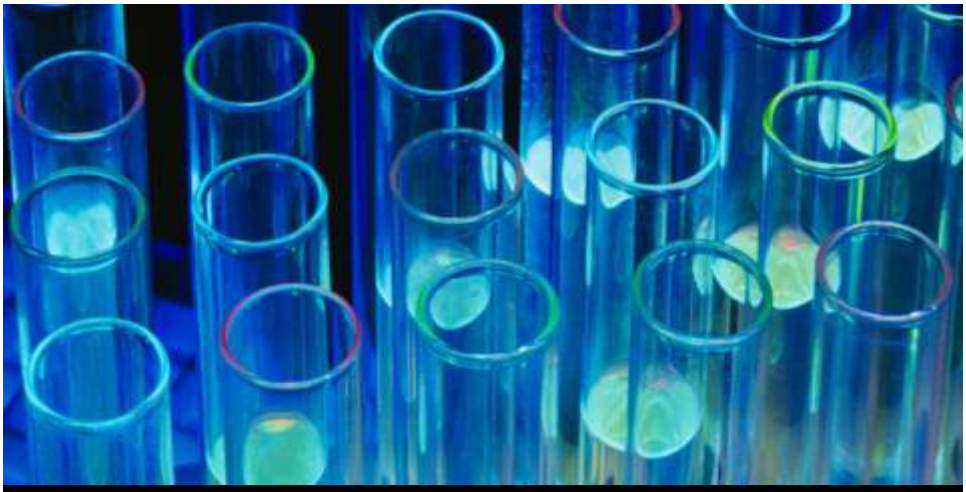


The Cost of Innovation in the Pharmaceutical Industry – A Review

Prof. Dr. Alexander Schuhmacher, Reutlingen University, March 2014

Conflict of interest: nothing to disclose

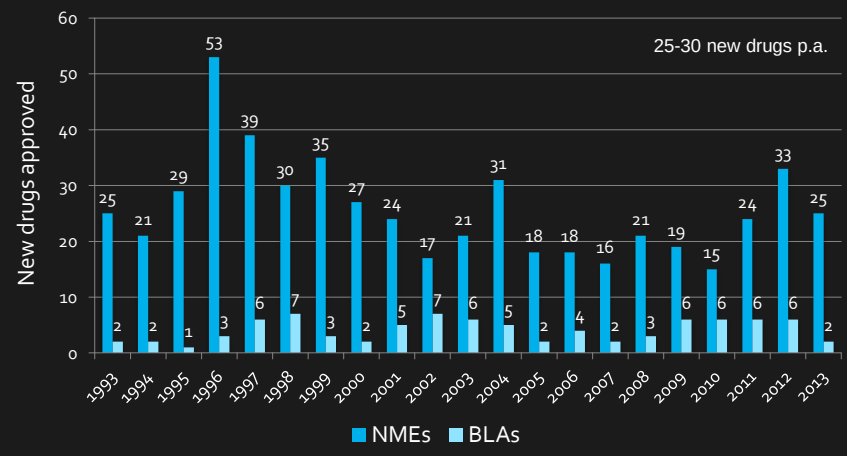
Executive Summary

- Despite scientific, technical and process-related advances in the past years and an escalating demand for medicine and a growing global healthcare market, the pharmaceutical industry is still facing huge challenges
- These are related to the nature of the pharmaceutical industry as its main driver of growth is innovation
- In the past years, the R&D costs per new drug increased and the R&D efficiency of pharmaceutical companies reduced
- Today, discovering and developing a new drug costs more than 1.8 billion USD

Key Facts on Pharmaceutical R&D

A detailed analysis of the situation

FDA approved 1,346 NMEs since 1950



NME (New Molecular Entity), BLA (Biologic License Application), **Source**: Hughes B. (2009) Nature Reviews Drug Discovery 8: 93-96; Mullard A. (2012) Nature Reviews Drug Discovery 11:91-94; Mullard A (2014) Nature Reviews Drug Discovery 13: 85-91; Munos B (2009) Nature Reviews Drug Discovery 8: 959-968; www. fda.org

