

# Prospective Workshop

Essec Santé – Centrale Santé

“Will the Pharma « bubble » collapse within 3 years?”

Analysis of pharmaceutical research and development  
What slows R&D productivity ?

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Research, Statitec

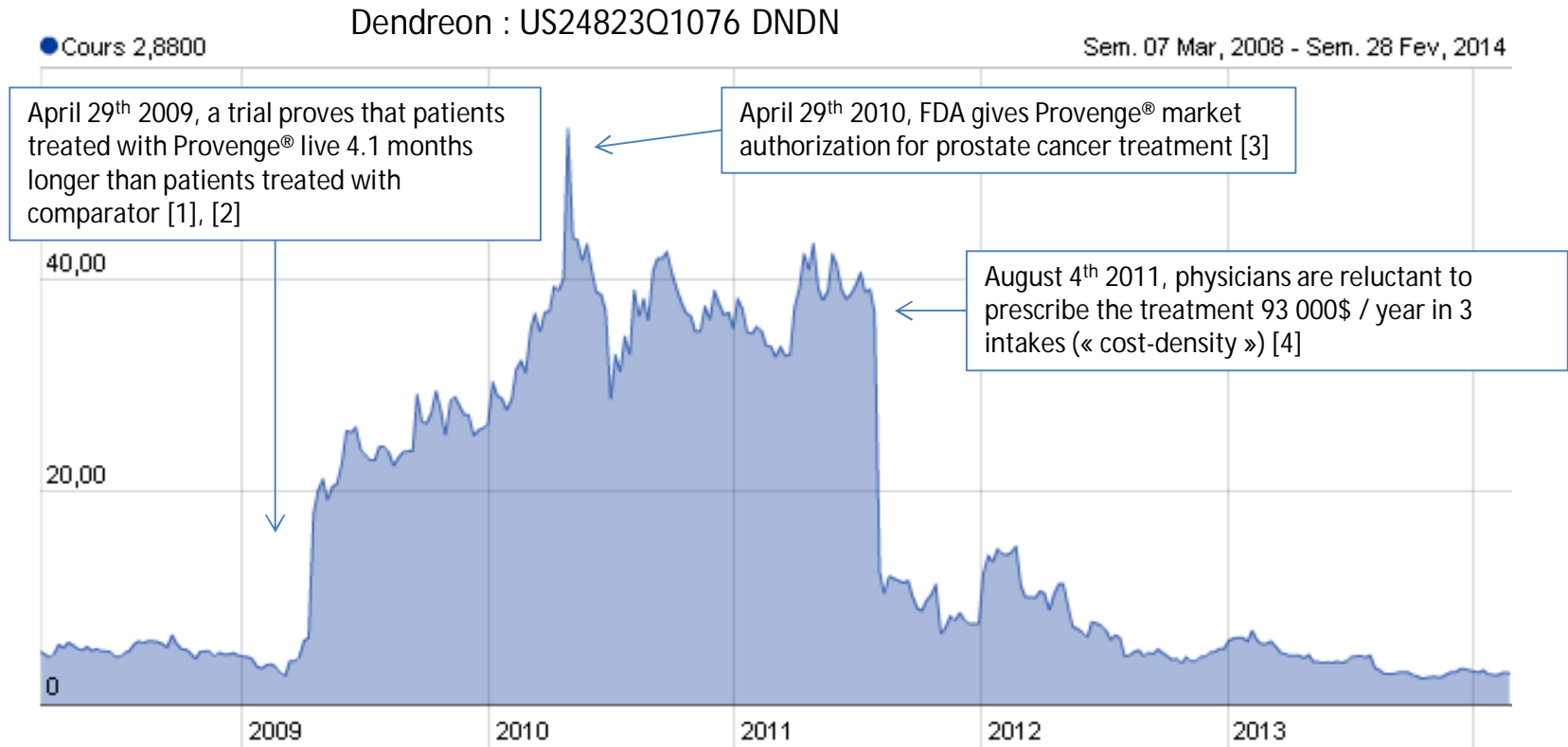
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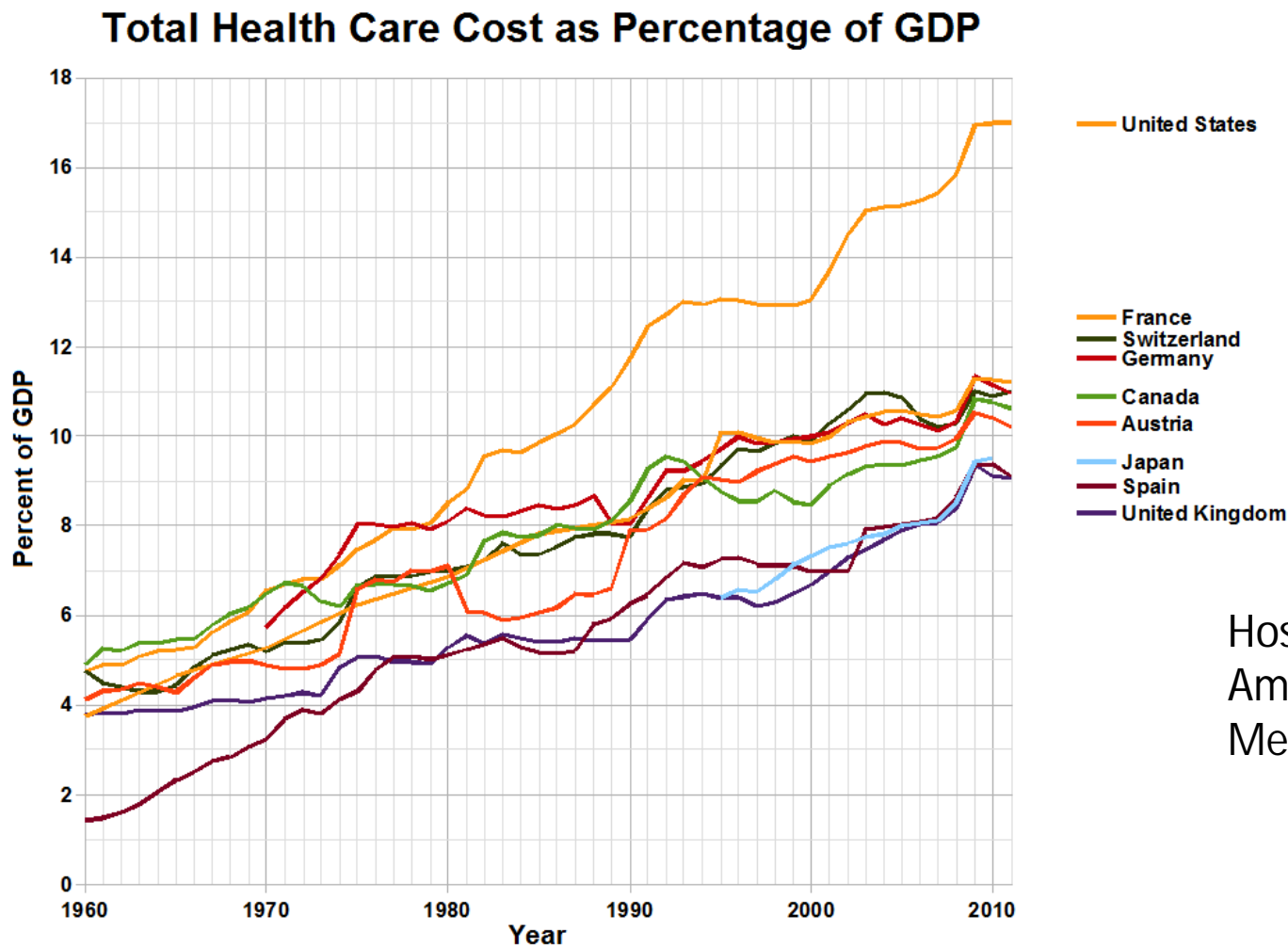
# Bubble ?



