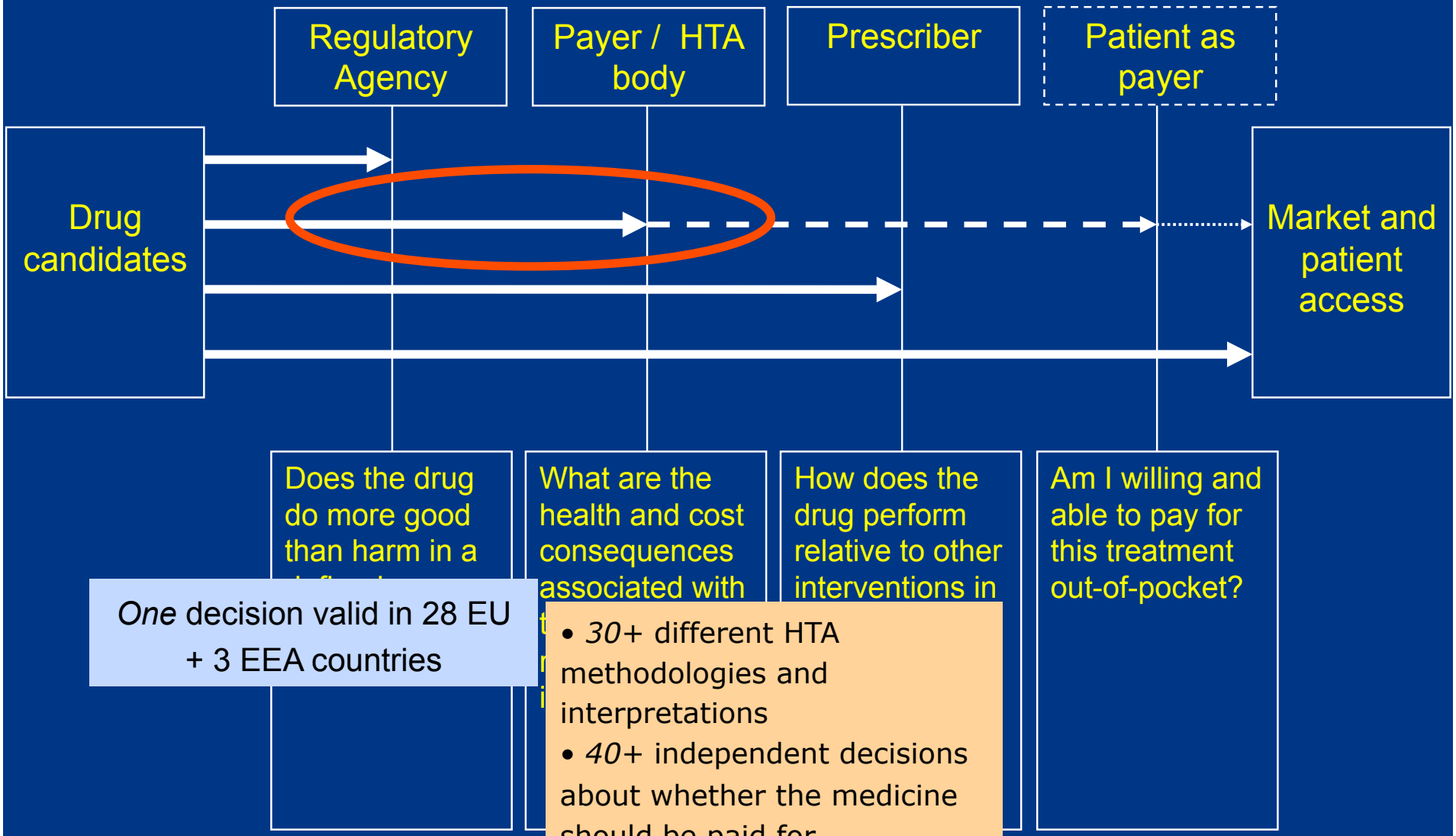
What comes out of the assessment

- Medicine licensed for a specific **therapeutic indication** within the patient population
  - Depends on the trial (e.g. vs. placebo, add-on, resistance to existing treatments)
  - Positive Risk/benefit ration cannot necessarily be extrapolated to different populations with the same disease (e.g. different age)
- Warnings and description of side effects
- Risk management measures

