Translational Medicine workshop, 5 January 2016

The multiple steps in drug innovation

Prof. Bruno FLAMION

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Past Chair, Commission for the Reimbursement of Medicines (**CRM-CTG**), INAMI, Belgium

Ex-advisor/expert for the Federal Agency for Medicinal and Health Products (**FAMHP**)

Professor of Physiology & Pharmacology, **University of Namur**, Belgium

What is drug innovation?

Innovation is incremental

Early Telegraph Key and Sounder

Alexander Graham Bell

Bell's Liquid Telephone

Bell's Centennial Model

Kellogg

Western Electric

WE Candlestick

WE 202

Sultan Reproduction

Scissors Gate Railroad Telephone

Strowger Dial 1905

Pink Princess

Western Electric 500

WE 2500 Desk Phone

Drug innovation is also incremental

Type 1 diabetes
before 1921

Type 1 diabetes
after 1921

Banting & Best, 1921

The Thomas Fisher Rare Book Library, University of Toronto, Banting and Best papers

Top transformative drugs

OPINION

The most transformative drugs of the past 25 years: a survey of physicians

Aaron S. Kesselheim and Jerry Avorn

Nature Reviews Drug Discov 2013; 12:425

Based on FDA approvals, 1985-2009

Justification	Frequency
Improved efficacy	55%
Novel mechanism of action	37%
Impact on practice in the field	24%
Scientific merit	15%
Improved safety	15%
Widespread use and impact	12%
Ease of patient use, convenience	12%
Application to multiple diseases	7%

Clinical field	N°1	N°2	>2010 (examples)
Anesthesiology	Propofol	Remifentanil	
Cardiology	Statins	ACE inhibitors Alteplase	
Dermatology	TNF blockers	Botox®	
Endocrinology	Bisphosphonates	Metformin	SGLT2 inhibitors
Gastroenterology	Omeprazole	TNF blockers	
Infectious diseases	HIV protease inhibitors	Zidovudine (HIV)	Sofosbuvir/Ledipasvir
Genetics	Algucerase	Nitisinone Eculizumab	Ivacaftor
Nephrology	ACE inhibitors	Epoetin	
Neurology	Triptans	Interferon-β Natalizumab	
Oncology	Imatinib	Rituximab Trastuzumab	Checkpoint inhibitors Palbociclib, etc.
Ophthalmology	Anti-VEGF agents	Latanoprost	
Psychiatry	Fluoxetine	Clozapine	
Pulmonary Med.	Epoprostenol	LABA-steroids	Pirfenidone
Rheumatology	TNF blockers	Bisphosphonates	
Urology	Sildenafil	Tamsulosin Finasteride	

Orphans

Legislation on orphan medicinal products

Orphan Drug Act of 1983

- The original aim is to help the companies to develop drugs when no reasonable expectation exists that the costs of developing and distributing these drugs will be recovered from the sales of the drugs

USA

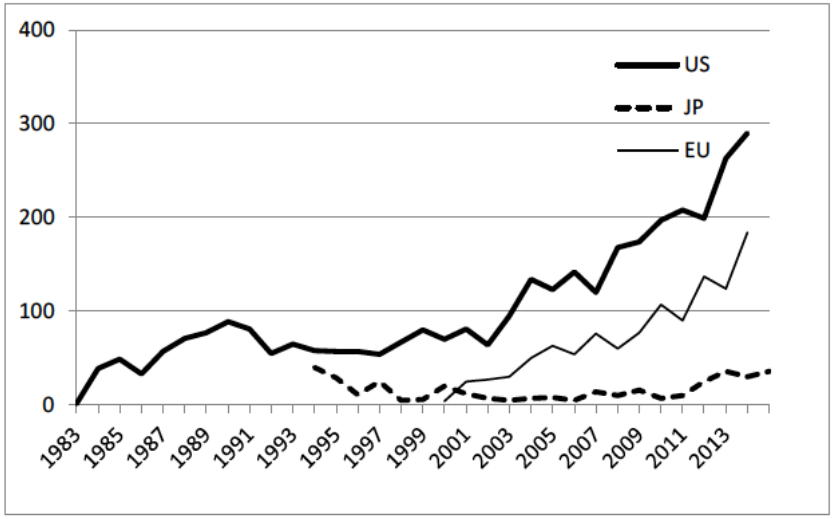


FIGURE 1 Number of orphan drug designations over time by region (all data)

Aids:

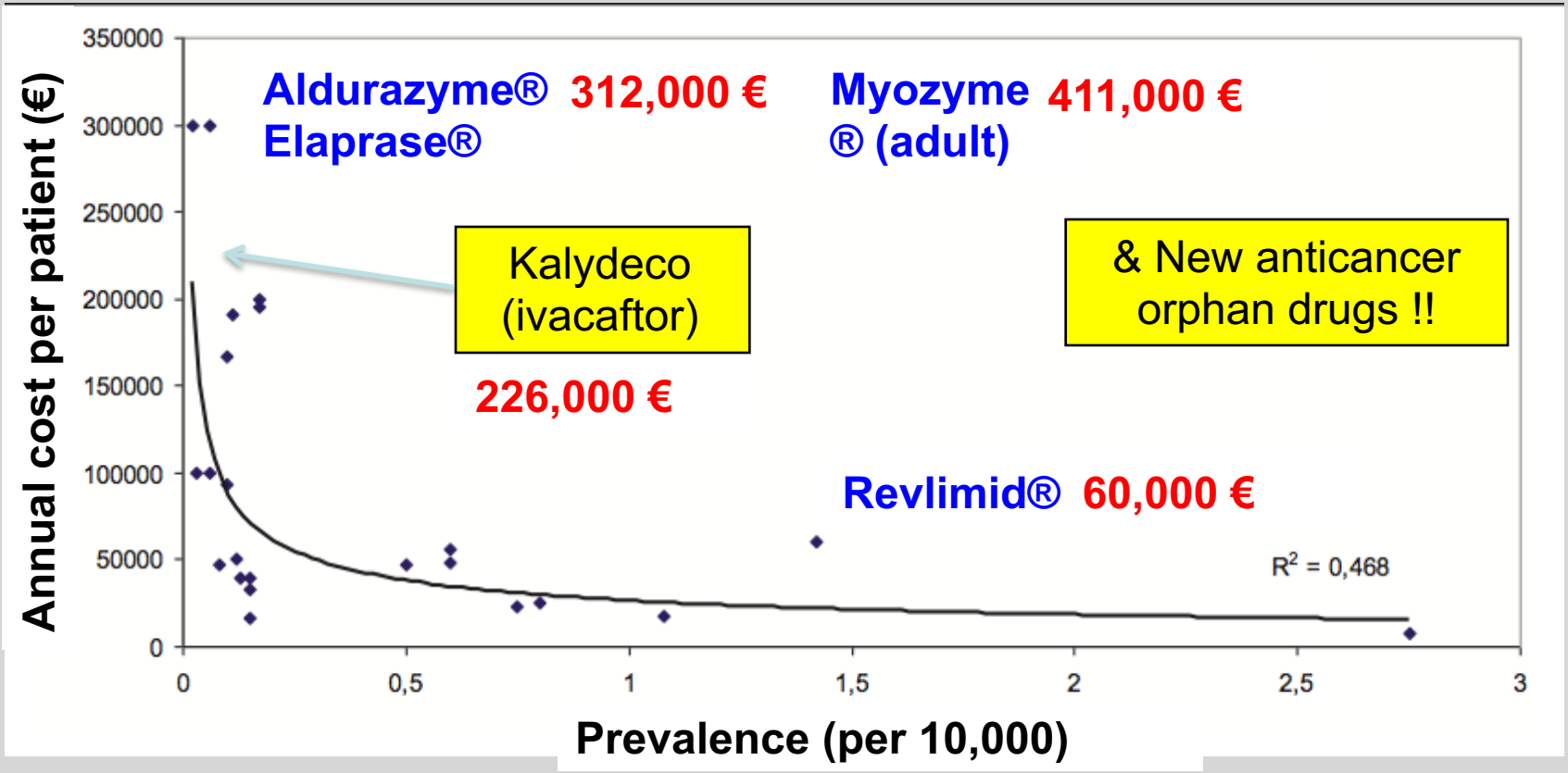
- Tax incentives
- Enhanced patent protection and marketing rights
- Clinical research financial subsidization

EU:

- Drug for life-threatening or chronic debilitating disease with a prevalence <5/10,000
- If treatment already exists: OMP must demonstrate significant benefit
- 30 millions patients suffer from rare diseases in EU

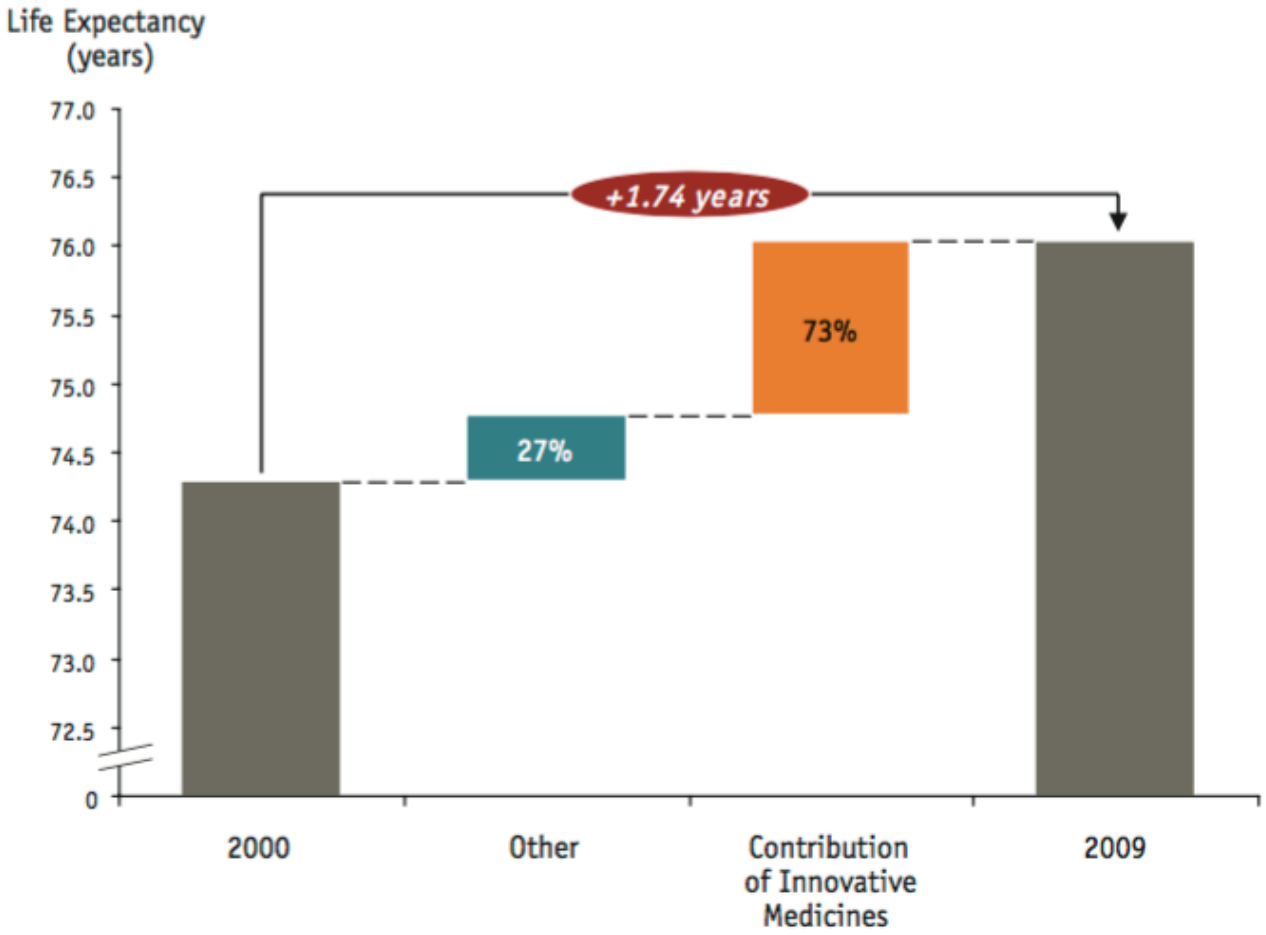
Cost of orphan medicinal products in Belgium

x **Soliris** (aHUS) **500,000 €**



Simoen et al., 2011 & Rapport KCE #112, 2009

CONTRIBUTION OF INNOVATIVE MEDICINES TO INCREASE IN LIFE EXPECTANCY (2000-2009)



Source: Lichtenberg, F: Pharmaceutical innovation and longevity growth in 30 developing OECD and high-income countries, 2000-2009 (2012)