Sources: [1] Higano, C. S., Schellhammer, P. F., Small, E. J., Burch, P. A., Nemunaitis, J., Yuh, L., ... & Frohlich, M. W. (2009). Integrated data from 2 randomized, double-blind, placebo-controlled, phase 3 trials of active cellular immunotherapy with sipuleucel-T in advanced prostate cancer. *Cancer*, [link](#); [2] Kantoff PW, Higano CS, Shore ND, et al. Sipuleucel-T immunotherapy for castration-resistant prostate cancer. *N Engl J Med* 2010; [link](#); [3] Food and Drug Administration. Summary review — summary basis for regulatory action: sipuleucel-T (Provenge). April 29, 2010. [link](#); [4] WSJ health blog [link](#)

1. Context
2. R&D productivity
3. Improvement strategies
4. Horizon

# Healthcare expenses have constantly increased over the past 50 years

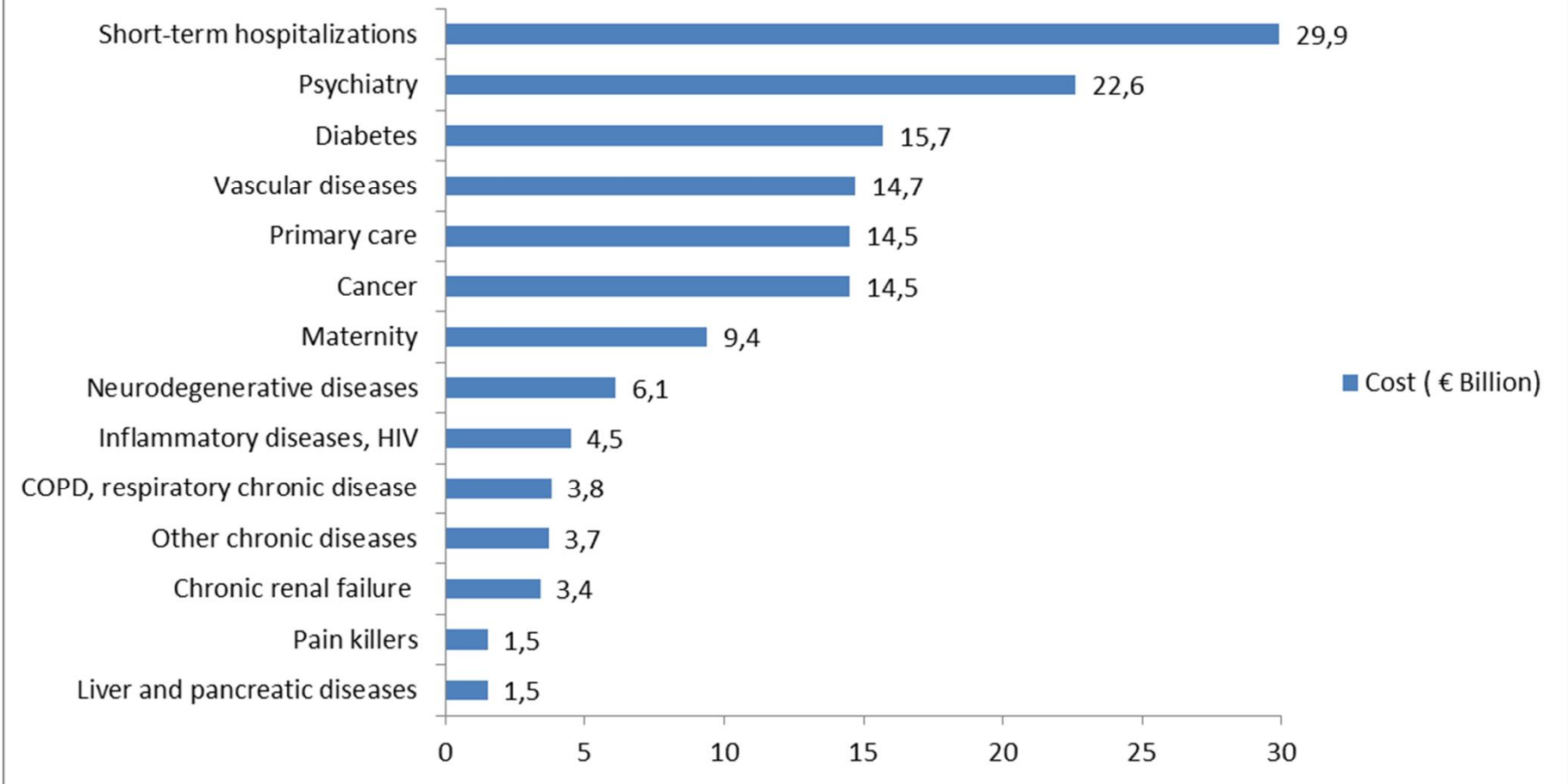


Hospitalization : 44 %  
Ambulatory care: 30 %  
Medical goods: 26 %

Source: OECD 2011

# € 146 billions have been spent in 2011 in France

## Healthcare expenditure by disease ( € Billion)

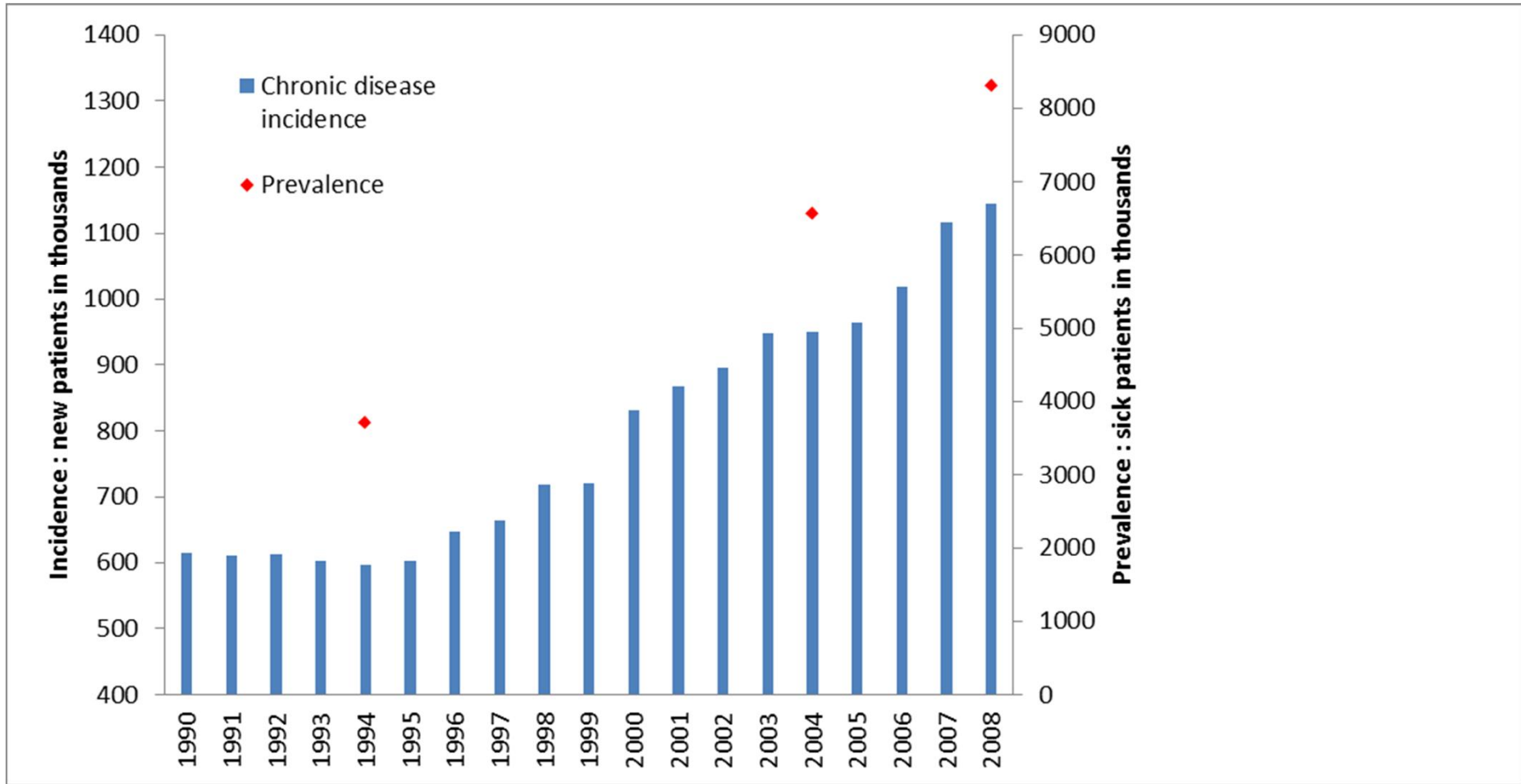


Source : CNAMTS Rapport Charges Produits 2014 [link](#)

# Chronic diseases represent a significant proportion of healthcare expenditure (2009 figures in France)

Code	Chronic disease	Frequency pro rata	Total expenses
30	Cancers	1 510 253	13 182 473 131
8	Type 1 & type 2 diabetes	1 379 516	8 228 278 081
23	Psychiatric chronic diseases	855 451	8 963 576 739
12	Hypertension	775 811	4 660 224 016
13	Coronary diseases	672 464	4 183 306 259
5	Severe vascular diseases	468 838	3 308 291 772