Only some pharmacos have been successful over a longer period of time

Approx. 4,300 pharmaceutical companies	Since 1950, 261 pharmacos have registered at least 1 NME	593 NMEs from 137 pharmacos that disappeared by M&A
21 companies have produced 50% of all NMEs since 1950	360 NMEs by 9 big pharmacos that exist since 1950	Most productive pharmacos since 1950: Merck & Co. (56), Eli Lilly (51), Roche (51)

Source: Munos B (2009) Nature Reviews Drug Discovery 8: 959-968, pharmacos (pharmaceutical companies)

76% of pharmacos with active R&D come from Europe and US and top pharmacos invest more than USD 5 billion p.a. in R&D

	Astra Zeneca	Eli Lilly	GSK	Merck &Co.	Novartis	Pfizer	Roche	Sanofi
Number of total employees:	57.200	38.080	97.389	86.000	123.686	103.700	80.129	113.719
Group R&D Expenditures (2011) [USD million]:	5.523	5.021	5.007	7.742	9.239	9.112	8.688	8.902
R&D rate (%):	16,4	20,7	14,2	16,1	20,8	15,8	19,0	20,1
Number of R&D employees:	11.300	7.400	12.687	11.000	23.000	14.000	18.000	18.000
Number of main R&D sites:	14	9	14	n.a.	11	10	18	25

Source: Evaluate Pharma®, Annual Company Reports 2011 and 2012

Pharmacos are among the top investors in R&D WW

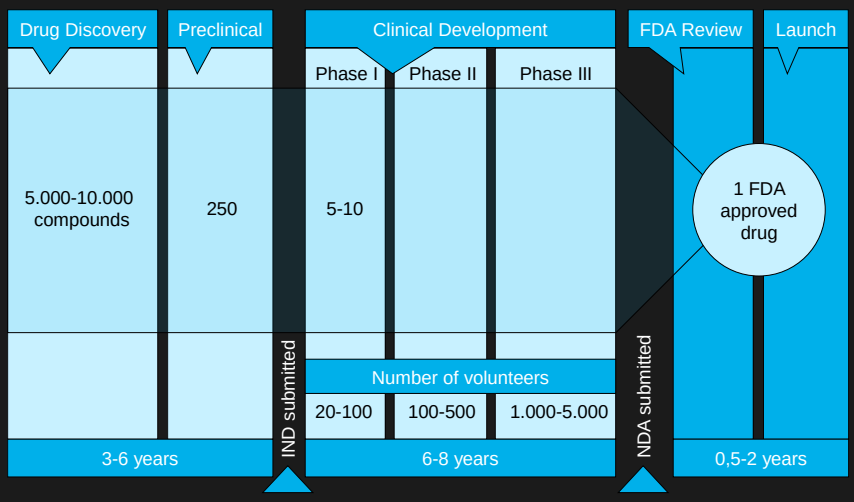
Toyota Motors 1st	**Roche 2nd**	Microsoft 3rd	Volkswagen 4th
Pfizer 5th	**Novartis 6th**	Nokia 7th	**Johnson& Johnson 8th**
	Sanofi Aventis 9th	Samsung 10th	

Source: European Comission, Joint Research Center, Directorate General Research (2010) The 2010 EU Industrial R&D Investment Scoreboard

The Pharma Innovation Process and the R&D Value Levers

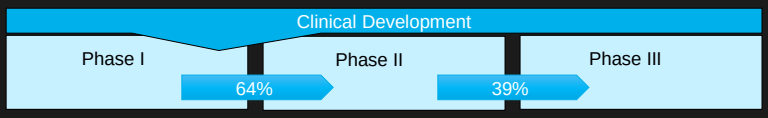
From Cost to Efficiency

The pharmaceutical R&D process is highly regulated, lengthy, and risky



IND (Investigational New Drug), NDA (New Drug Application), FDA (Food and Drug Administration)
Figure adapted from PhRMA (2011) Pharmaceutical Industry 2011 Profile

Pharmaceutical R&D has a low probability of success



- Cumulated phase transition rate from Phase I to submission[1]: 16%
- Only 8% of drug candidates successfully make it to the market[2]
  - Probability of success (PoS) for SMOLs: 7%
  - PoS biologics: 11%
- Most failures in Phase II and III resulted from lack of efficacy[3,4]
- PoS that a company is generating 2 or 3 NMEs p.a. is 0,06% and 0,003%, respectively[5]