Columbia University, National Bureau of Economic Research

Efficiency of drug innovation

The decreasing efficiency of drug development…

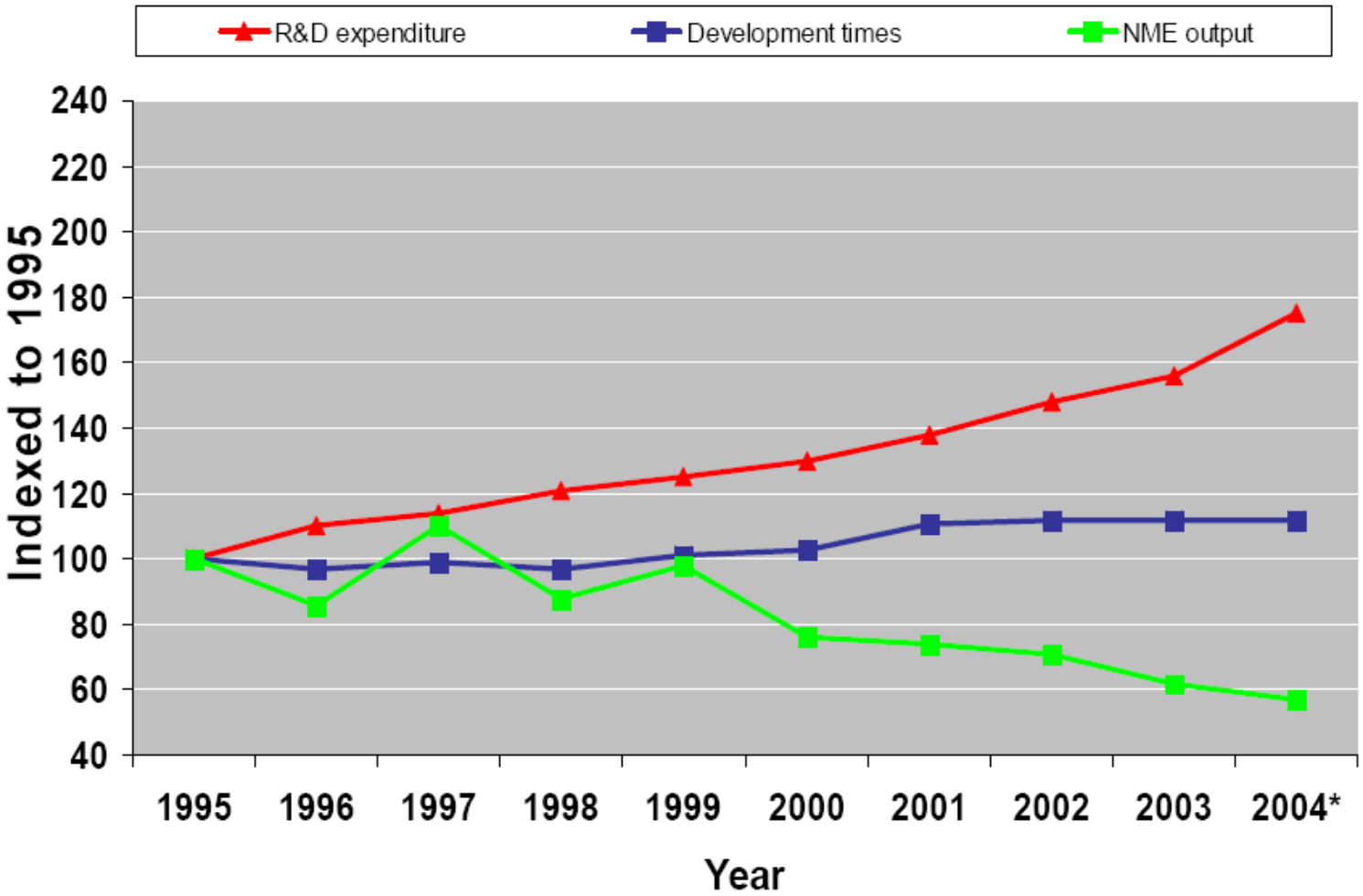
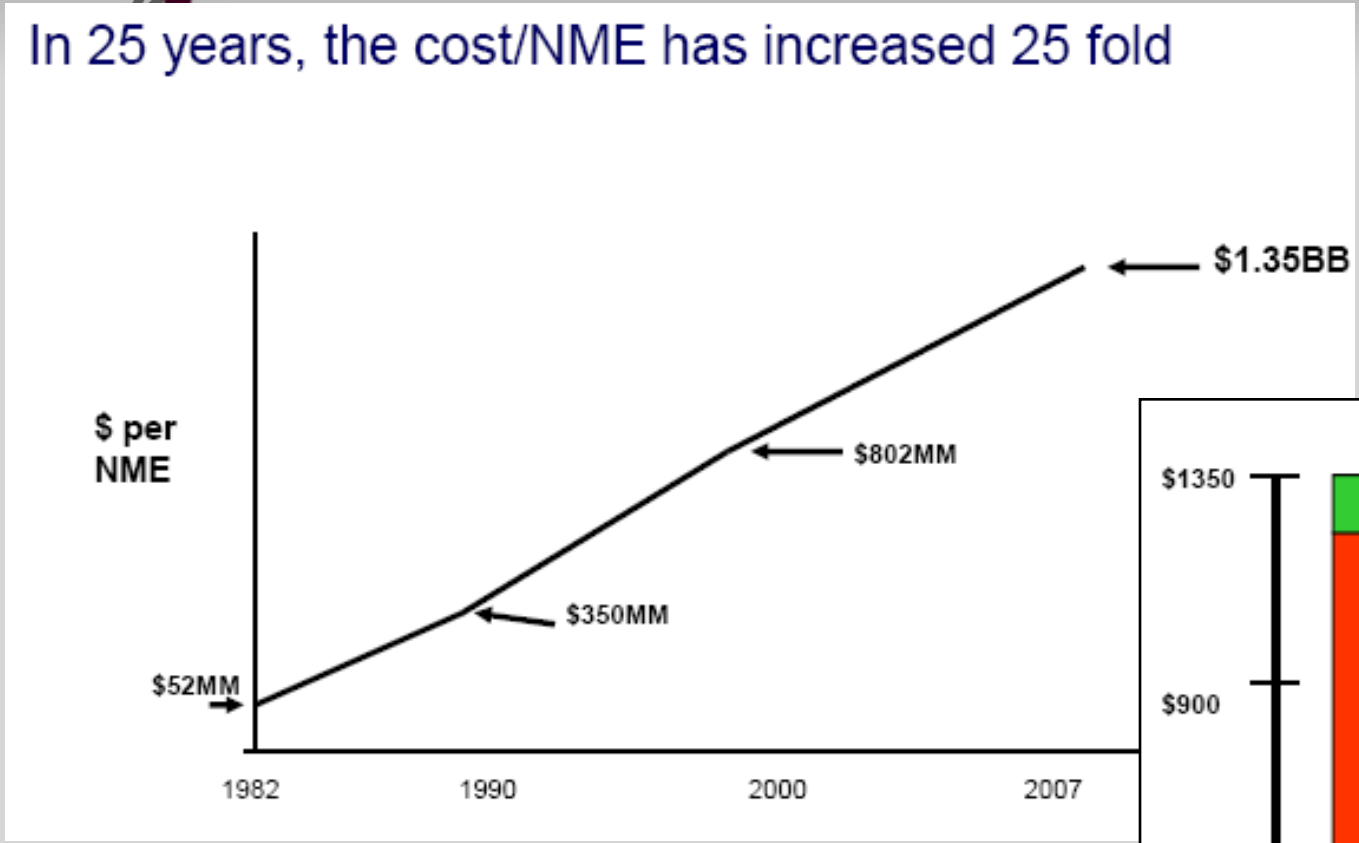


Figure 3 : Global R&D Expenditure, Development Times and NMEs 1995–2004[5]

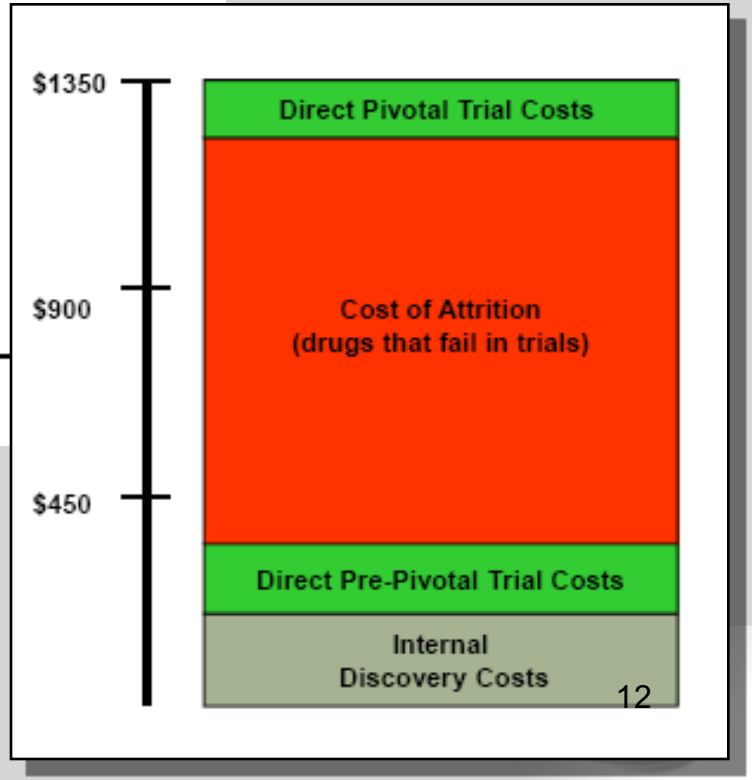
From CMR Factbook, 2005

NME = new medicinal entity

… and its high cost...