3	Arteriopathies with ischemia	294 937	2 181 704 105
14	COPD	232 054	1 742 853 731
1	Stroke	197 835	1 765 732 973
15	Alzheimer disease and dementia	181 745	1 479 453 954
9	Severe muscular and neurological disease (Myopathy), epilepsy	173 944	1 251 073 573
22	Severe progressive rheumatoid arthritis	141 338	930 402 050
6	Liver disease and cirrhosis	128 810	956 036 436
24	Crohn disease and ulcerative colitis	100 548	474 722 675
7	Immune deficit, HIV infection	84 989	1 100 059 269
19	Nephropathy	68 634	1 545 548 101
16	Parkinson disease	64 603	591 216 019
25	Multiple sclerosis	59 486	692 896 604
27	Spondylitis	58 747	316 966 411
21	Polyarteritis nodosa, Systemic lupus erythematosus, progressive systemic sclerosis	44 948	275 055 501
17	Inherited Metabolic Diseases requiring prolonged treatment specialist	39 091	277 632 138
20	Paraplegia	27 759	419 443 711
11	Haemophilia and serious constitutional disorders of hemostasis	20 152	394 801 176
26	Evolutionary structural scoliosis (whose angle is less than 25 °) until spinal maturation	18 036	52 839 890
10	Hemoglobinopathies, hemolysis	11 584	105 618 678
2	Bone marrow failure and other chronic cytopenias	9 545	178 584 302
29	Active tuberculosis and leprosy	8 021	50 856 034
18	Mucoviscidosis	5 194	116 618 234
28	Organ transplant follow-up	4 398	81 762 923
4	Complicated schistosomiasis	126	723 794
	Total patients suffering from chronic diseases (French ALD 30 classification)	7 638 856	59 508 752 282

... and the number of patients diagnosed with chronic diseases is raising



Source : Etude CNAMTS 1990-2008 [link](#)