The Problem of comparative effectiveness

Comparative effectiveness research is the generation and synthesis of evidence that compares the benefits and harms of alternative methods to prevent, diagnose, treat, and monitor a clinical condition or to improve the delivery of care

Decision makers on the road to market access



One decision valid in 28 EU + 3 EEA countries

- *30+* different HTA methodologies and interpretations
- *40+* independent decisions about whether the medicine should be paid for

Nature Rev Drug Disc, 2010

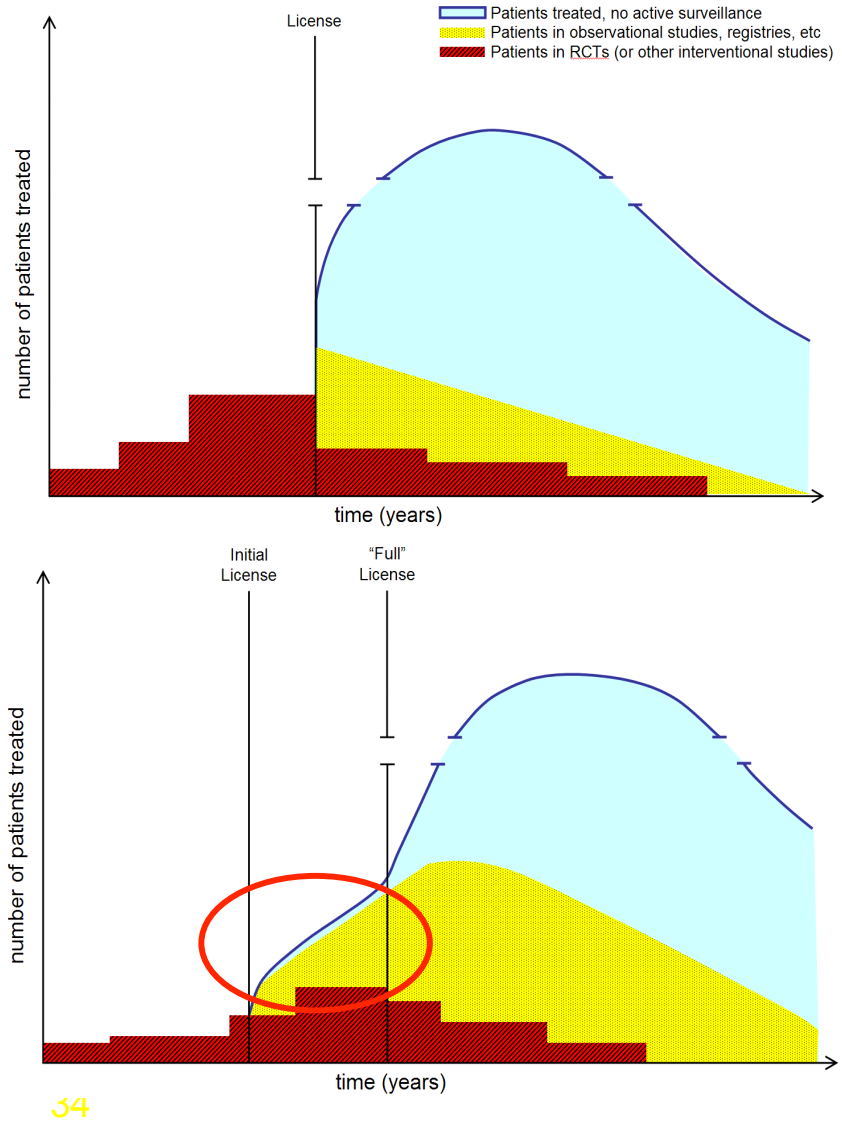
EMA initiatives helping innovative products

- Reinforce relationships and support to Academia and SME
- New EU clinical trial regulation
- Guidelines (for biologics, biosimilars, clinical trials, etc)
- Scientific advice
- Medicines Adaptive Pathways to the Patients

  - Accelerated MA for innovative orphan drugs
  - Early HTA
  - Adaptive licensing

- Open data, access to documents

Adaptive Licensing (pilot, EU)



Current scenario:

Post-licensing, treatment population grows rapidly; treatment experience does not contribute to evidence generation