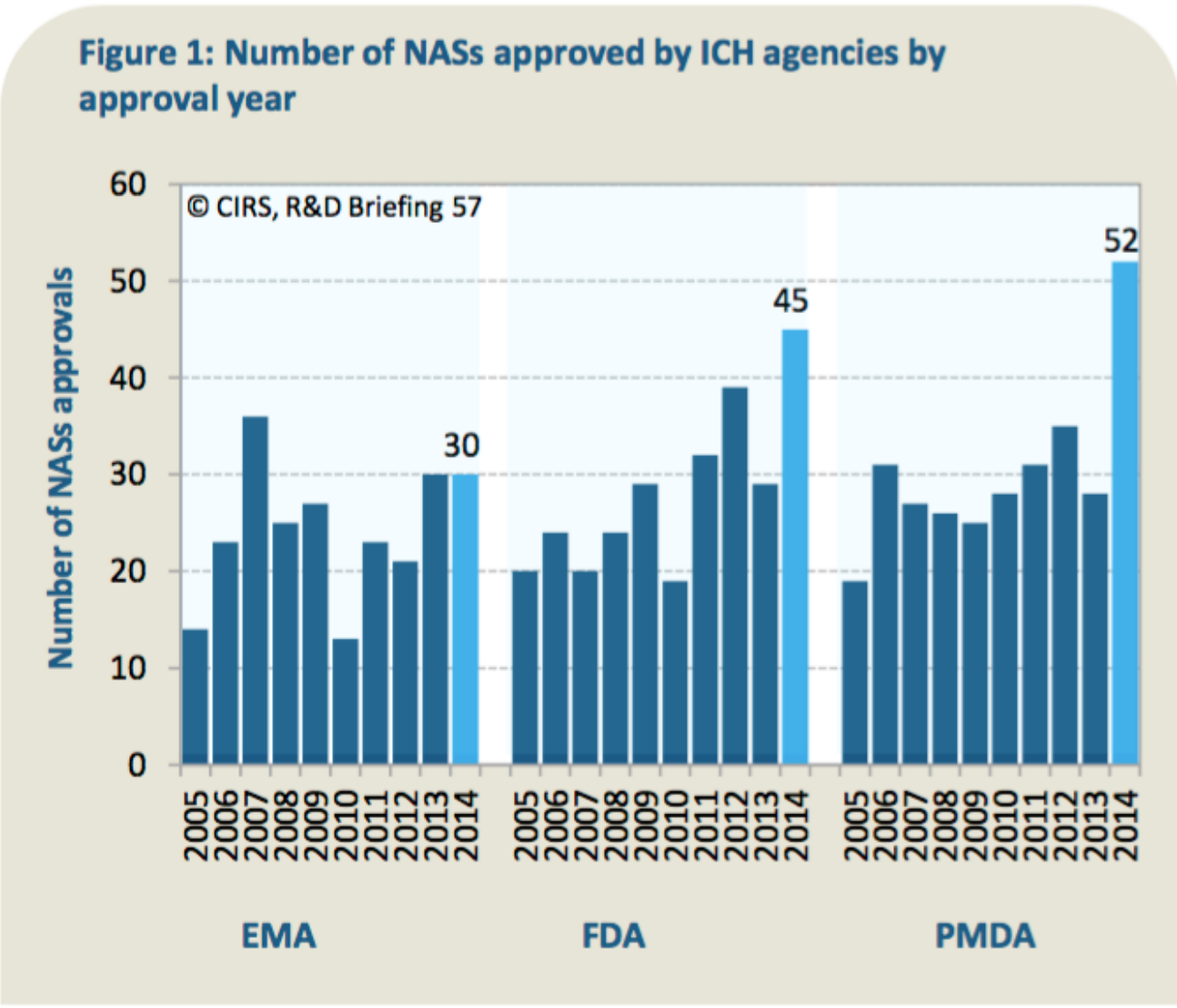


Attrition



From Charles Hoban
Cambridge Healthtech Associates, 2008

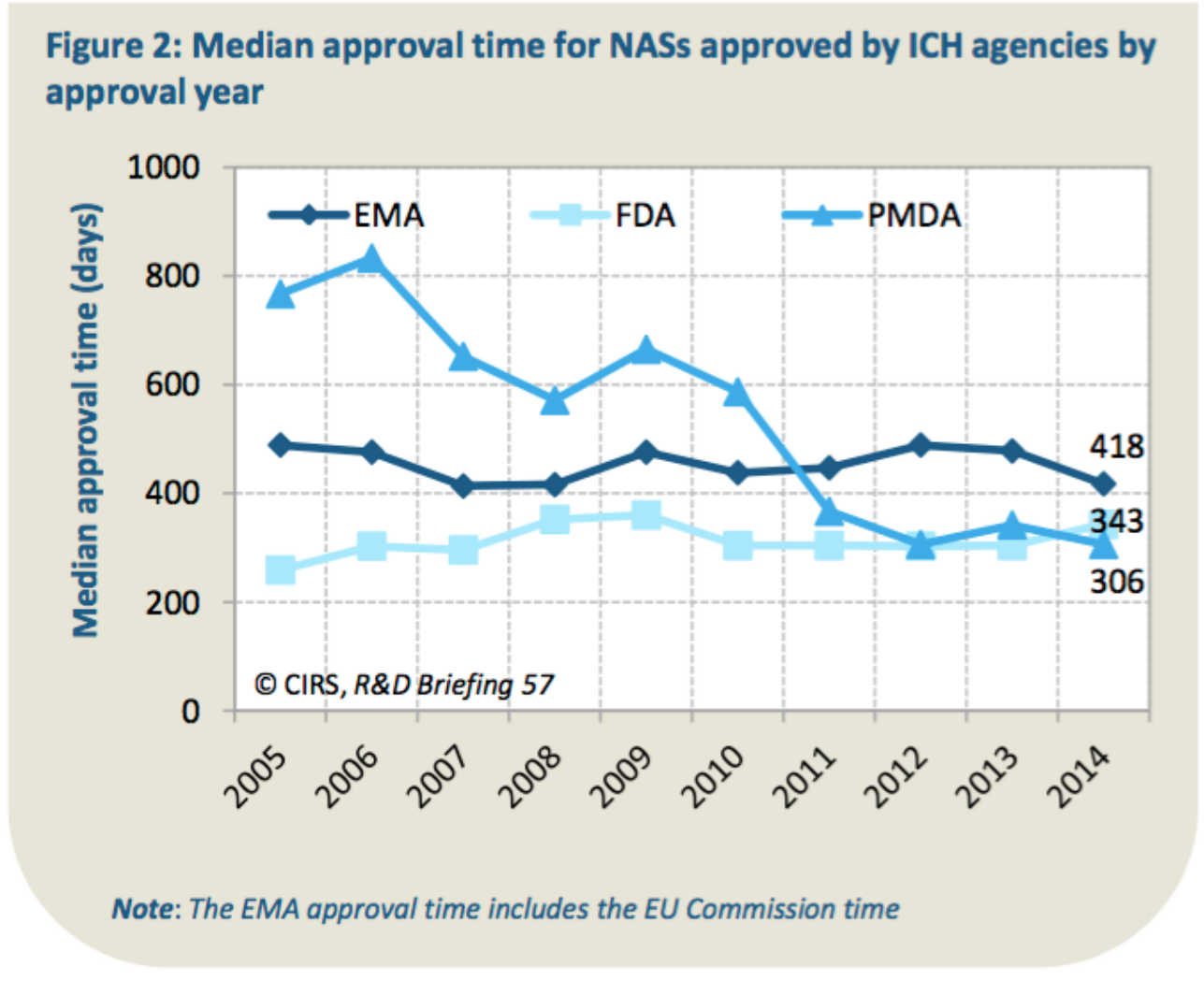
…. may have been halted



NAS = new active substance

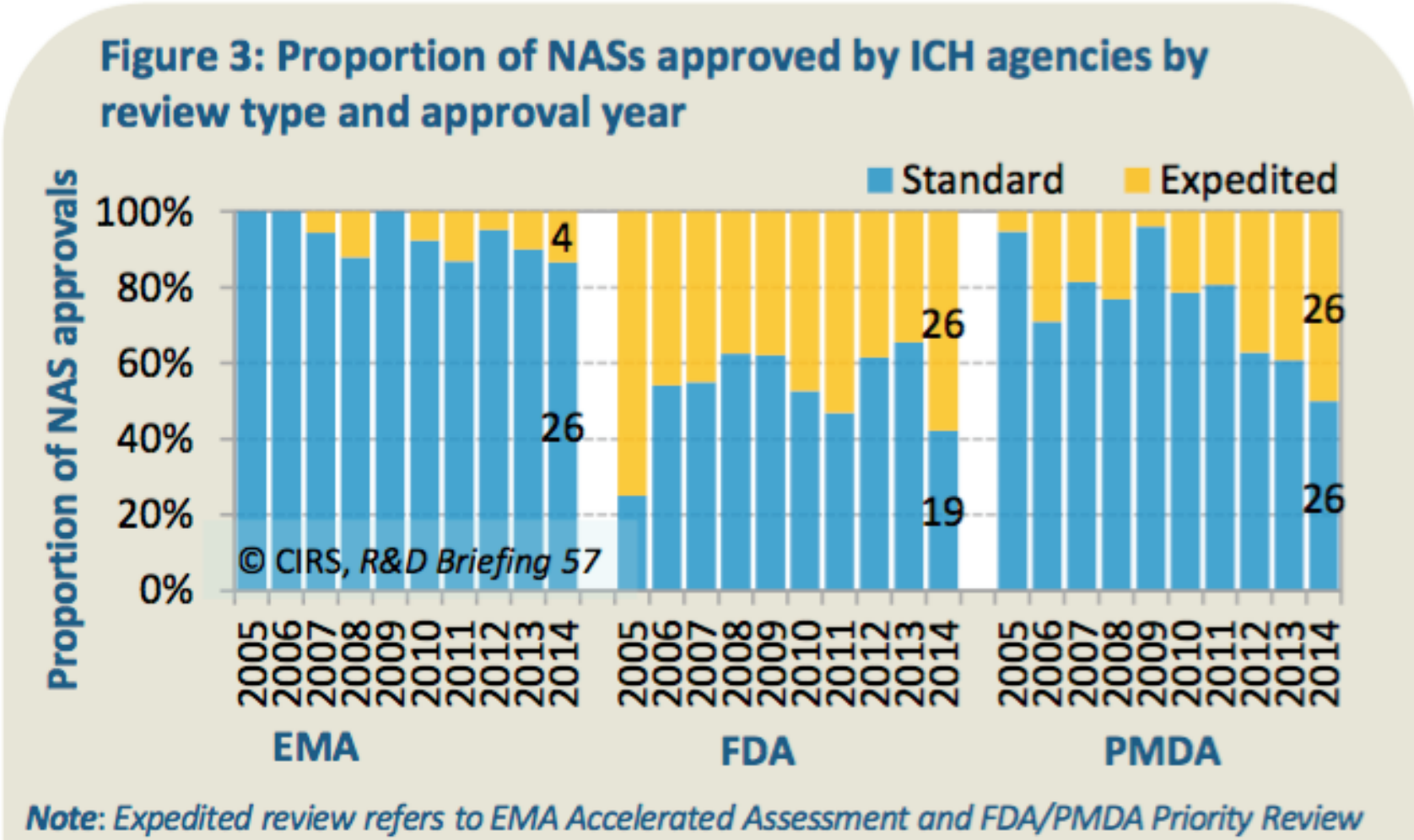
From CIRS R&D Briefing, 2015

No increase in regulatory review times



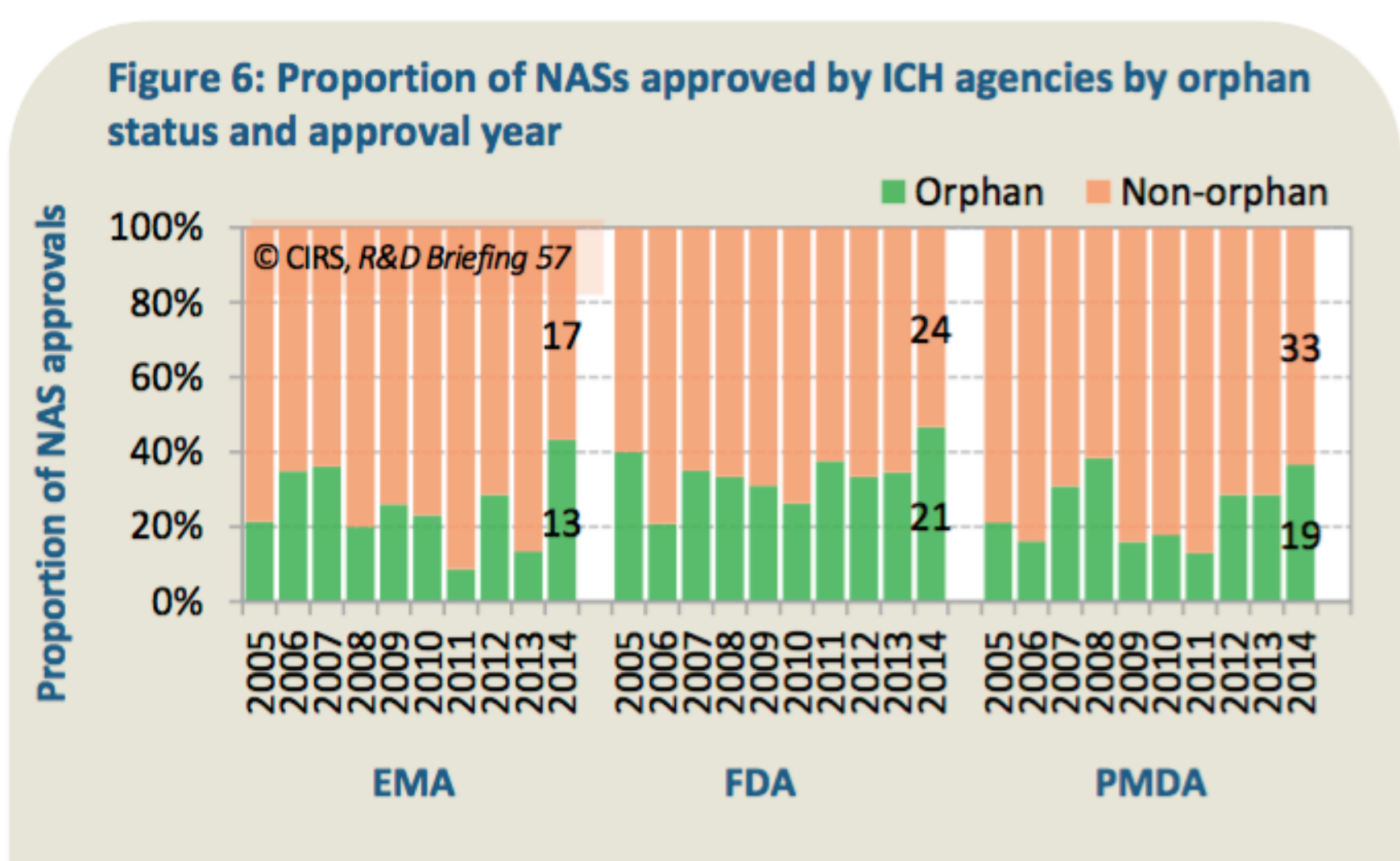
From CIRS R&D Briefing, 2015

High proportion of expedited reviews in US



From CIRS R&D Briefing, 2015

High proportion of orphan drug approvals



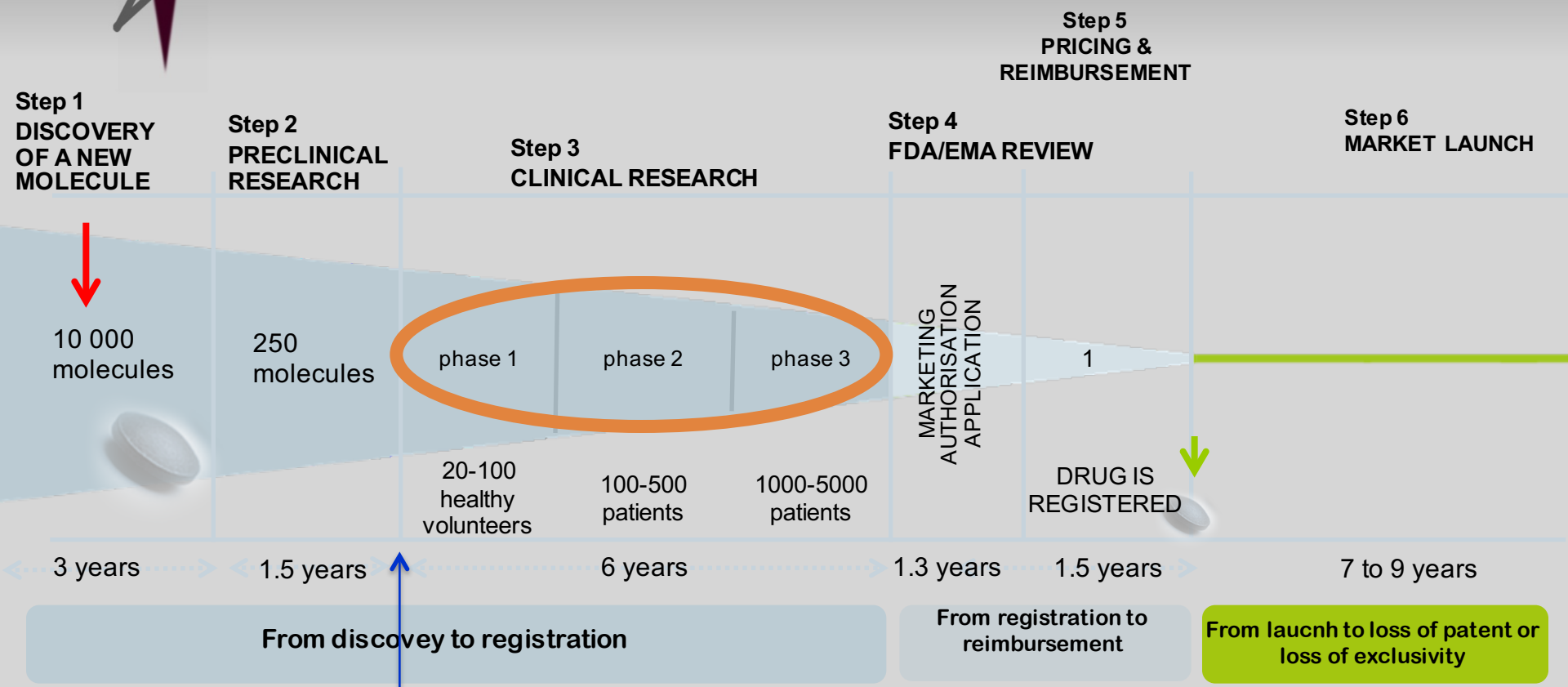
From CIRS R&D Briefing, 2015

Innovative approaches by pharma industry

Innovative industrial approaches

- Classical « funnel » approach but using new technologies
- Consolidation between pharmaceutical companies
- Outsourcing
- Partnerships with small biotech companies
- Academic alliances
- Public-private partnerships
- Global strategy: emerging markets
- Orphan drugs incentives