# Regulatory constraints are more and more demanding

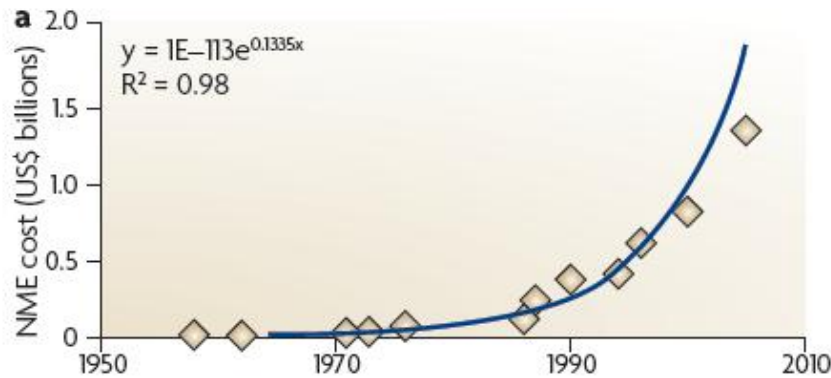
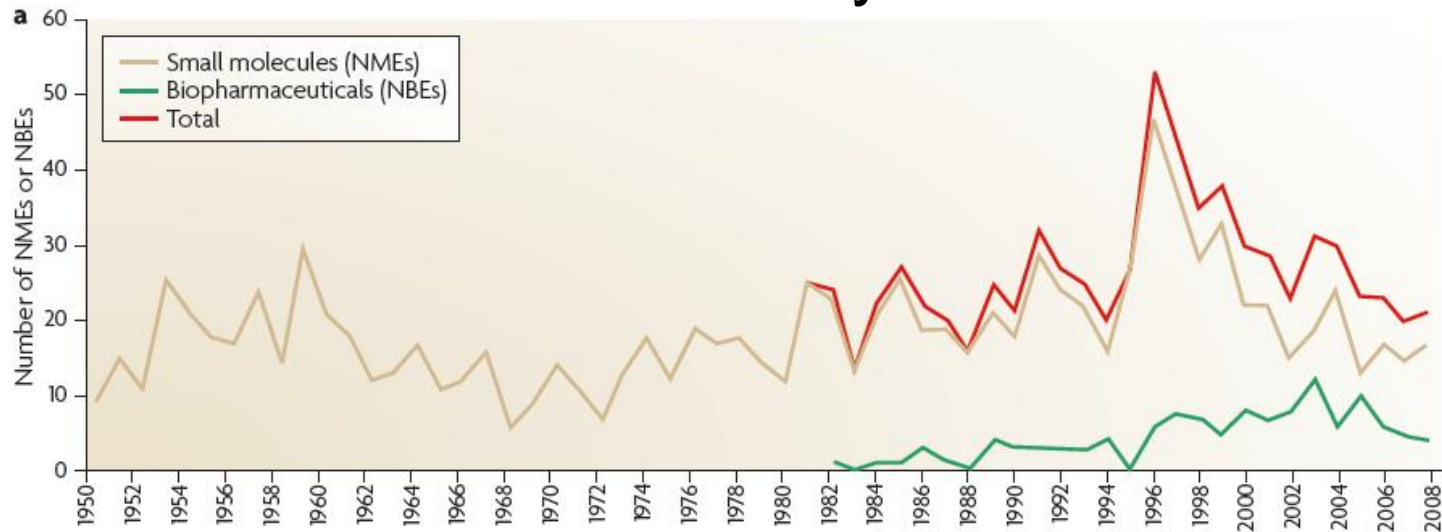
- ✓ 1990: evidence based medicine [1]
- ✓ 2010: value based medicine [2]
- ✓ 2014: evidence based policy [3]

Sources : [1] Sackett, D. L., Rosenberg, W. M., Gray, J. A., Haynes, R. B., & Richardson, W. S. (1996). *Evidence based medicine: what it is and what it isn't*. *BMJ: British Medical Journal*, 312(7023), 71. [link](#)  
[2] Porter, M. E. (2010). *What is value in health care?*. *New England Journal of Medicine*, 363(26), 2477-2481. [link](#) Annexes [link](#)  
[3] Mission Quinet, 2013, CGSP [link](#)



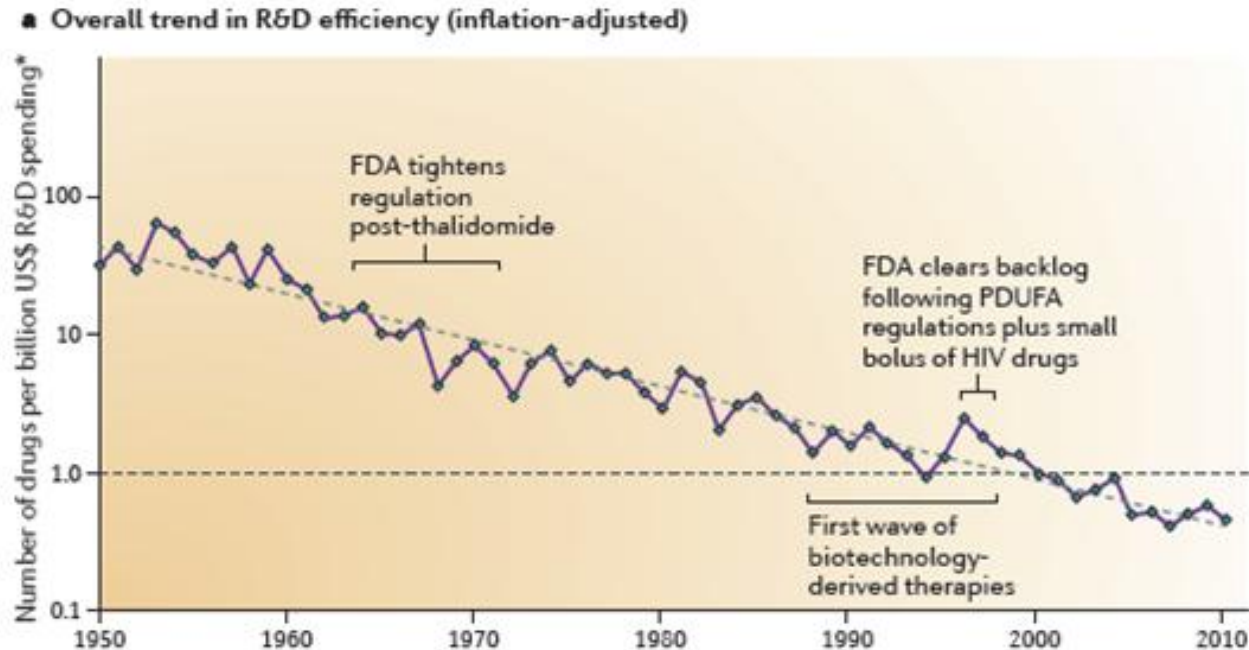
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The number of new molecular entities (NMEs) approved per year stays stable whereas investments have constantly increased



Source : Munos, B. (2009). Lessons from 60 years of pharmaceutical innovation. *Nature Reviews Drug Discovery*, 8(12), 959-968.

# Why do we see R&D productivity erosion ?



Is it because R&D is more expensive ?

Is it because R&D is less able to bring products to market authorization approval ?

Source : Scannell, J. W., Blanckley, A., Boldon, H., & Warrington, B. (2012). Diagnosing the decline in pharmaceutical R&D efficiency. *Nature reviews Drug discovery*,