[1]DiMasi JA et al. (2010) Clinical Pharmacology & Therapeutics 87 (3): 272-277, [2]Bergren R et al. (2012) Nature Reviews Drug Discovery 11: 435-436, [3]Arrowsmith J (2011) Nature Reviews Drug Discovery 10: 1, [4]Arrowsmith J and Miller P (2013) Nature Reviews Drug Discovery 12: 569, [5]Munos B (2009) Nature Reviews Drug Discovery 8: 959-968

Possible reasons for high attrition rates in R&D despite scientific and technical advances in the last years

- Shift towards developing drugs for chronic diseases correlate with reduced PoS[1]
  - Average PoS for chronic diseases: 6.88%
  - Average PoS for acute diseases 8.77%
- Target-based drug discovery contributes to the high attrition rates in pharmaceutical R&D[2]

[1]Pammolli F et al. (2011) Nature Reviews Drug Discovery 10: 428-438, [2]Swinney DC and Anthony J (2011) Drug Discovery Today 10:507-519

Drug R&D last for decades

- Average time of clinical development phases ranges from 6-8 years[1, 2]
- The total time for drug R&D increased in the past years to 14 years (2013)[2,3]
  - Not including time for basic research, target identification and validation or Phase IV trials

➡ New drug approvals today are associated with R&D expenditures that were invested many years ago

[1]Pammolli F et al. (2011) Nature Reviews Drug Discovery 10: 428-438, [2]Reichert JM (2003) Nature Reviews Drug Discovery 2: 695-702, [3]Remnant J et al. (2013) Measuring the return from pharmaceutical innovation 2013, accessible via http://thomsonreuters.com/business-unit/science/subsector/pdf/uk-manufacturing-measuring-the-return-from-pharmaceutical-innovation-2013.pdf

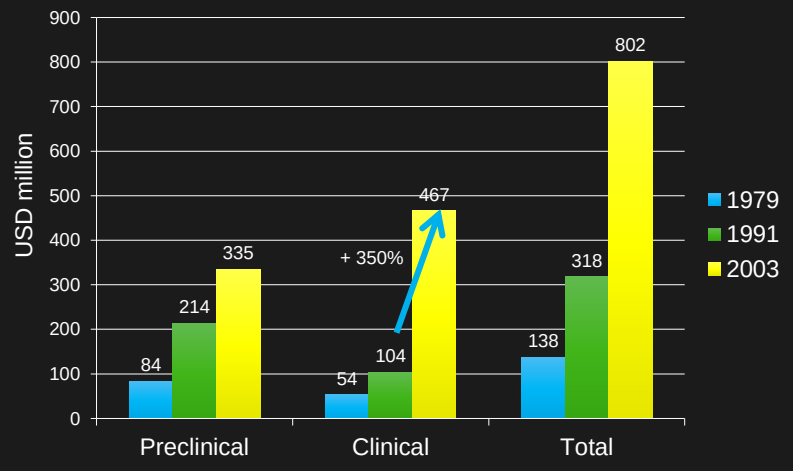
The costs of pharmaceutical R&D increased significantly (1950s – 1987)

Period	R&D Costs	Literature	Commentary
1950s-1960s	USD 0.5 million	Schnee JE (1972) Development costs: Determinants and overruns, Journal of Business: 347-374	Partial cost estimation: Discovery costs and costs of unsuccessful R&D projects not considered, no capitalization
1976	USD 54 millions	Hansen RW (1980) Pharmaceutical development costs by therapeutic categories, University of Rochester Graduate School of Management Working Paper No. GPB-80-6	Full cost estimation
1987	USD 231 millions	DiMasi JA (1991) Journal of Health Economics 10: 107-142	Full cost estimation: Out of the pocket costs USD 114 million, 9% discount rate
2003	USD 802 millions	DiMasi JA (1991) Journal of Health Economics 23: 151-185	Full cost estimation: Out of the pocket costs USD 403 million and discount rate of 11%

→ Since mid 1980s, out-of-the-packet costs and capitalized costs per NME increased by 7,6% and 7,4% p.a. (above general price inflation), respectively

Data derived from: DiMasi JA (1991) Journal of Health Economics 10: 107-142; DiMasi JA et al. (2003) Journal of Health Economics 22: 151-185

Substantially higher costs of clinical development have resulted in higher R&D costs