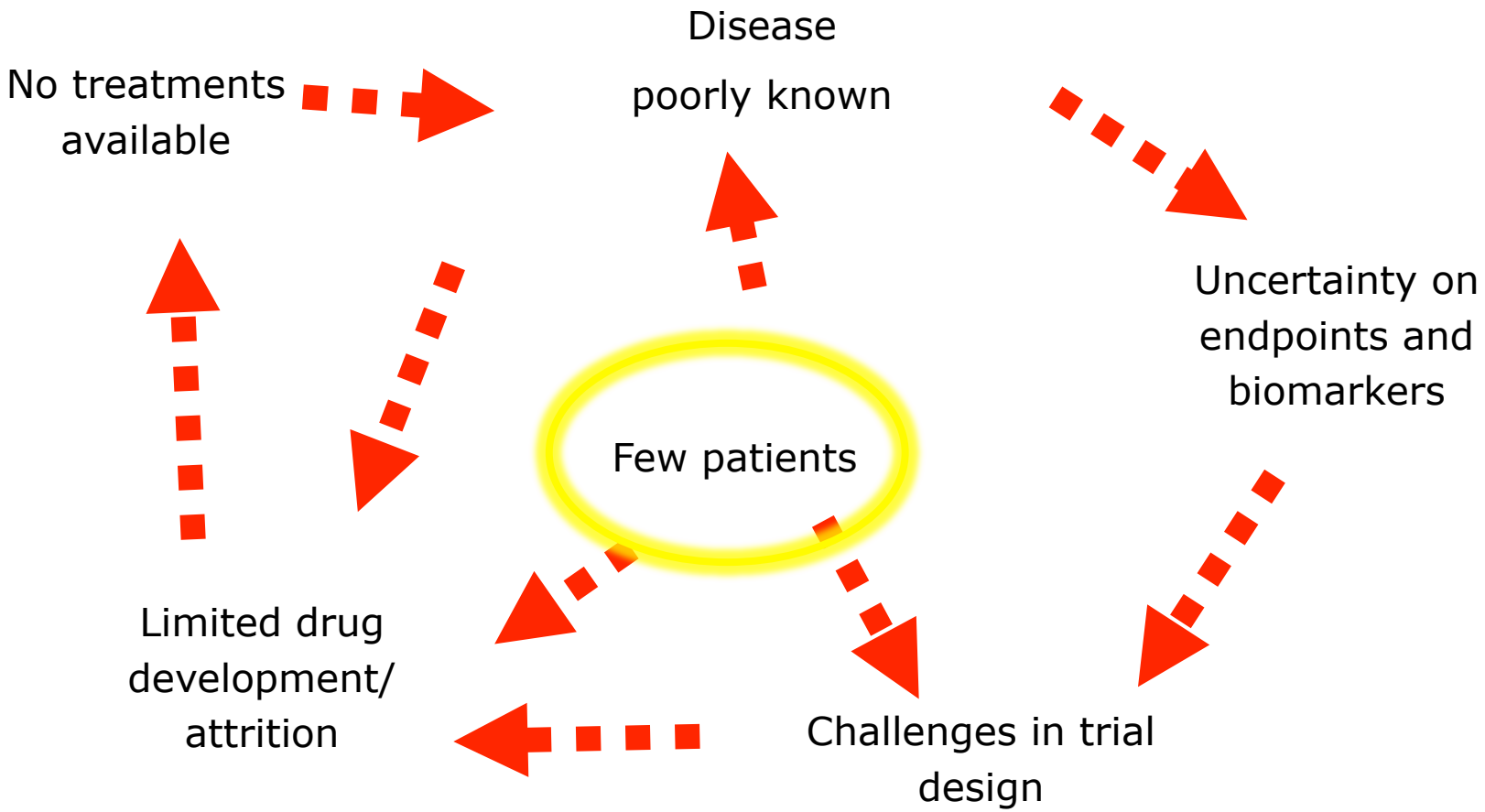
Adaptive Licensing:

after initial license, number of treated patients grows more slowly, due to restrictions;

patient experience is captured to contribute to real-world information

Where to?