# Phase-2 and phase-3 attrition rates are constantly increasing

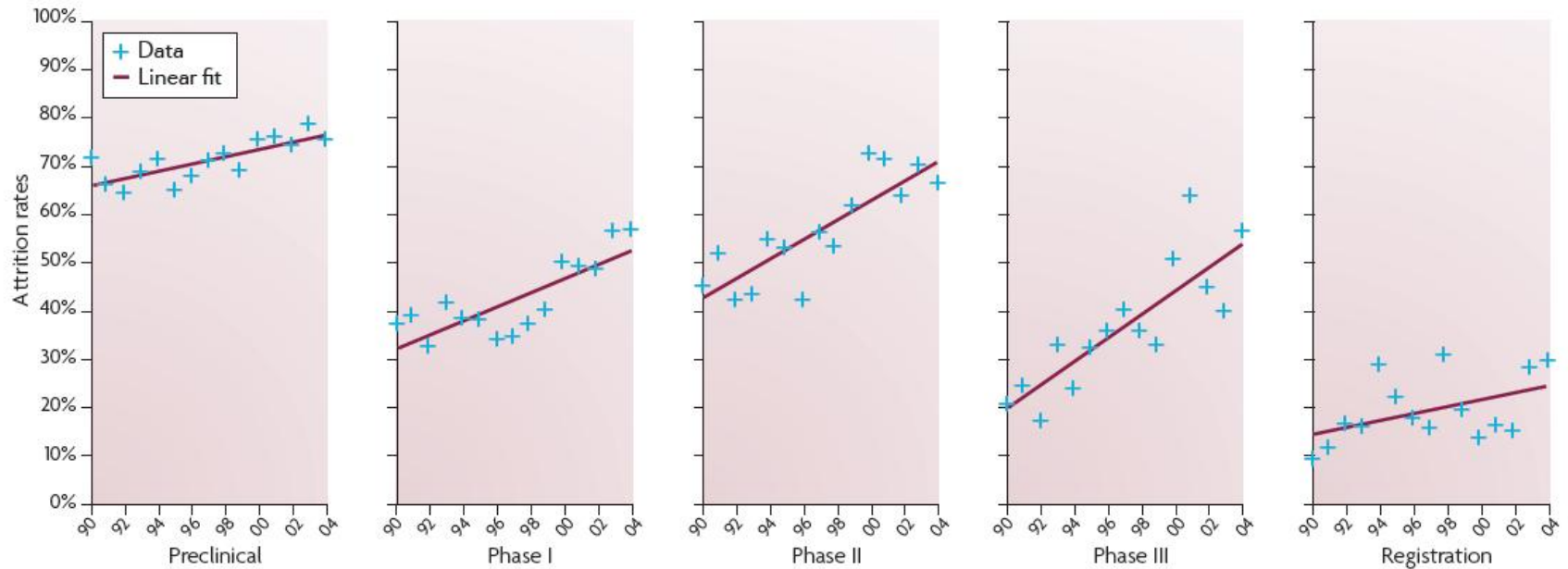
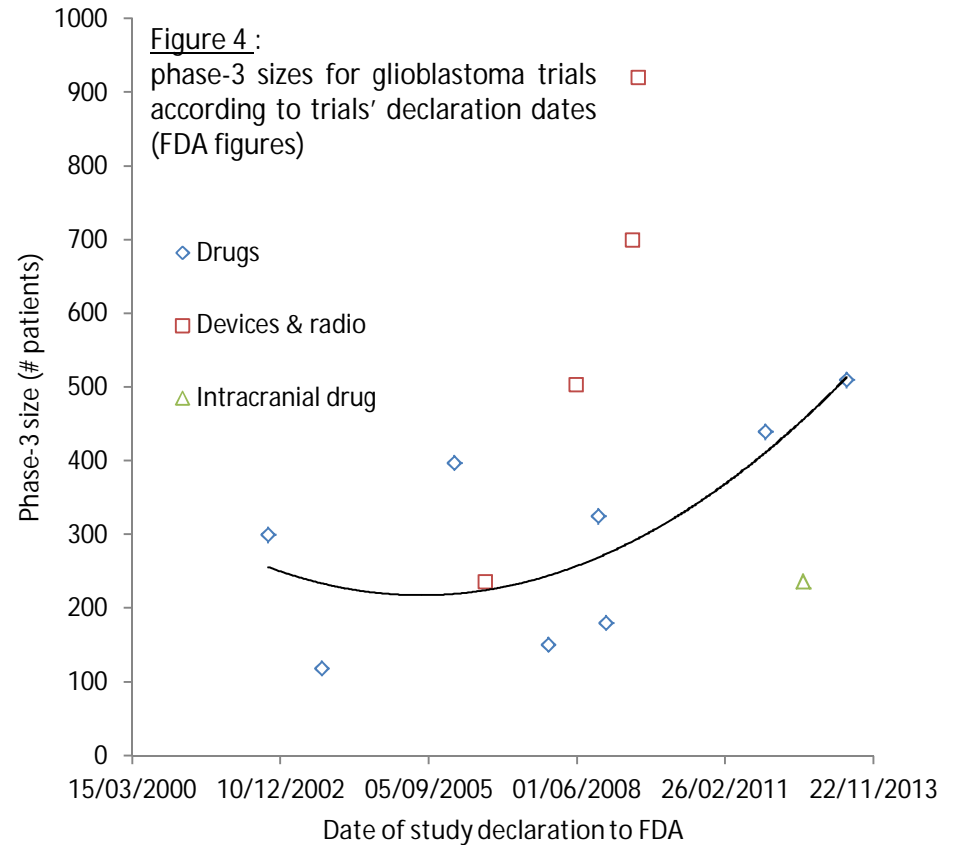
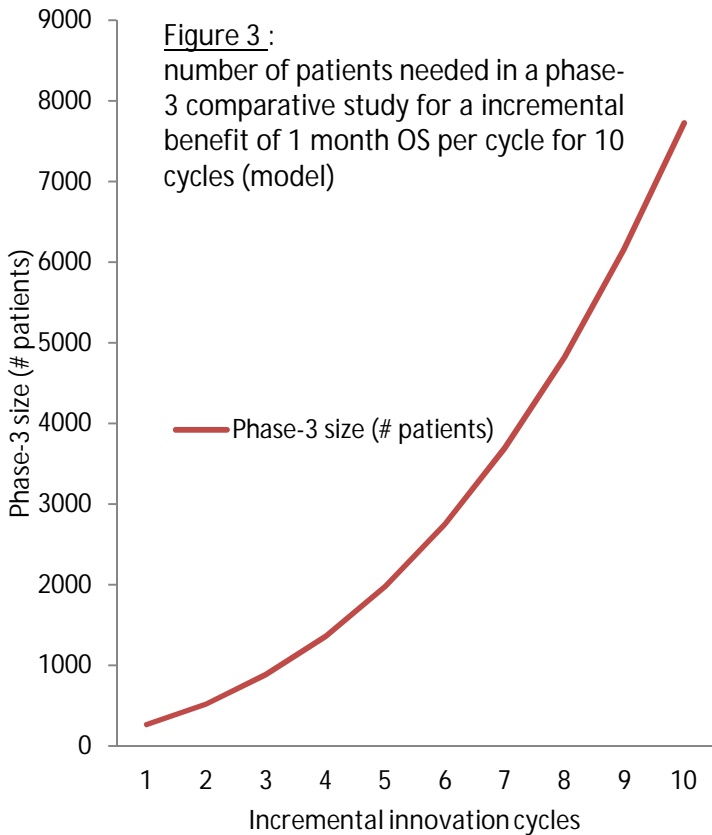


Figure 1 | **Trends in attrition rates of drug development projects.** Data are for projects started between 1990 and 2004 in the United States, Europe and Japan. Source: analysis of the Pharmaceutical Industry Database (BOX 1).