Source: DiMasi et al. (2003) Journal of Health Economics 23: 151-185

Development costs of biologics are higher

- Capitalized costs per biologic: USD 1,318 million[1]
- The capitalized costs of drug development per new asset increased from USD 1,019 million (2010) to USD 1,219 million (2013)[2]
- Calculations do not include Phase IV (post-approval) costs, costs for regulatory approval in non-US markets or new indications

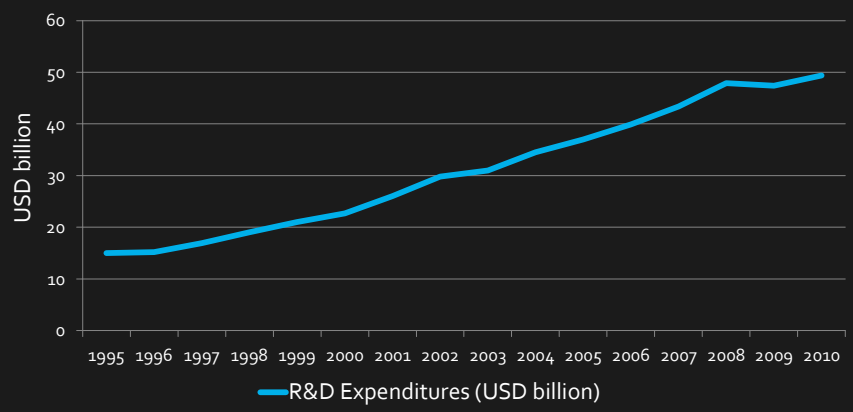
[1]DiMasi JA, Grabowski HG (2007) Managerial and Decision Economics 28: 469-479, [2]Remnant J et al. (2013) Measuring the return from pharmaceutical innovation 2013, accessible via http://thomsonreuters.com/business-unit/science/subsector/pdf/uk-manufacturing-measuring-the-return-from-pharmaceutical-innovation-2013.pdf

Today, capitalized costs per launch are USD 1.8 billion and clinical development accounts for 63% of total costs

	Target-to-hit	Hit-to-lead	Lead optimi-zation	Pre-clinical	Phase I	Phase II	Phase III	Sub-mission to launch	Launch
p(TS)	80%	75%	85%	69%	54%	34%	70%	91%	
WIP needed for 1 launch	24,3	19,4	14,6	12,4	8,6	4,6	1,6	1,1	1
Cycle times (years)	1,0	1,5	2,0	1,0	1,5	2,5	2,5	1,5	
Cost per launch (million USD)	24	49	146	62	128	185	235	44	873
Capitalized costs per launch (million USD)	94	166	414	150	273	319	314	48	1.778

Source: Paul SM et al. (2010) Nature Reviews Drug Discovery 9: 203-214

Total pharma R&D expenditures increased



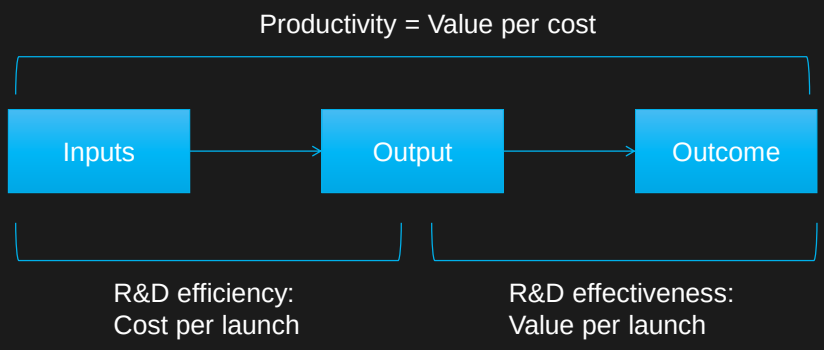
Source: PhRMA (2011) Pharmaceutical Industry 2011 Profile; PhRMA (Pharmaceutical Research and Manufacturers of America); substantial proportions of R&D expenditures are missing: (1) expenditure of in-licensed drugs and (2) not every pharmaceutical company is PhRMA member