The funnel approach to drug discovery



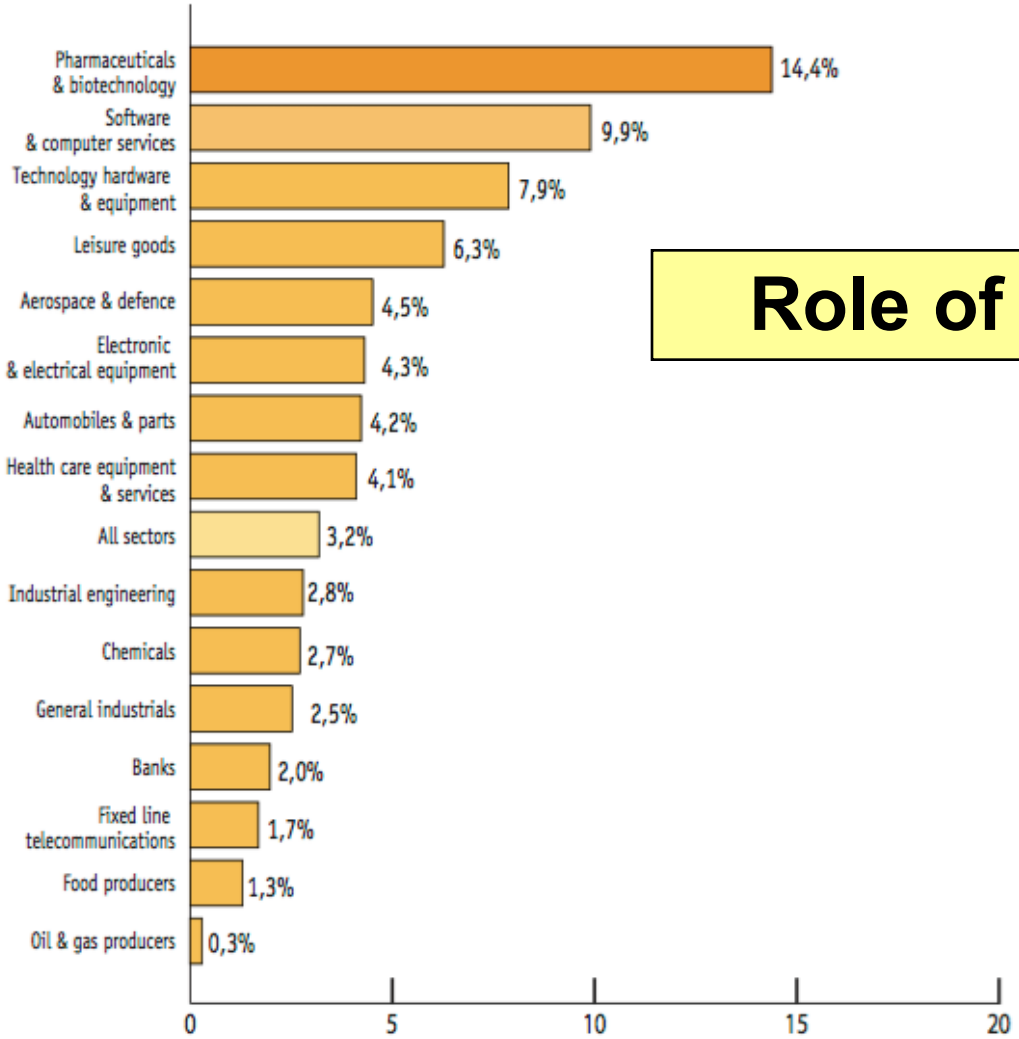
At FDA: new product is designated « IND » (investigational new drug »)

Mean duration of each phase: source CMR International Factbook 2004 (Centre for Medicines Research International)

New technologies

- **High throughput screening** (robotics and automation, cell based assays, miniaturization, high content screening…)
- **Bioanalytical instruments** (mass spectrometry, NMR, micro plate readers and chemotherapy instruments)
- **Pharmacogenomics**
- **Combinatorial chemistry**
- **Genomics** (functional and structural genomics)
- **Biochips** (DNA and proteomic microarrays, lab on a chip)
- **Bioinformatics**
- **Proteomics** (2DGE, two hybrid systems, isotope encoding and activity based assays)
- **RNAi** (siRNA, miRNA, ddRNAi, short hairpin RNAs)
- **Nanotechnology** (Atomic force microscopy, nano mass spectroscopy, other nanotechnologies)

Role of R&D



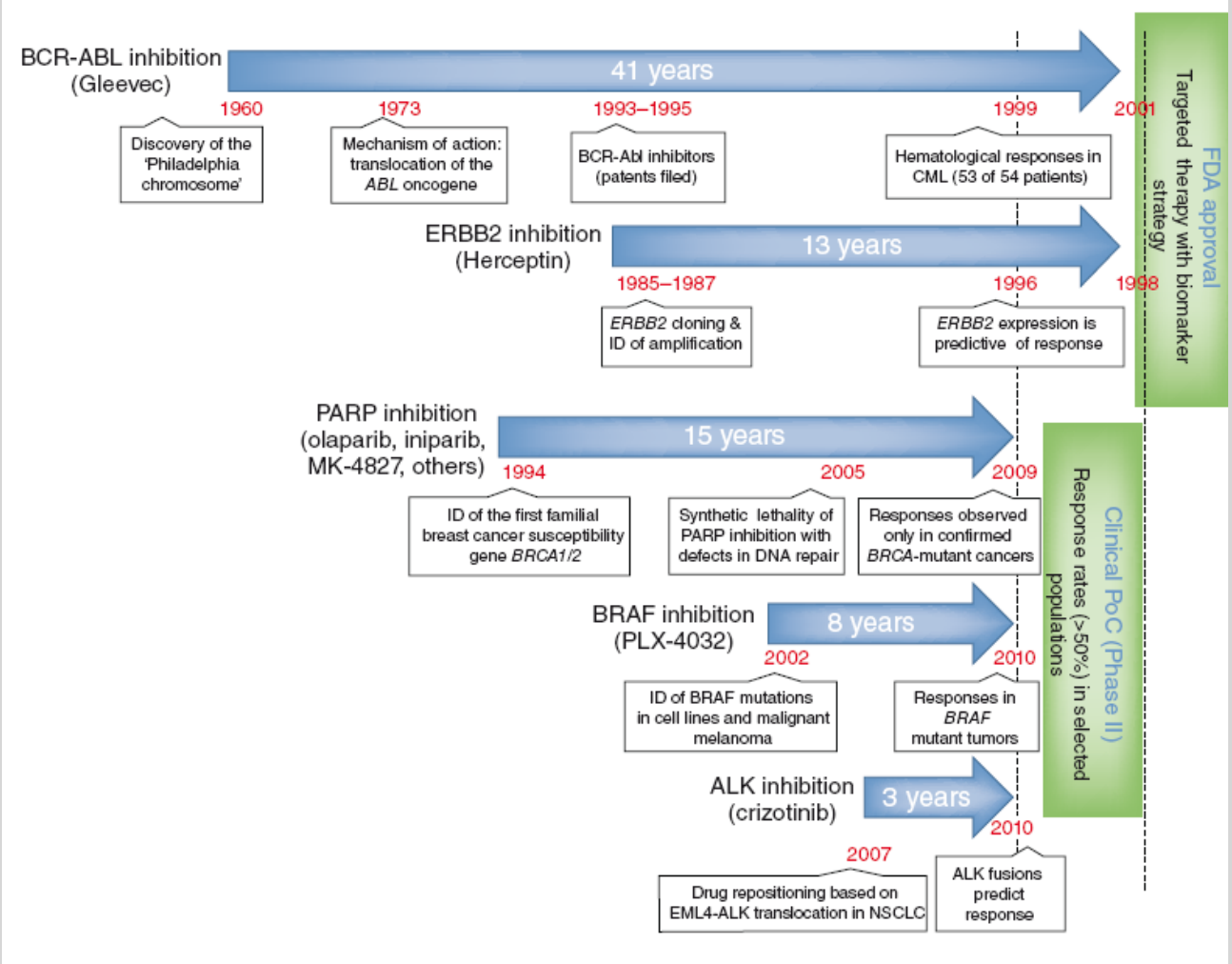
Note: Data relate to the top 2,000 companies with registered offices in the EU (527), Japan (353), The USA (658) and the Rest of the World (462), ranked by total worldwide R&D investment (with R&D investment above € 22.6 million)

Source: The 2013 EU Industrial R&D Investment Scoreboard, European Commission, JRC/DG Research & Innovation

The pharmacogenomics & biomarker approach

Cancer genomics: from discovery science to personalized medicine

Lynda Chin[1–3], Jannik N Andersen[1] & P Andrew Futreal[4]

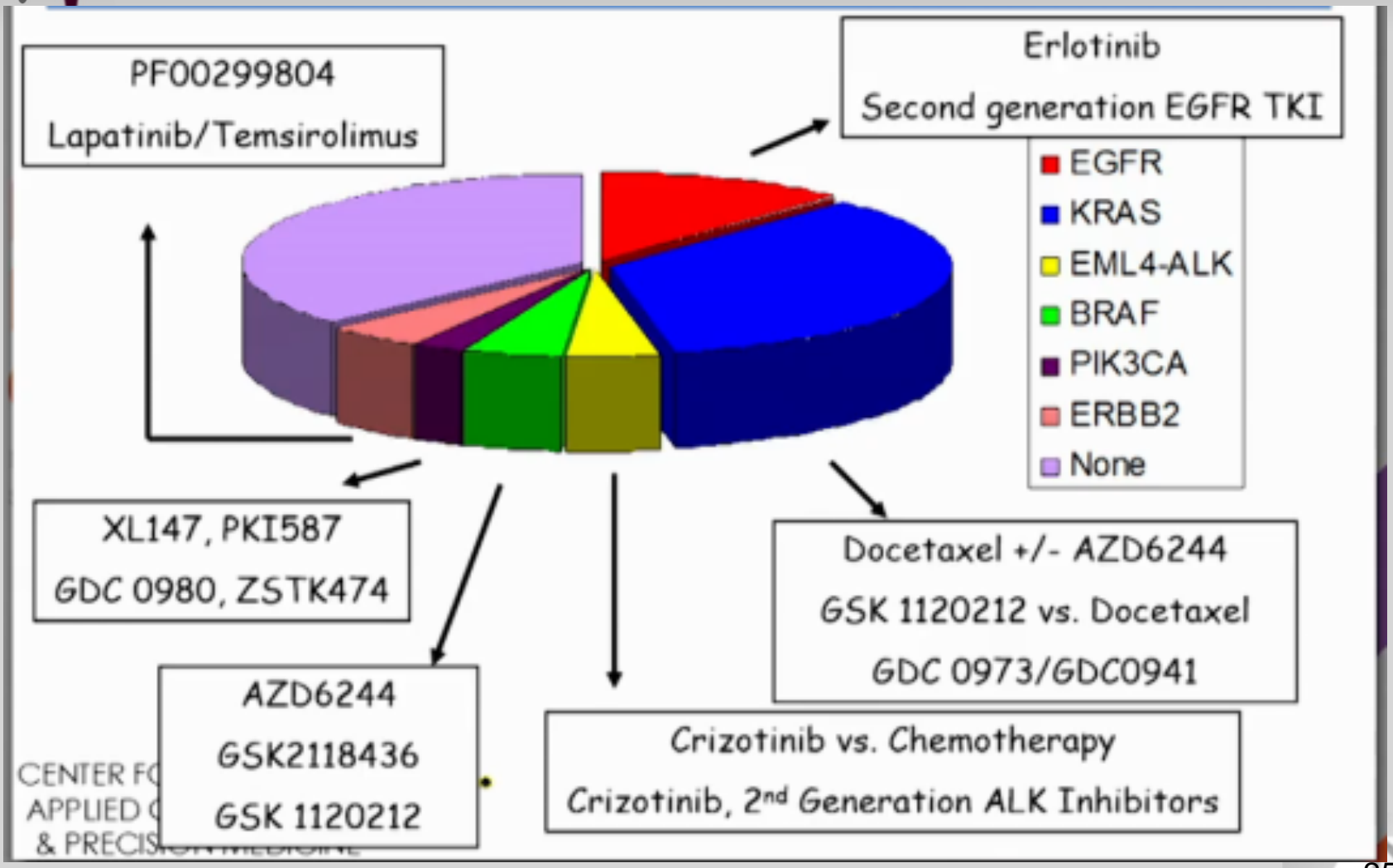


Nature Medicine, March 2011

EMA-approved « genomic biomarker » drugs

Product	Test	
Glivec® (imatinib), etc.	bcr-abl, c-kit	Cancer
Ziagen® (abacavir)	HLA-B5701	
Celsentri® (maraviroc)	CCR5	
Herceptin® (trastuzumab), Tyverb® (lapatinib), Perjeta®(pertuzumba), Kadcyla®(trastuzumab emtansine),	HER2	C
Vectibix® (panitumumab), Erbitux® (cetuximab)	KRAS wild-type	C
Iressa® (gefitinib), Tarceva® (erlotinib), Giotrif® (afatinib)	EGFR-TK mutation	C
Zelboraf® (vemurafenib), Tafinlar (dabrafenib)	BRAF V600 mutation	C
Xalkori® (crizotinib), Zykadia®(ceritinib)	ALK	C
Lymparza® (olaparib)	BRCA mutation	C
Kalydeco® (ivacaftor)	CFTR G551D mutation	