→ Success rates have decreased, suggesting that R&D is less able to bring products to market authorization approval

Source : Pammolli, F., Magazzini, L., & Riccaboni, M. (2011). *The productivity crisis in pharmaceutical R&D.* *Nature Reviews Drug Discovery*, 10(6), 428-438

# Incremental innovation leads to larger phase-3 to prove superior efficacy

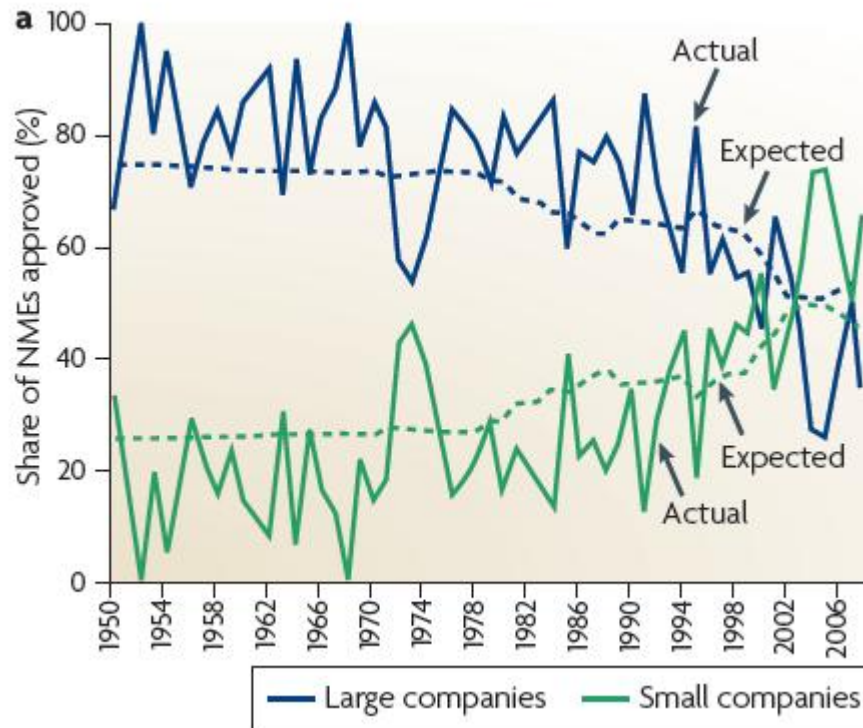


→ With a incremental innovation dynamic, regulatory constraints leads to more expensive research with greater chances of failure

Source : STATITEC, ad hoc research and simulation  
Data from [www.clinicaltrials.gov/](http://www.clinicaltrials.gov/)

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# Solution 1: the innovation network



- Small companies are more efficient in terms of R&D productivity
- R&D efficiency might be improved by involving small companies in the development process

Source : Munos, B. (2009). Lessons from 60 years of pharmaceutical innovation. *Nature Reviews Drug Discovery*, 8(12), 959-968.

# Solution 2: early selection

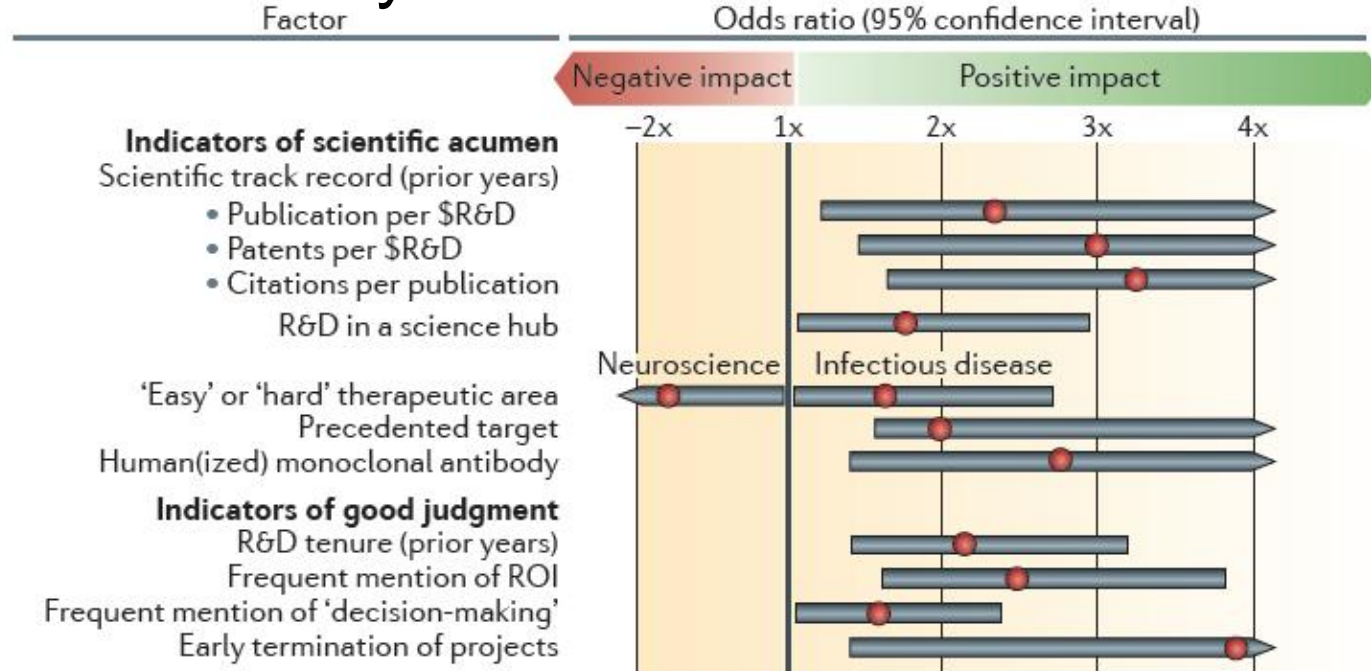


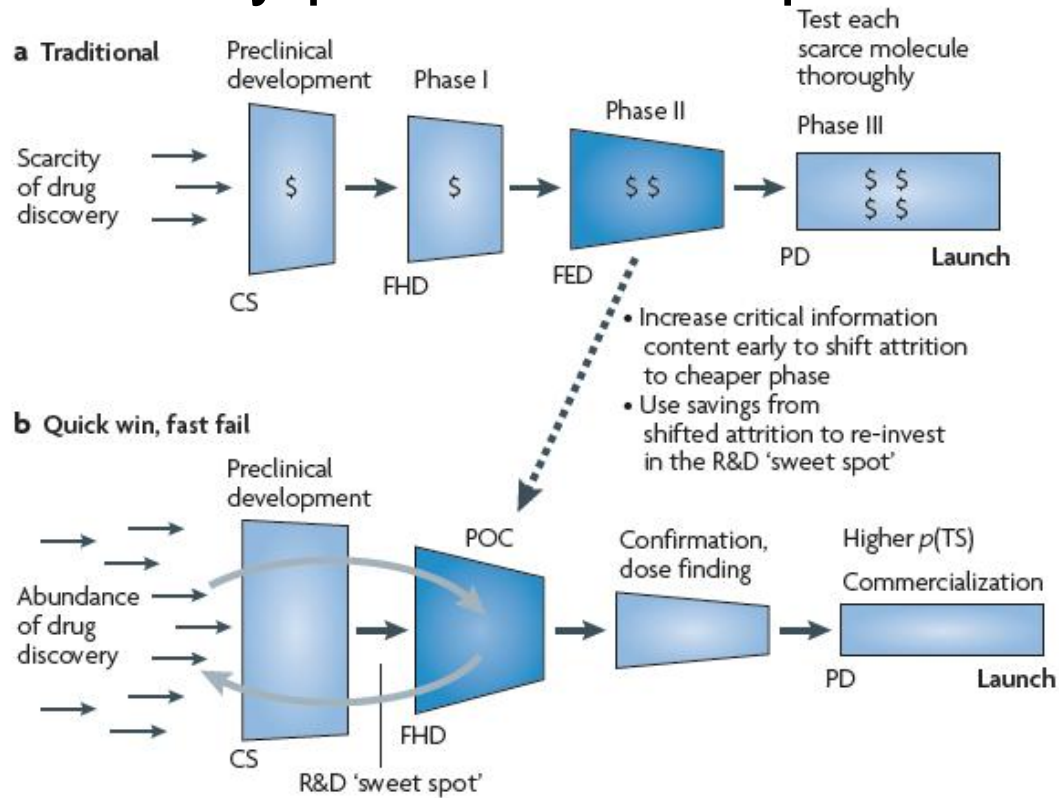
Figure 2 | **Factors correlated with success or failure in drug development.** These factors (laid out as in FIG. 1) have a statistically significant relationship with success or failure in our data set of 842 molecules. For details of the data set and analysis, see Supplementary information S1 (box). R&D, research and development; ROI, return on investment.