R&D costs increased by 8.6% p.a. since 1950

- Annual increase in capitalized R&D costs since 1950: 12.3%[1]
- Inflation since 1950: 3.7% p.a.
- Remaining 8.6% p.a. may result from
  - Advanced complexity of drug targets
  - Greater complexity of clinical trials
  - Higher demands of regulatory authorities
  - More R&D personnel[2]→ Clinical development functions account for more than 50% of all R&D expenditures

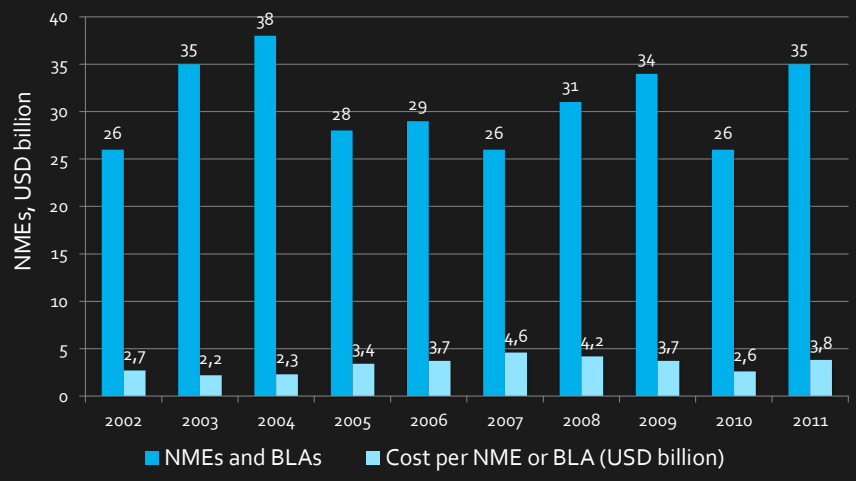
[1]Munos B (2009) Nature Reviews Drug Discovery 8: 959-968, [2]Cohen FJ (2005) Nature Reviews Drug Discovery 4: 78

The dimensions of R&D efficiency are cost per launch



Source: Paul SM et al. (2010) Nature Review Drug Discovery 9: 203-214

What are the costs per launch?



Source: PWC (2012) From vision to decision Pharma 2020 (www.pwc.com/pharma2020)

What are the costs per launch?

Number of approved drugs	Median (USD million)	Mean (USD million)
8-13	5,459	5,998
4-6	5,151	5,052
2-3	1,803	2,303
1	351	953

10 years R&D spending (USD million)	Median (USD million)	Mean (USD million)
>20,000	6,348	6,623
>5,000	2,883	2,961
>2,000	1,917	2,480
>1,000	1,459	741

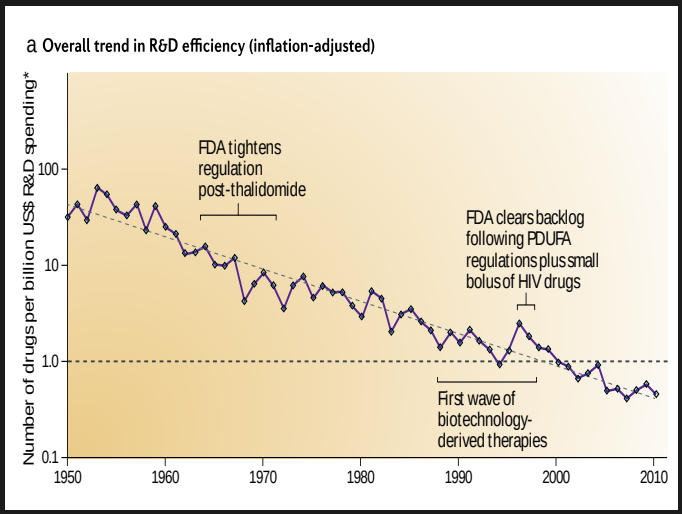
Source: http://www.forbes.com/sites/matthewherper/2013/08/11/how-the-staggering-cost-of-inventing-new-drugs-is-shaping-the-future-of-medicine/

What are the costs per launch?