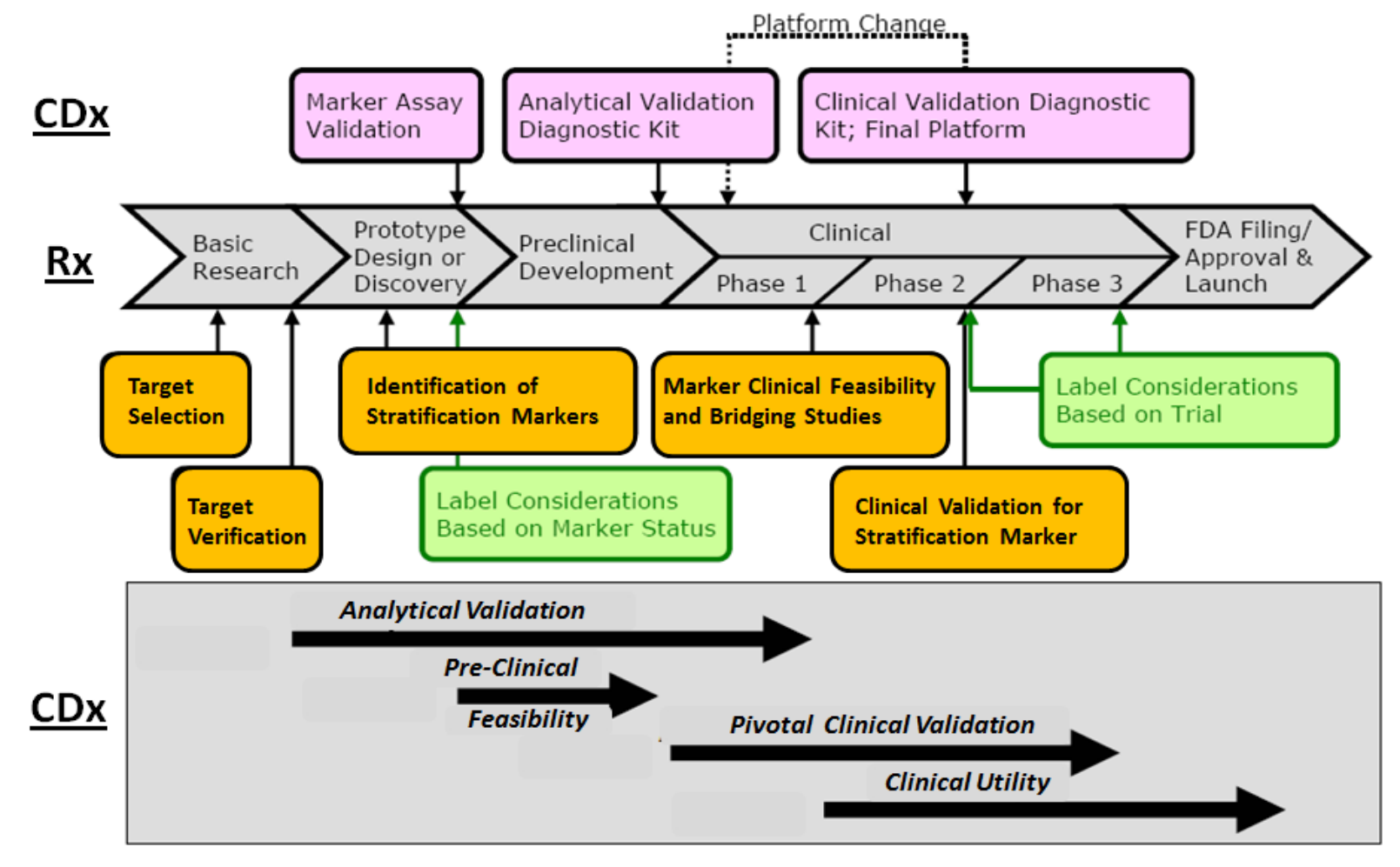
Lung adenocarcinoma genotypes



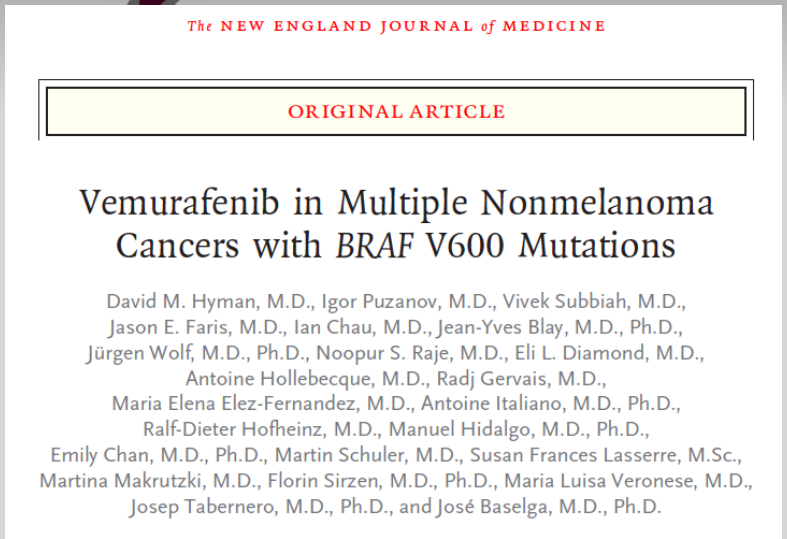
Recently developed molecular tests

Test	*Indication*
Oncotype DX®	21-gene tumor RNA signature (breast cancer) or 12-gene signature (colon carcinoma)
Mammaprint®	70-gene tumor RNA signature (breast cancer)
AlloMap®	11-gene blood RNA signature to predict cardiac alllograft rejection
Corus CAD®	23-gene blood RNA signature to predict risk of coronary artery disease

Rx-CDx co-development



Results of the first *basket trials* in oncology

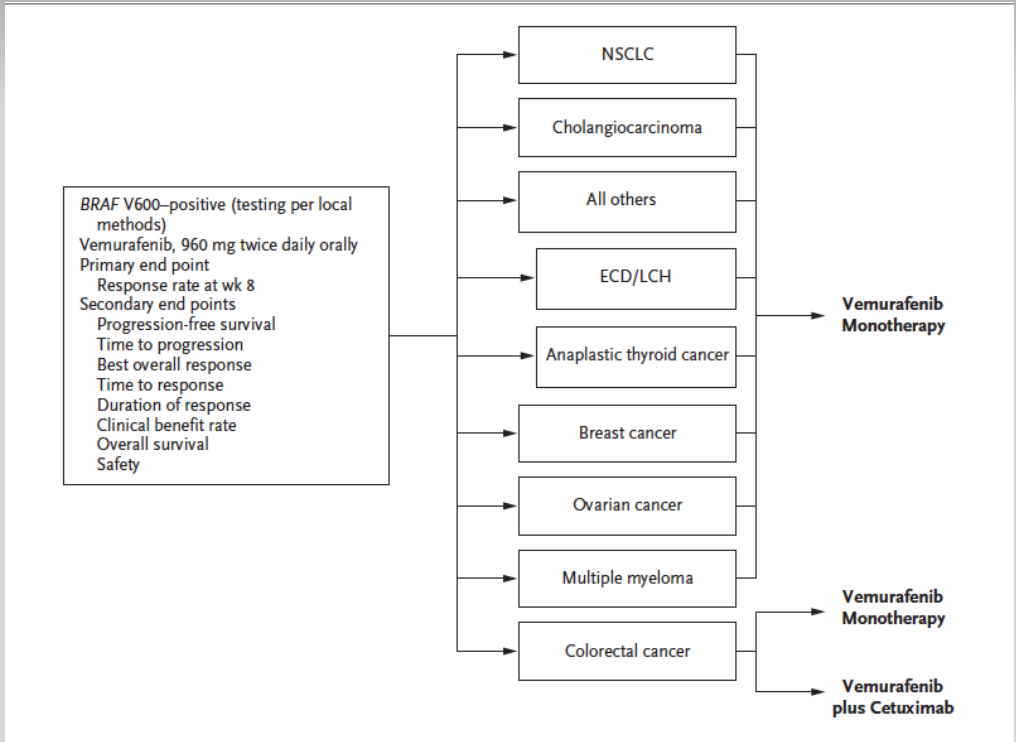

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Vemurafenib in Multiple Nonmelanoma Cancers with *BRAF* V600 Mutations

David M. Hyman, M.D., Igor Puzanov, M.D., Vivek Subbiah, M.D., Jason E. Faris, M.D., Ian Chau, M.D., Jean-Yves Blay, M.D., Ph.D., Jürgen Wolf, M.D., Ph.D., Noopur S. Raje, M.D., Eli L. Diamond, M.D., Antoine Hollebecque, M.D., Radj Gervais, M.D., Maria Elena Elez-Fernandez, M.D., Antoine Italiano, M.D., Ph.D., Ralf-Dieter Hofheinz, M.D., Manuel Hidalgo, M.D., Ph.D., Emily Chan, M.D., Ph.D., Martin Schuler, M.D., Susan Frances Lasserre, M.Sc., Martina Makrutzki, M.D., Florin Sirzen, M.D., Ph.D., Maria Luisa Veronese, M.D., Josep Tabernero, M.D., Ph.D., and José Baselga, M.D., Ph.D.

NEJM, 20/8/2015



Positive results (at least 45% response) for vemurafenib in:

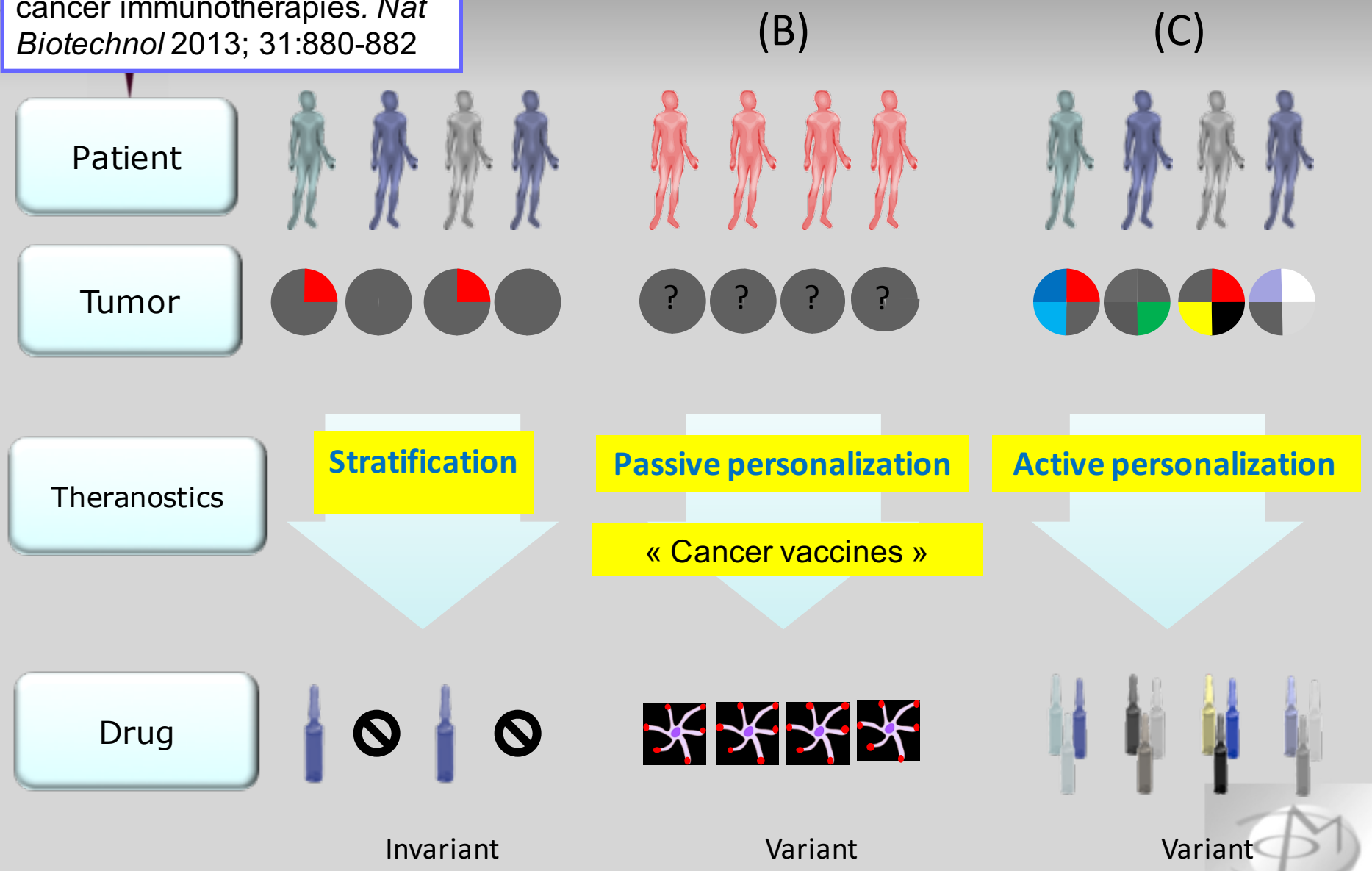
- NSC lung cancer
- Erdheim-Chester disease
- Langerhans-cell histiocytosis

But **Not** in breast cancer, colon carcinoma, myeloma, etc.

➔ *To be completed using observational databases*

Britten, Singh-Jashua, Flamion et al. The regulatory landscape for actively personalized cancer immunotherapies. *Nat Biotechnol* 2013; 31:880-882

Three levels of individualization



Innovative collaborations

FDA-Approved Drugs Discovered through Public-Sector Research, 1990–2007

Table 2. FDA-Approved Drugs Discovered through Public-Sector Research, According to Type of Review and Chemical Type, 1990–2007.*

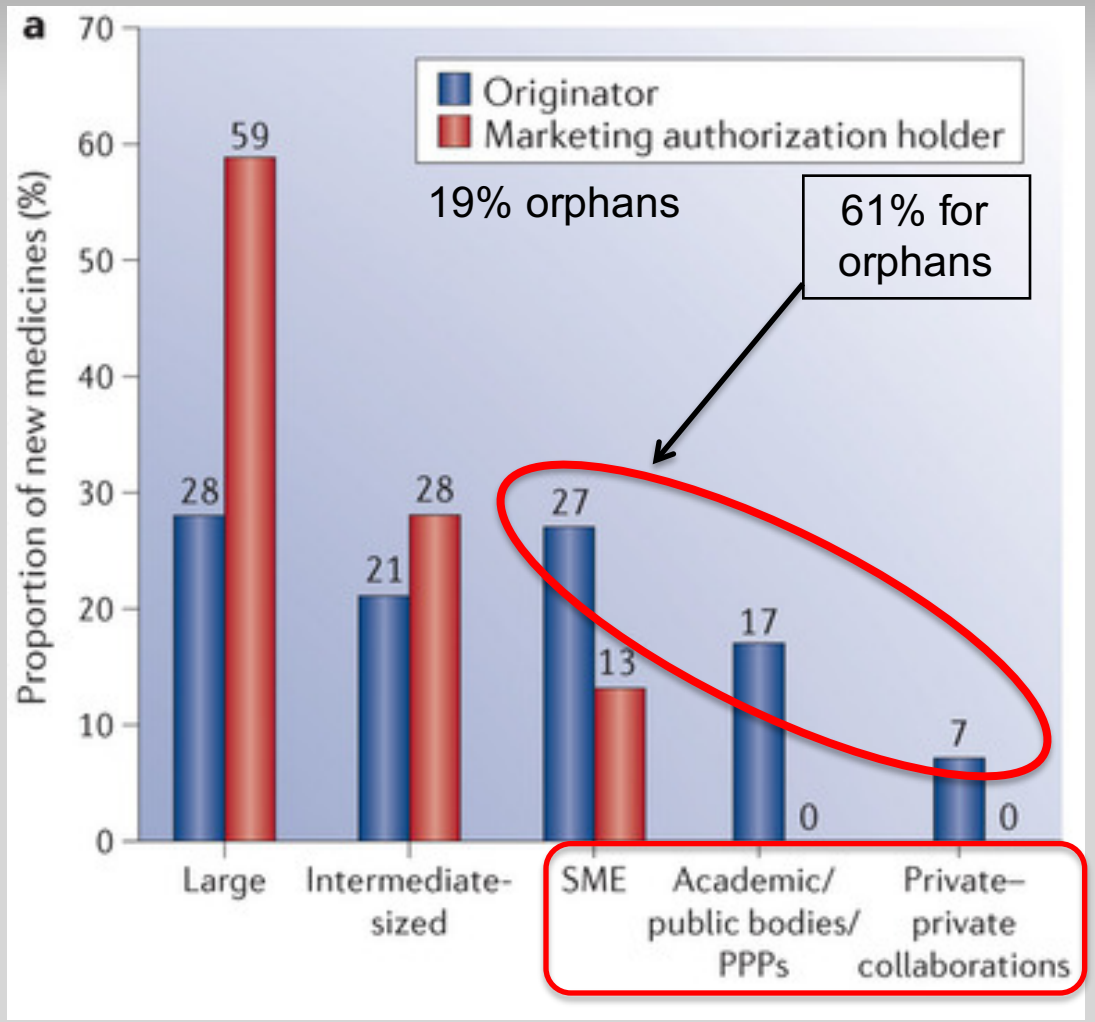
Type of Review	New Molecular Entity	New Ester, Salt, or Derivative	New Formulation	New Combination	New Manufacturer	New Indication	Already Marketed	Total
Priority review								
Discovered by PSRI (no.)	44	1	17	3	0	1†	0	66
All FDA approvals (no.)	209	6	99	20	14	0	0	348
Rate of PSRI discovery (%)	21.1	16.7	17.2	15.0	0	NA	NA	19.0
Standard review								
Discovered by PSRI (no.)	20	0	36	6	7	8	0	77
All FDA approvals (no.)	274	33	631	96	137	10	12	1193
Rate of PSRI discovery (%)	7.3	0	5.7	6.3	5.1	80.0	0	6.5
All approvals								
Discovered by PSRI (no.)	64	1	53	9	7	9	0	143
All FDA approvals (no.)	483	39	730	116	151	10	12	1541
Rate of PSRI discovery (%)	13.3	2.6	7.3	7.8	4.6	90.0	0	9.3

* NA denotes not applicable, and PSRI public-sector research institution.
† The second new-drug application approved for Pfizer's Sutent, in 2006, was classified as type 6 (new indication) and given a priority review. However, the totals supplied by the FDA showed no priority reviews for new-indication applications in 2006 or any other year.