- Early termination of projects has a positive impact on R&D productivity
- Mastering this steering process would increase R&D productivity

Source : Ringel, M., Tollman, P., Hersch, G., & Schulze, U. (2013). Does size matter in R&D productivity? If not, what does?. *Nature Reviews Drug Discovery*.



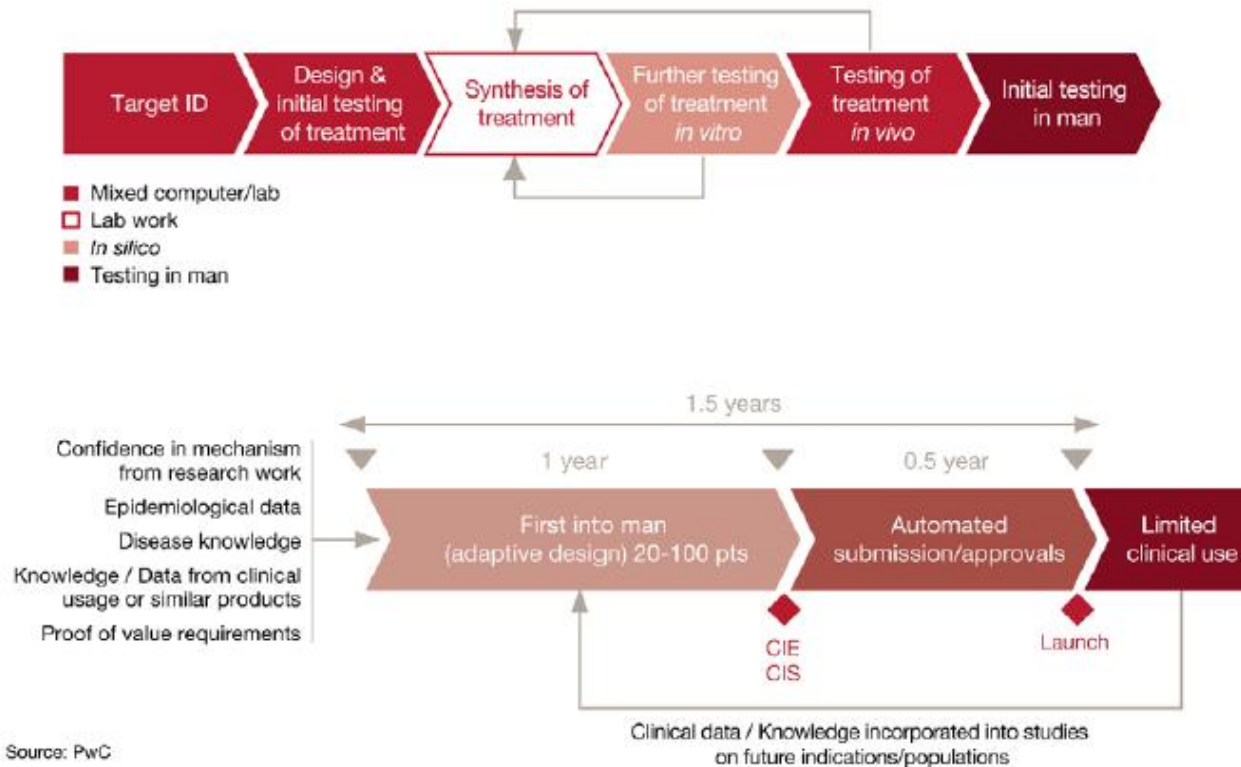
# Solution 3: early proof of concept



→ Performing multi-indication Proof Of Concept (POC) with predefined doses in preclinic would shorten drug development process

Source : Paul, S. M., Mytelka, D. S., Dunwiddie, C. T., Persinger, C. C., Munos, B. H., Lindborg, S. R., & Schacht, A. L. (2010). How to improve R&D productivity: the pharmaceutical industry's grand challenge. *Nature reviews Drug discovery*, 9(3), 203-214.

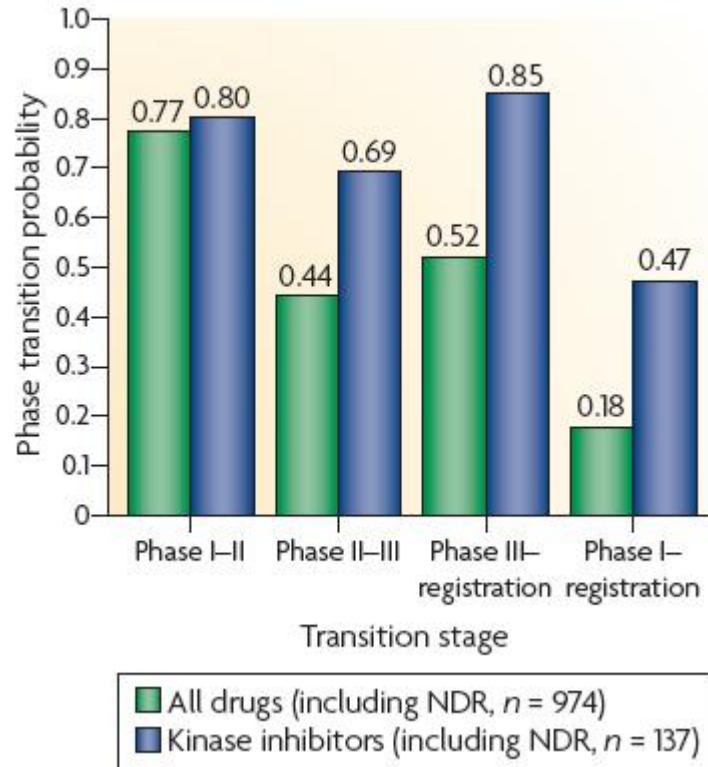
# Solution 4: regulatory process shortcut (virtual R&D)



→ Previous research use (thesaurus, modeling) would permit to reduce pre-clinical development cycle.