Rank	Company	NMEs	10 years R&D spending (USD million)	R&D costs per drug (USD million)
1	Abbott/Abbvie	1	13,183	13,183
2	Sanofi	6	60,768	10,128
3	AstraZeneca	4	38,245	9,561
4	Roche	8	70,928	8,866
5	Pfizer	10	77,786	7,779
6	Wyeth	3	22,702	7,567
7	Eli Lilly	4	26,710	6,678
8	Bayer	5	33,118	6,624
9	Schering-Plough	3	18,845	6,282
9	Novartis	10	60,727	6,073
10	Takeda	4	24,132	6,033

Source: http://www.forbes.com/sites/matthewherper/2013/08/11/the-cost-of-inventing-a-new-drug-98-companies-ranked/

Number of NMEs per billion USD of R&D spending has nearly halved every 9 years since 1950



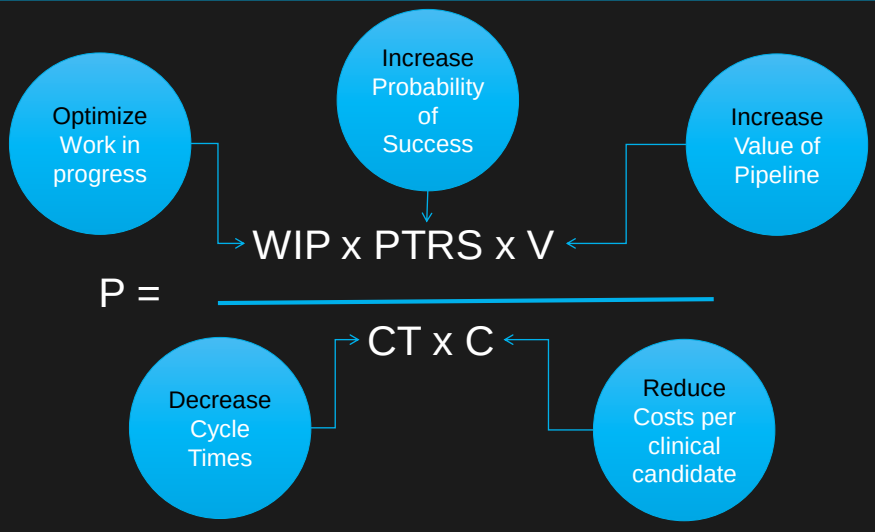
Source: Scannell JW et al. (2012) Nature Reviews Drug Discovery 11: 191-200

Possible reasons for the reduced R&D efficiency

- Insufficient number of projects in preclinical and early clinical phases[1]
- Increasing number of approved drugs raise the hurdle for approval and reimbursement of new drugs[2]
- A lower risk tolerance of drug regulators increases both the challenges for launching new drugs and the development-associated costs[2]
- Target-based screening in drug discovery replaced an older and perhaps more productive method of drug research (phenotypic screening)[2]
- Increasing number of mergers might have influenced pharmaceutical R&D negatively[3]

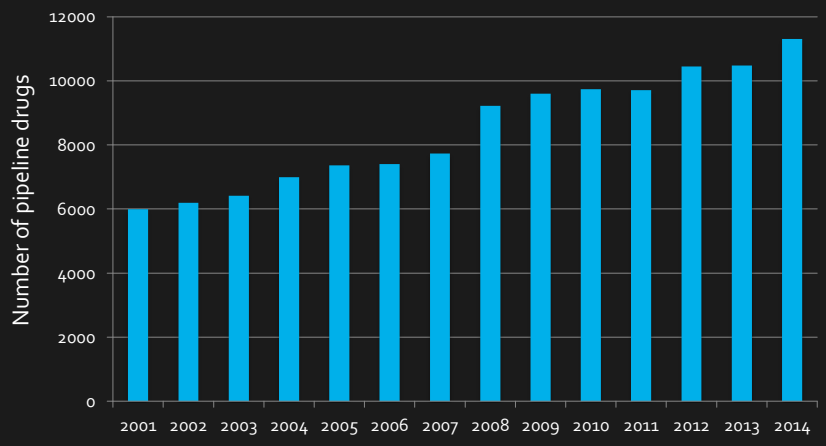
Source: [1]Paul SM (2010) Nature Reviews Drug Discovery 9: 207, [2]Scannell JW et al. (2012) Nature Reviews Drug Discovery 11: 191-200, [3]LaMattina JL (2011) Nature Reviews Drug Discovery 10: 559-560

How did the pharmaceutical industry react?



Source: Paul SM et al. (2010) Nature Review Drug Discovery 9: 203-214

The global R&D pipeline is growing ...