Stevens AJ et al. N Engl J Med 2011;364:535-541.

The NEW ENGLAND JOURNAL of MEDICINE

New trends in pharmaceutical innovation

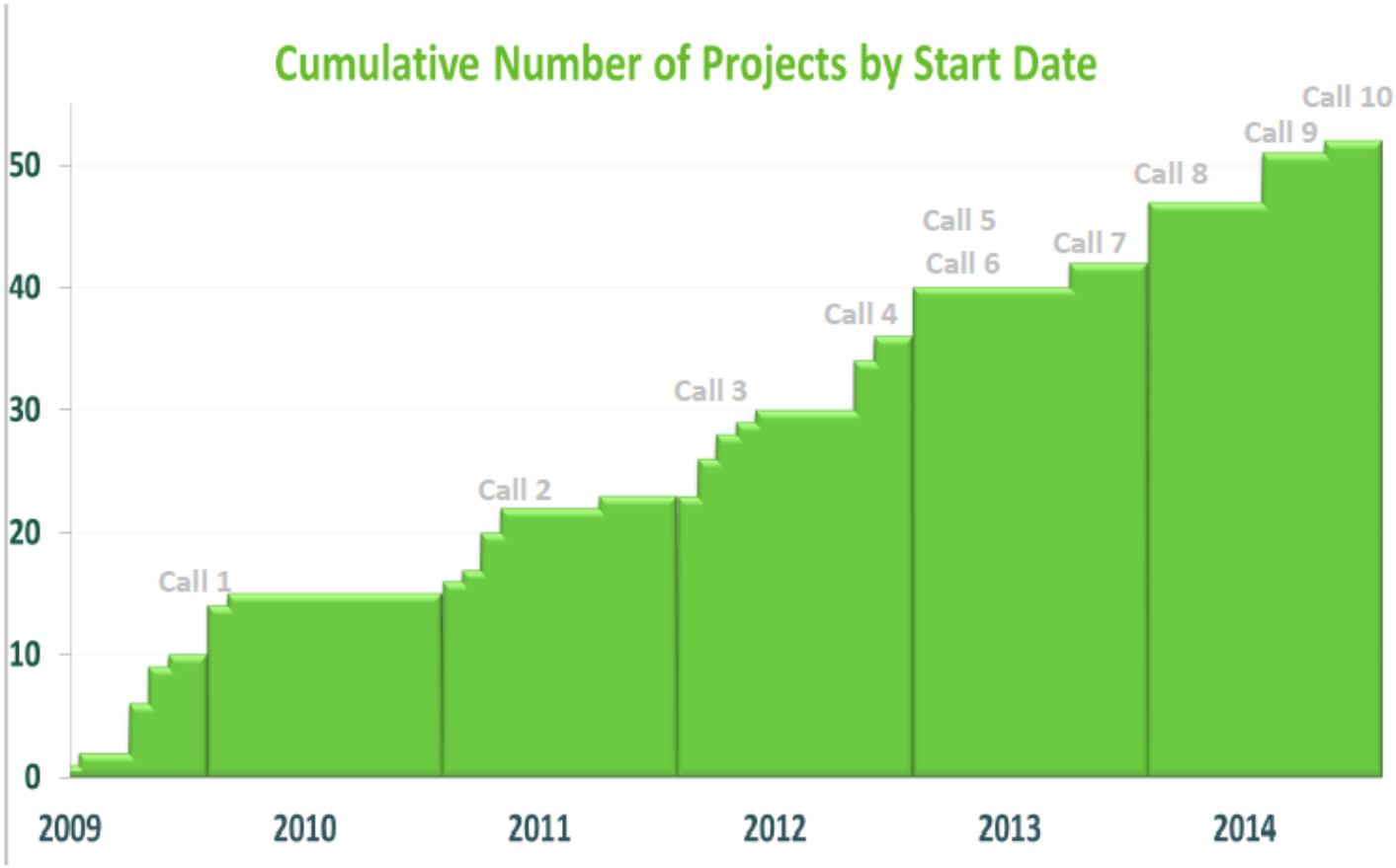


Data for marketing authorisations 2010-2012

Linker H. et al. Where do new medicines originate from in the EU?
Nature Rev Drug Discov 2014 (13) 92

IMI achievements

Since 2009, 42 projects launched - total budget €1.6 billion



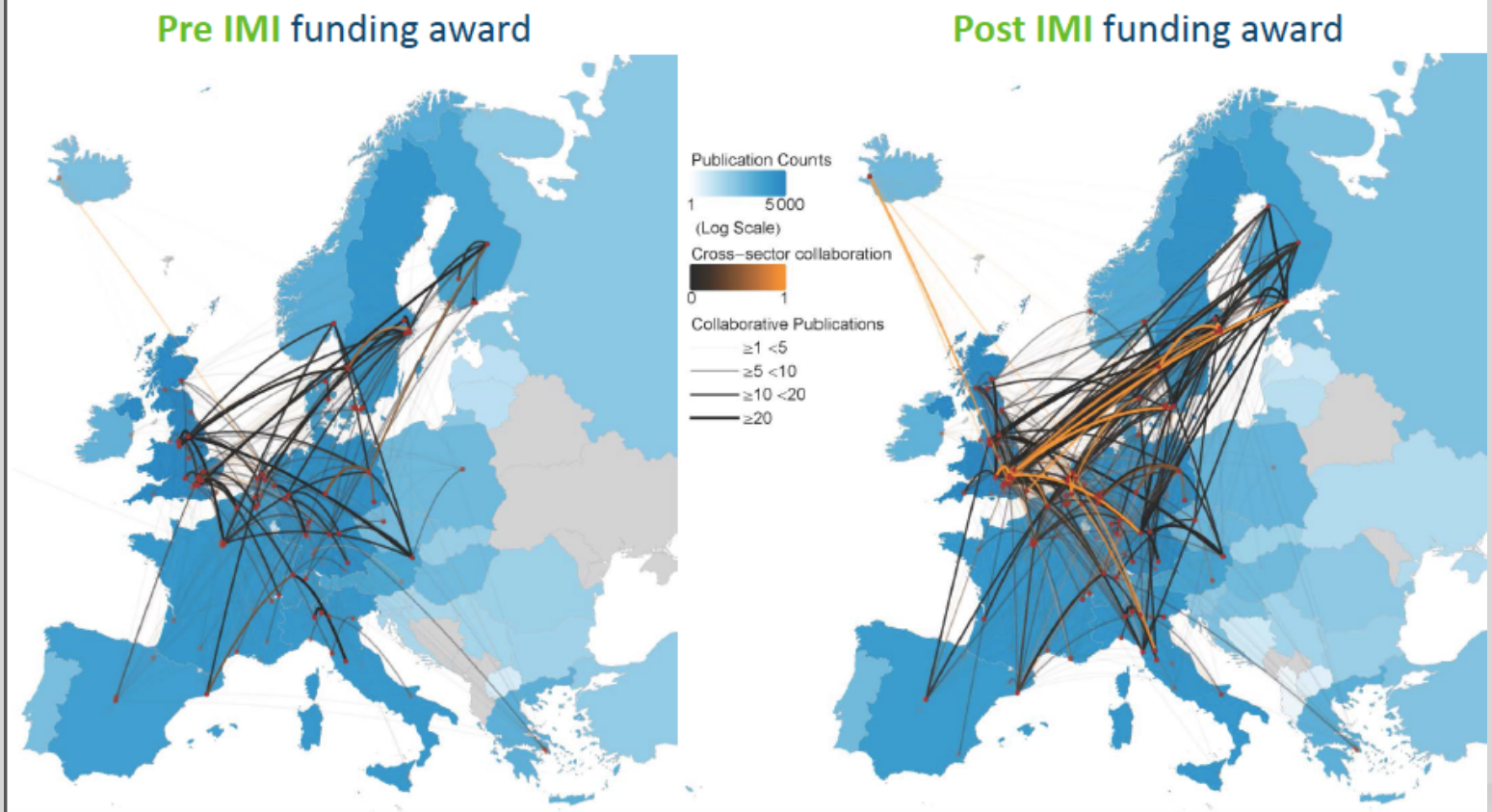
From EFPIA, 2014

IMI = Innovative Medicines Initiative

IMI achievements

Creation of unprecedented collective intelligence networks

Collaborative publications among IMI researchers -Call 1-4



Data & analysis: Thomson Reuters (*Custom Analytics & Engineered Solutions*)

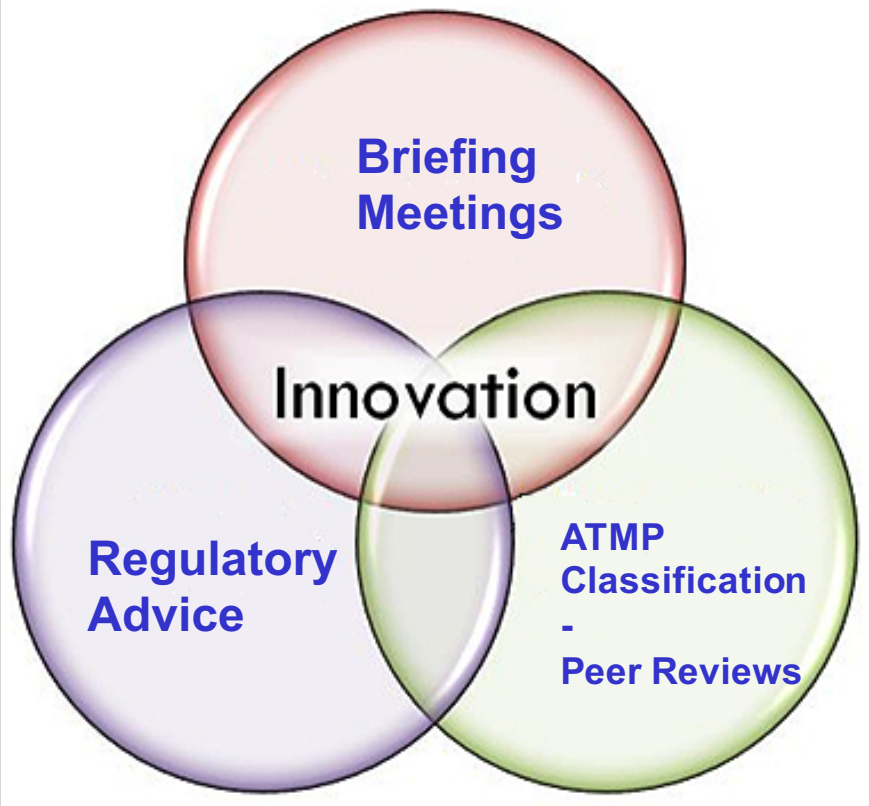
From EFPIA, 2014

Regulatory innovation

How to receive assistance at EMA

From Melanie Carr (EMA), 2011

Innovation Task Force (ITF) at EMA



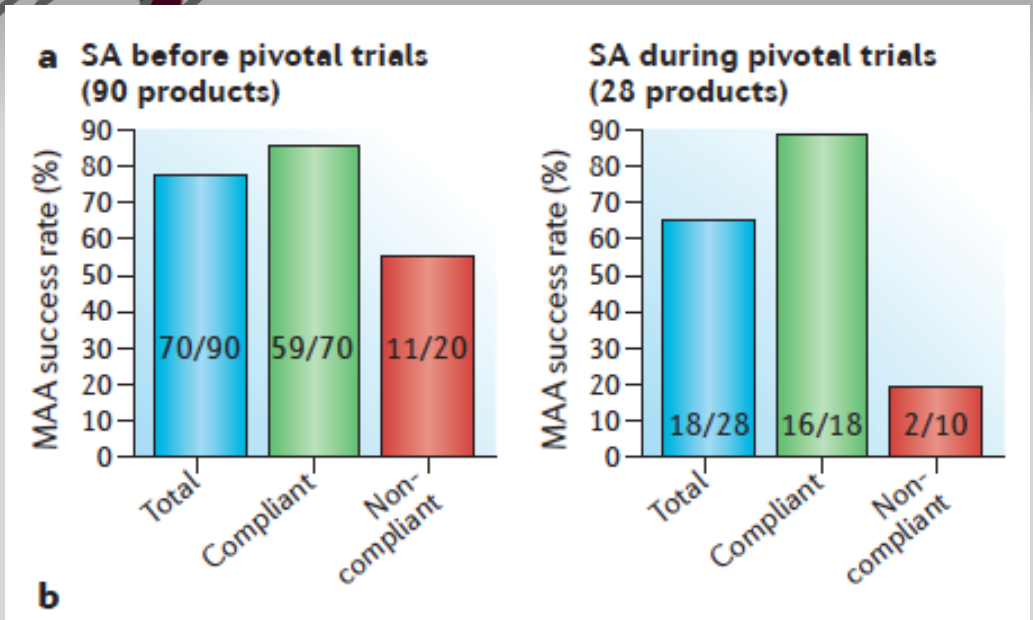
Involved, e.g., in discussions on:

- pharmacogenomics
- nanomedicines
- synthetic biology
- biomaterials
- modelling and simulation
- m-health ('mobile health').