Sources: PriceWaterhouseCoopers, *Pharma 2020: Virtual R&D – Which path will you take?*, 2008.  
PriceWaterhouseCoopers, *Introducing the Pharma 2020 Series*, 2011.

# Solution 5: biomarker use



974 innovative cancer drugs analyzed ([link](#)) from Jan 1995 to Sept 2007:

- Global success rate 18%
- Success rate for kinase with diagnostic biomarker 47%

NDR : *No Development Reported*

→ Use of biomarker improves the success rate of drug development in oncology

Source : Walker, I., & Newell, H. (2008). Do molecularly targeted agents in oncology have reduced attrition rates?. *Nature reviews Drug discovery*, 8(1), 15-16.

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# Horizon

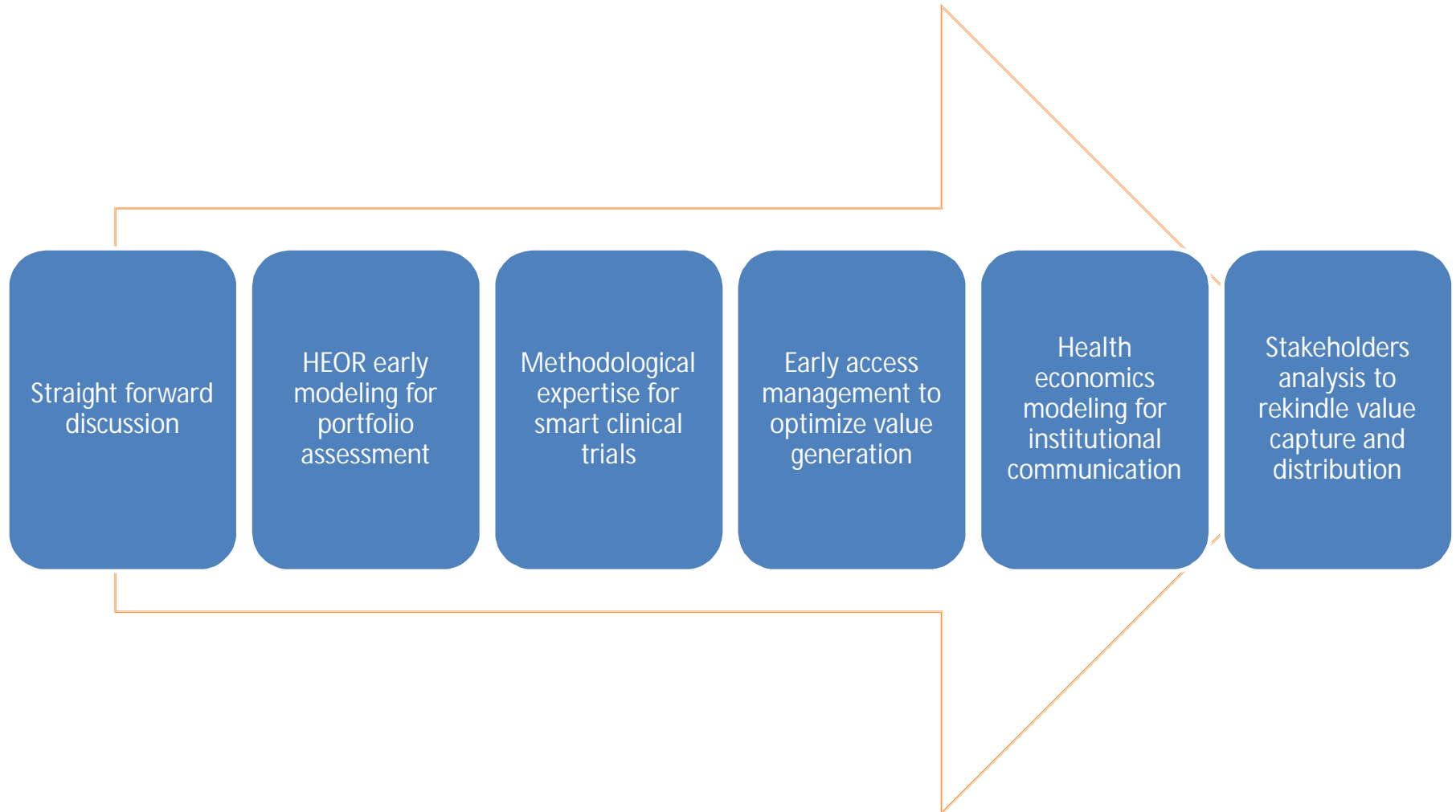
- How did we get there ?
- What improvements are possible ?
- What means are available to make these improvements ?
- When will we measure the effects of these new initiatives ?
- Is this an opportunity to think different ?

# Impulses

Current levers	Process improvement	Tap the human potential
<ul style="list-style-type: none"> <li>✓ Taxes credit for R&amp;D</li> <li>✓ Early access schemes</li> <li>✓ Level of education (Engineers, Phd)</li> <li>✓ Level of research in medicine and innovation adoption by physicians</li> </ul>	<ul style="list-style-type: none"> <li>✓ Use of current exhaustive data to streamline project steering (<i>Dry Lab</i>)</li> <li>✓ Use indirect comparison tools to speed up POC or evidence of effect (Bayesian statistics)</li> <li>✓ Stable frame of theoretical innovation (social demand, utility, spillovers, value split)</li> <li>✓ Industry and regulation with common goals and proactive communication (guidance, forecasting task forces)</li> </ul>	<ul style="list-style-type: none"> <li>✓ Promote creativity times and “divergent thinking” in companies [1]</li> <li>✓ Generate innovation communities in life sciences (<i>intellectual venture alike in open source</i>) [2]</li> <li>✓ Constantly train talent resources on critical competencies necessary to tackle future challenges</li> <li>✓ Heterotopias [3] : catalytic spaces/times where people collides and gives birth to new concepts and prototypes (coderDojo, fablab)</li> <li>✓ Set challenges like Millennium Prize Problems in Mathematics [4]</li> <li>✓ Switch from « individual knowledge » economy (cognition) to « collaborative challenge » economy (conation) [5]</li> </ul>

Source : [1] RSA animate Changing Education Paradigms, [link](#)  
 [2] RSA animate The surprising truth about what motivates us, [link](#)  
 [3] Wikipedia Heterotopia definition according to Michel Foucault work, [link](#)  
 [4] Wikipedia Millennium Prize Problems, [link](#)  
 [5] Damasio, A. (1994). Descartes' error: Emotion, reason and the human brain

# How can we prepare ourselves to this evolution ?



# Analysis of pharmaceutical research and development

## What slows R&D productivity ?

### Questions ?

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