Source: Citeline (2013) Pharma R&D Annual Review (http://www.citeline.com/wp-content/uploads/Citeline_2013_RD_Annual_Review1.pdf)

… as pharmacos have increased the number of R&D projects in their pipelines

Position in 2014	Company	Number of R&D pipeline drugs (2014)
1	GlaxoSmithKline	261
2	Roche	248
3	Novartis	223
4	Pfizer	205
5	AstraZeneca	197
6	Merck & Co.	186
7	Sanofi	180
8	Johnson & Johnson	164
9	BMS	133
10	Takeda	132

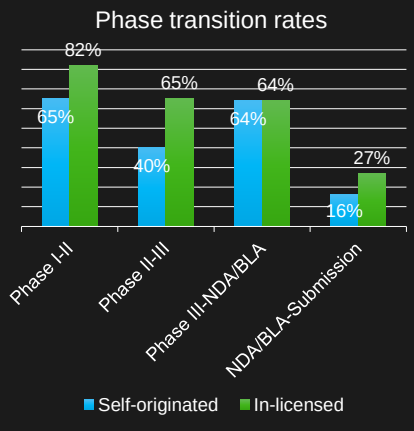
Source: Citeline (2013) Pharma R&D Annual Review (http://www.citeline.com/wp-content/uploads/Citeline_2013_RD_Annual_Review1.pdf)

Pharmacos have reduced their R&D costs …

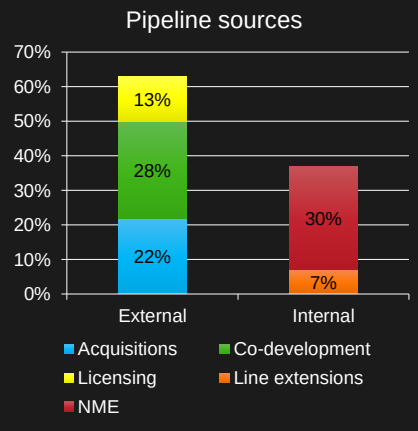
- Pharmacos have reduced their personnel in R&D[1]
- Outsourcing to provide lean and flexible R&D organizations
- Some pharmacos reduced their R&D rates under the historical benchmark of 20%
  - AstraZeneca (2011): 15,6%
  - Sanofi (2011): 15,1%
  - Pfizer (2011): 14,8%
  - GlaxoSmithKline (2011): 14,5%

Source: Germann PG et al. (2013) Human Genomics 7: 5

…and focused on licensing and acquiring drug candidates from external sources



Source: DiMasi JA et al. (2010) Clinical Pharmacology & Therapeutics 87 (3): 272-277



Source: Remnant J et al. (2013) Measuring the return from pharmaceutical innovation 2013, accessible via http://thomsonreuters.com/business-unit/science/subsector/pdf/uk-manufacturing-measuring-the-return-from-pharmaceutical-innovation-2013.pdf

Did these measures effect an increased R&D efficiency?

- "*…the drug industry produces no more NMEs today than 60 years ago*."[1]
- Average of 25-30 NMEs p.a. "*… may reflect the innovative capacity of the established R&D model*."[1]

[1]Munos B (2009) Nature Reviews Drug Discovery 8: 958-968

How many NMEs are required for large pharma?

" *… large pharmaceutical companies ... need to produce an average of 2-3 NMEs per year to meet their growth objectives, the fact that none of them has ever approached this level of output is concerning*."[1]

"*Pfizer with pharmaceutical revenues in 2003 of approximately USD 45 billion, will need to generate approximately nine high-quality NCEs per annum*."[2]

[1]Munos B (2009) Nature Reviews Drug Discovery 8: 958-968, [2]Kola I and Landis J (2004) Nature Reviews Drug Discovery 3: 711