Rare Catch 22

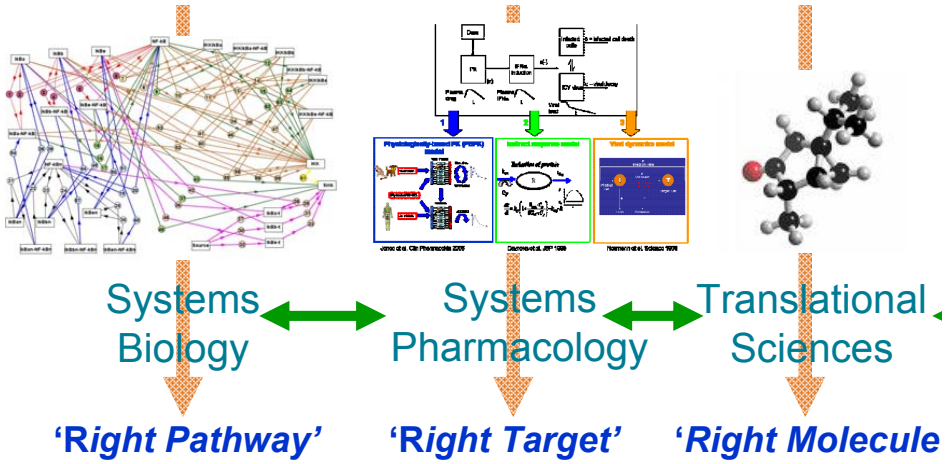


Some actions

- Stimulate companies to early dialogue with regulators on innovative products (gene therapy, oligonucleotides, etc)
- Help and promote the study of phenotypes/different forms of the disease (registries)
- Participate in discussion and creation of endpoints (e.g. patient reported outcomes, discussions on CT scan)
- Stimulate scientific community to consistency in trial design
- Stimulate real-life studies for comparative effectiveness!!
- Participate in development of treatments for COPD in general

The right medicines for the right disease

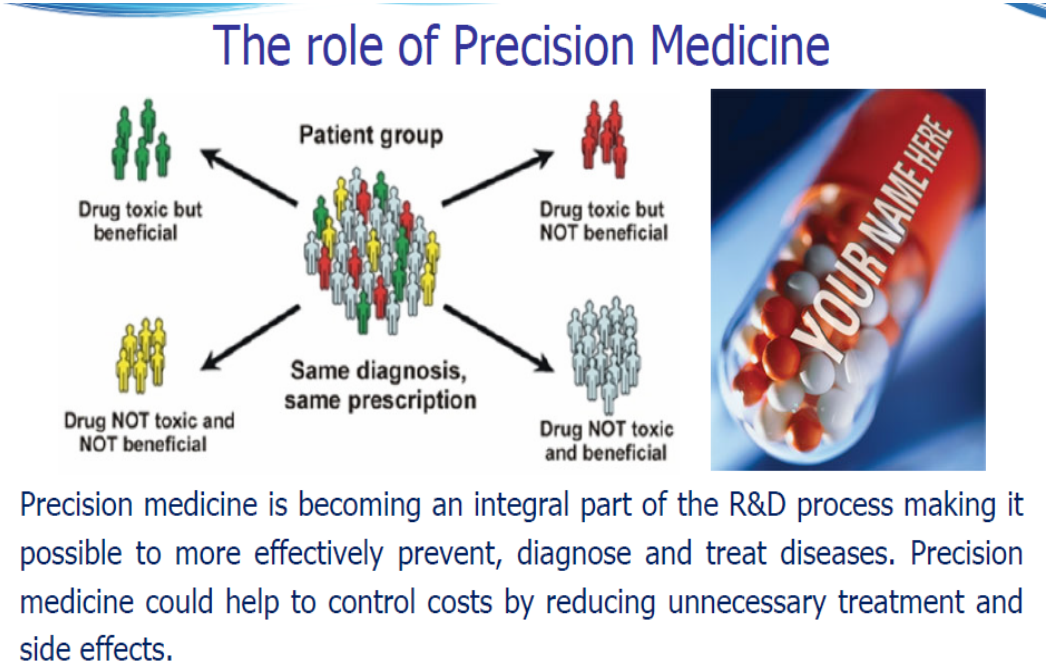
- Good knowledge of a disease together with coherent work on preclinical and clinical data can improve medicines development



- negative studies, translatability relative to potential therapeutic use, identification of phenotypes, standardization of endpoints, etc.

Clinical research and real-life effectiveness

- *Identification of responder's phenotypes---*risk to reduce even more population size for establishing efficacy/effective*ness*



"Real life" effectiveness studies --- also allowing impact of non-drug interventions (e.g. lung disease)

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Thank you
for your attention

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