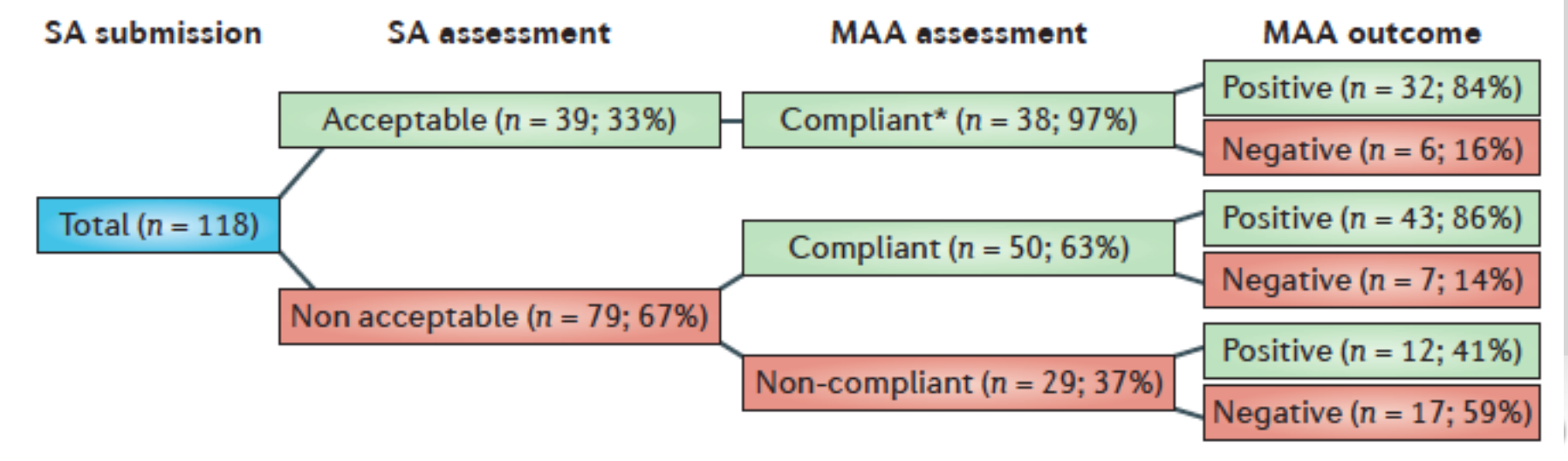
Marisa Papaluca-Amati / Mayeul Boucaumont

ITFsecretariat@emea.europa.eu

Impact of EMA scientific advice



Nature Reviews Drug Discovery, May 2015



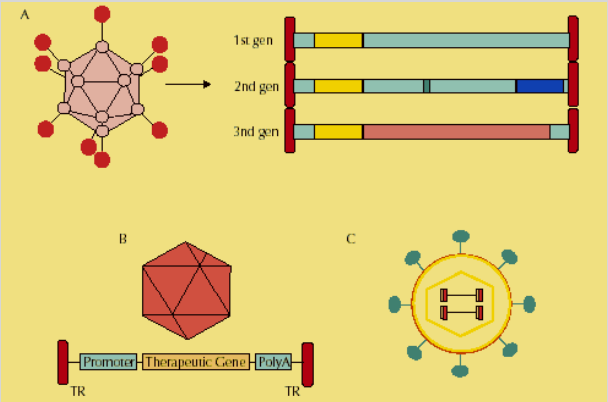
Advanced therapy medicinal products (ATMPs)

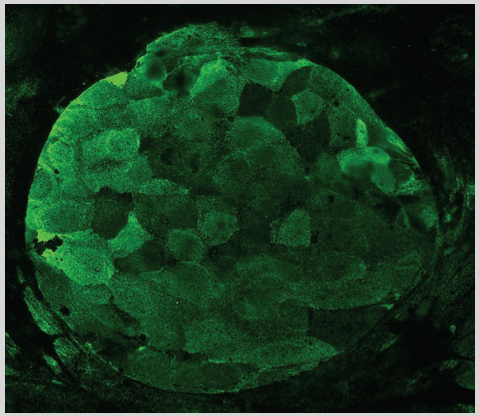
Gene therapy medicinal products

Somatic cell therapy medicinal products

Tissue engineering products

Genetically modified cells





EN Official Journal of the European Union

REGULATION (EC) No 1394/2007 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL

of 13 November 2007

on advanced therapy medicinal products and amending Directive 2001/83/EC and Regulation (EC) No 726/2004

EMA: the CAT

(Committee for Advanced Therapies)

EMA-approved ATMPs

Year	Product	Indication
2009	**Chondrocelect®** (viable autologous cartilage cells expanded *ex vivo*)	Repair of single symptomatic cartilage defects of the femoral condyle of the knee (*i.art.*)
2012	**Glybera®** (alipogene tiparvovec) = human LPL gene variant LPL^{S447X} in a vector	Familial lipoprotein lipase deficiency with severe or multiple pancreatitis attacks (*i.m.*)
2015	**Imlygic®** (talimogene laherparepvec) = engineered HSV-1 producing GM-CSF	Advanced melanoma (*i.tumoral*)

EMA Article 58

(Directive EC/76/2004, Article 58)

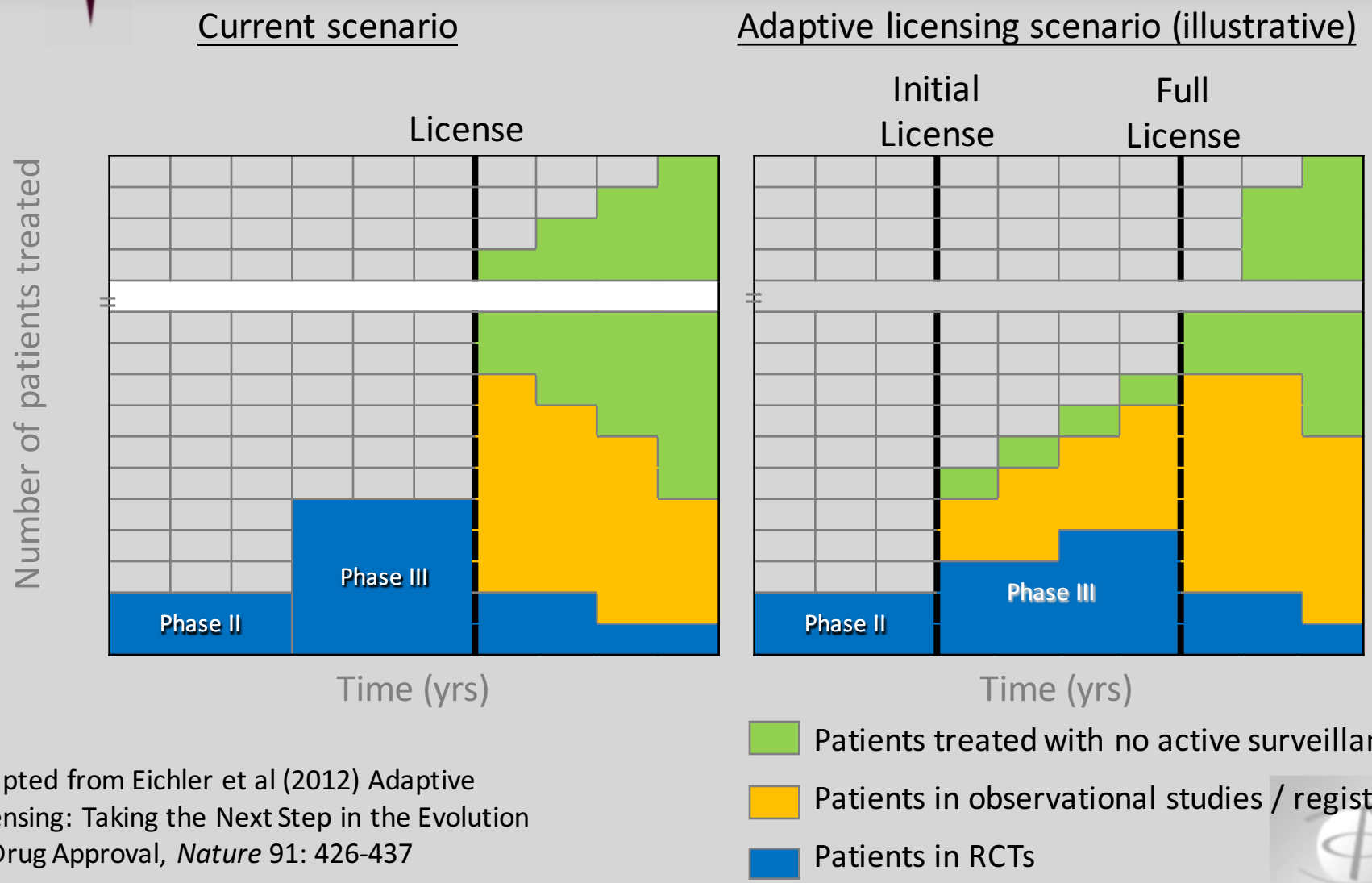
The Agency may give a scientific opinion, in the context of cooperation with the WHO, for the evaluation of certain medicinal products for human use **intended exclusively for markets outside the EC**.

Examples of products approved through Article 58:

- **Aluvia** (lopinavir/ritonavir) for HIV
- **Hemoprostol** (misoprostol) for post-partum hemorrhage if iv oxytocin not available
- **Pyramax** (pyronaridine/artesunate) for acute, uncomplicated malaria infection
- **Hexaxim** (DTP, HBV, poliomyelitis (inactivated) and *Haemophilus influenzae* type B conjugate vaccine)
- **Tritanrix HB** (DTP, HBV vaccine) – NB. submitted to sunset clause in EU and withdrawn from EU market in end 2013

EU regulatory innovation: MAPP

Medicines Adaptive Pathway to Patients



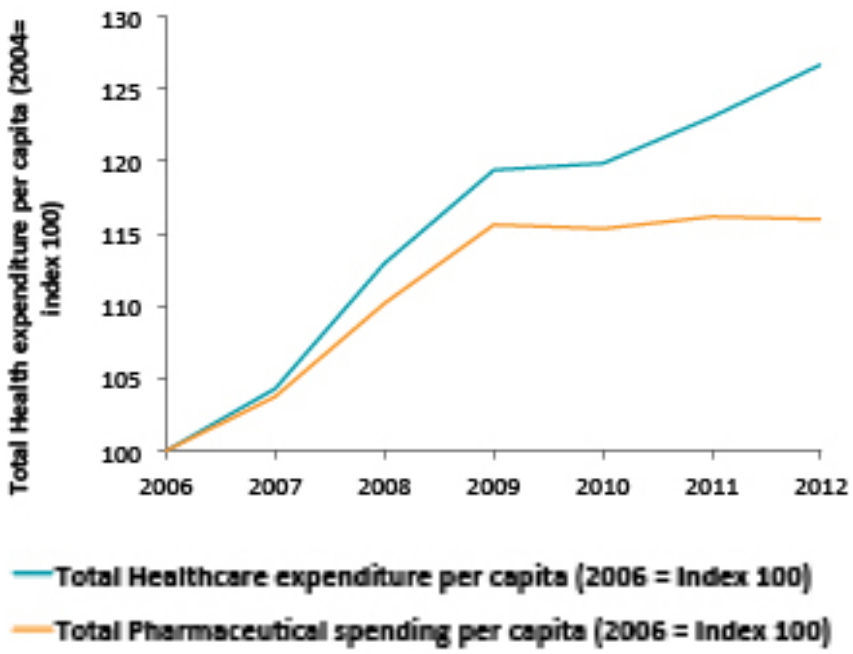
Adapted from Eichler et al (2012) Adaptive Licensing: Taking the Next Step in the Evolution of Drug Approval, *Nature* 91: 426-437

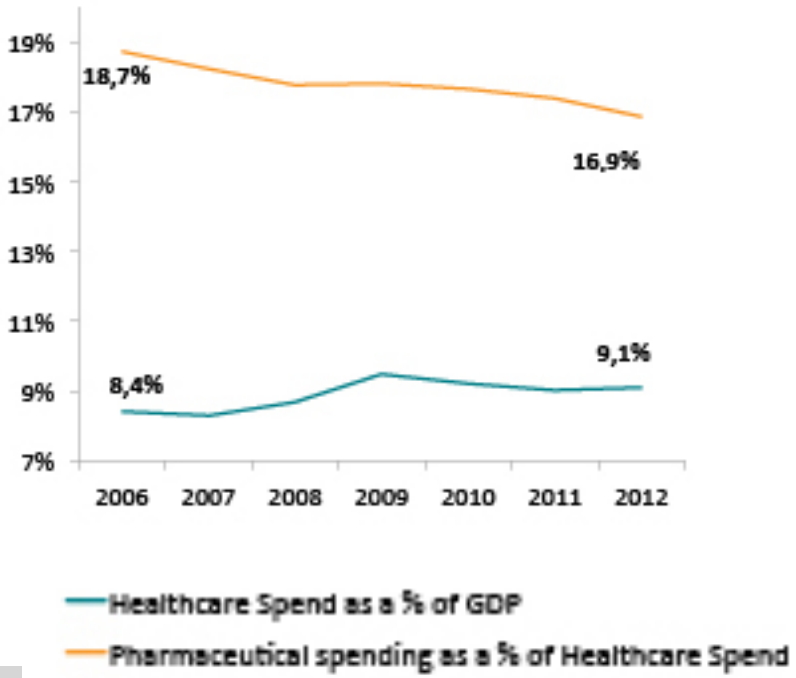
Healthcare aspects of innovative medicines

EU drug expenditure has been growing at a slower pace

Across Europe growth of retail medicines expenditure is lagging behind growth in total healthcare expenditure

Total healthcare expenditure per capita and pharmaceutical expenditure per capita (2006 – 2012, 21 EU OECD Countries, population-weighted, current prices, PPP, $)

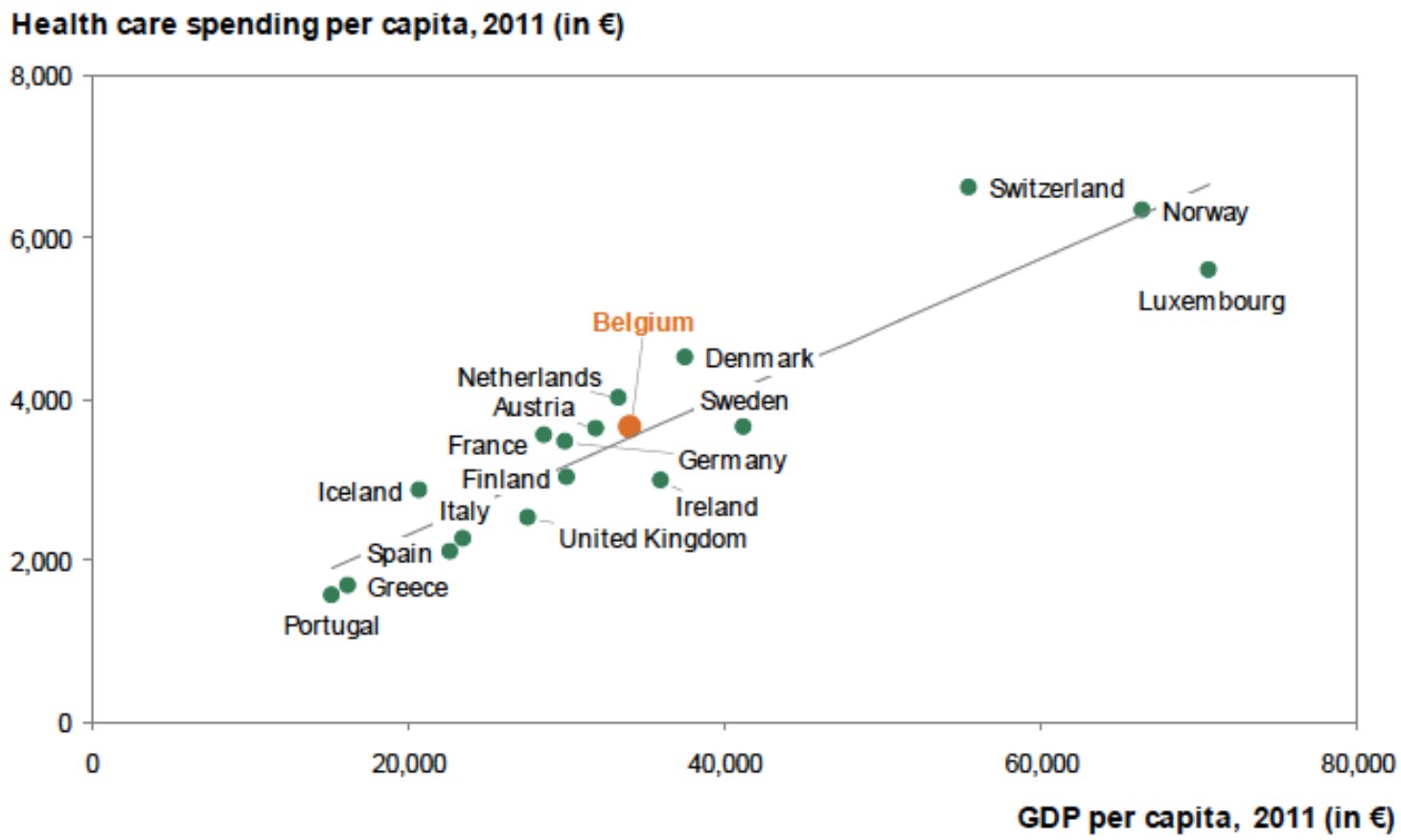




Source: OECD database, 2015

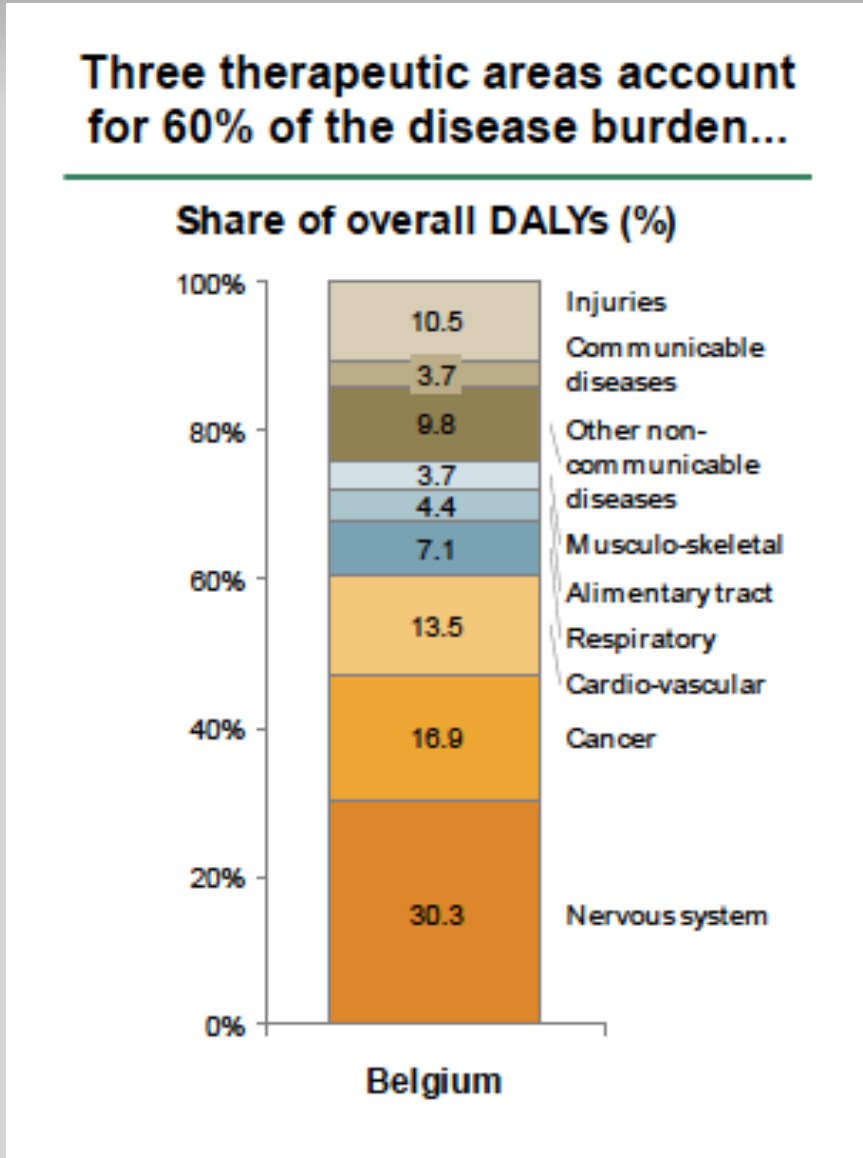
Healthcare spending correlates with wealth…

Exhibit 1: Belgium's health care spending is commensurate with its economic productivity compared to peer countries



Source: OECD; Economist Intelligence Unit

… but do we spend in the right domains?

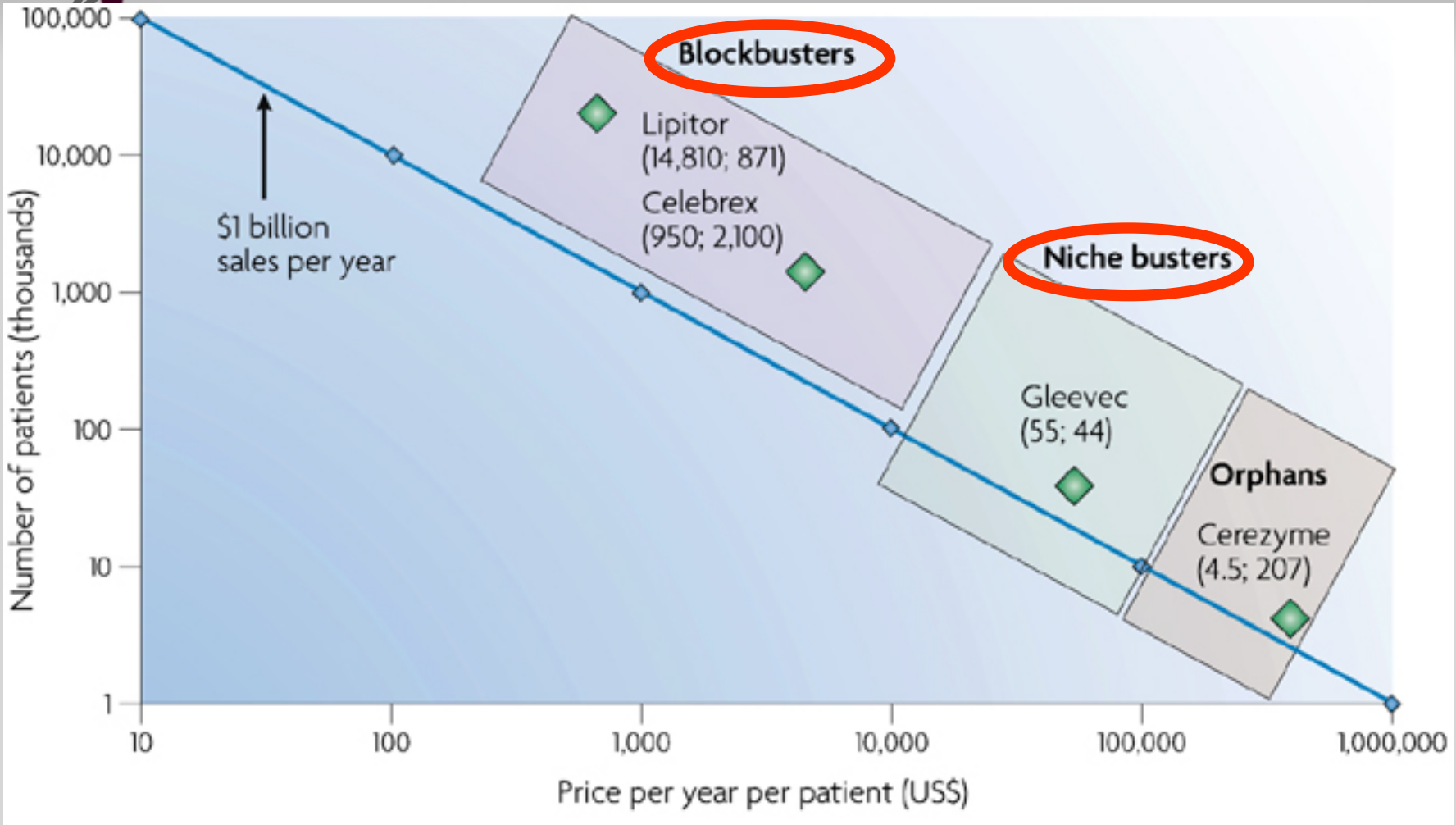


Source: IMS Health, 2014

How do pharma companies make their choices of innovative compounds?

- Exploitable science, new targets
- Market opportunity, including competitive landscape and reimbursement environment
- Challenges for development (high challenges for neuropsychiatric and neurodegenerative disorders)
- Orphan medicinal products
- *Unmet medical needs ?!*

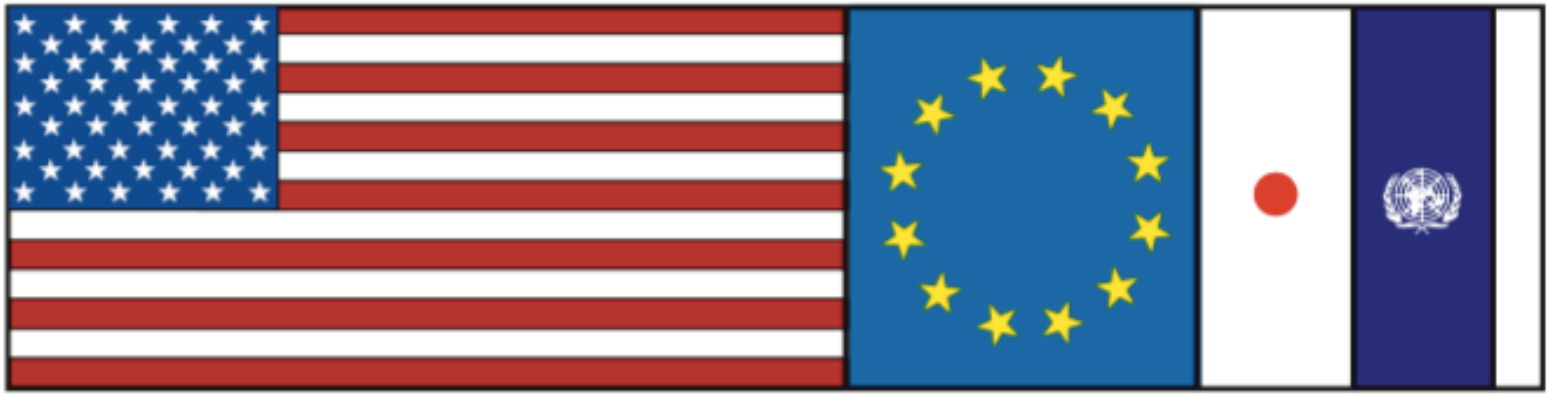
Not (necessarily) the end of the blockbuster



Trusheim, M.R. et al, Nature Rev Drug Disc 287-293 (April 07)

Most of the profit is in the US

GEOGRAPHICAL BREAKDOWN (BY MAIN MARKETS) OF SALES OF NEW MEDICINES LAUNCHED DURING THE PERIOD 2009-2013



55% USA | 23% Europe | 10% Japan | 9% Rest of the World | 3% Pharmerging

Note: New medicines cover all new active ingredients marketed for the first time on the world market during the period 2009-2013
Pharmerging comprises 21 countries ranked by IMS Health as high-growth pharmaceutical markets (Algeria, Argentina, Brazil, Colombia, China, Egypt, India, Indonesia, Mexico, Nigeria, Pakistan, Poland, Romania, Russia, Saudi Arabia, South Africa, Thailand, Turkey, Venezuela, Vietnam and The Ukraine)

Source: IMS Health (MIDAS April 2014)

Unmet needs → role of translational medicine !!

Thank you !!

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The new EMA building in Canary Wharf, London, UK