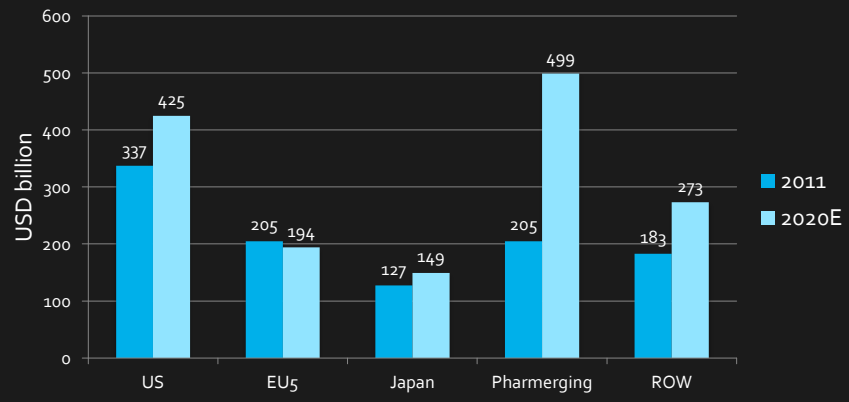
As the R&D efficiency is reduced, could the pharmaceutical industry increase the value resulting from drug R&D?

- Projected revenues of NMEs launched between 2012 and 2016 (USD 58 billion[1]) will not compensate the revenue losses by patent expirations between 2010 and 2014 (USD 89.5 billion)
- Average peak sales per NME is expected to decline from 900 million USD (2012) to 600 million USD (2015), showing the increasing difficulty of offering benefits over existing treatments in light of the increasing price pressure[1]

[1]Bergren R et al. (2012) Nature Reviews Drug Discovery 11: 435-436

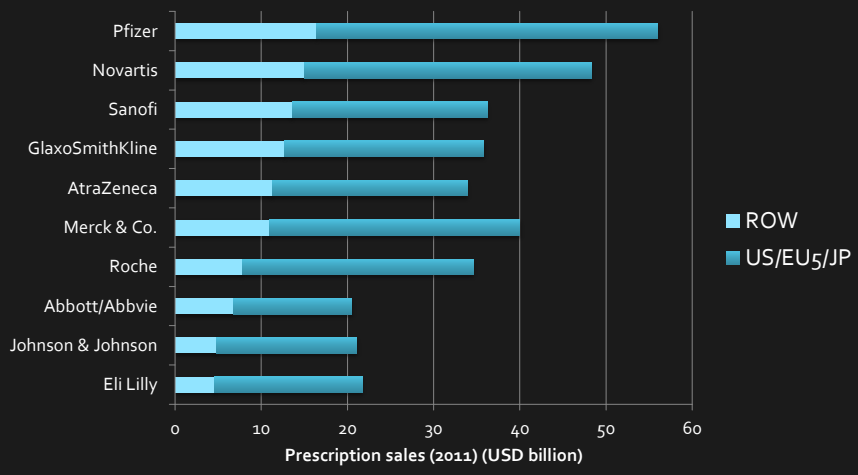
Are there any alternatives in view of these challenges?

There is a rapidly increasing demand for medicines in emerging countries



Source: PWC (2012) From vision to decision Pharma 2020 (www.pwc.com/pharma2020)

Consequently, four big pharmacos already earn a third of their revenues outside the main markets



Source: PWC (2012) From vision to decision Pharma 2020 (www.pwc.com/pharma2020)

Patients in the growth markets can‘t afford costly new drugs, such as biologics

	Private share of healthcare expenditures (%)	Per capita health spending, 2010 (USD)	Population with net assets of USD 10.000 or less (%)
Brazil	53,0	990	62,1
China	46,4	221	66,4
India	70,8	54	92,8
Russia	37,9	525	75,4

- Growing countries currently lack the financial power to reward innovation
- Increase in pharma sales is expected to come from generics

Source: PWC (2012) From vision to decision Pharma 2020 (www.pwc.com/pharma2020)

What else could be done to increase efficiency of pharmaceutical R&D and the value of pharmaceutical innovation?

Research & Development

- Focus on therapeutic areas and compounds with the greatest probability of success
- R&D focused on patients' needs
- Personalized medicine
- Opening R&D towards external innovation (e.g. crowdsourcing, licensing)
- Further reducing R&D costs (e.g. outsourcing, virtual R&D)

Marketing & Sales

- Specialty products
- Oncology as a key revenue generator
- Higher value of biologics

Thank you for your attention

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Back-up Slides

Defining Innovation

- "*Innovation encompasses both the development and application of a new product, process or service. It assumes novelty in the device, the application, or both. Thus, innovation can include the use of an existing type of product in a new application or the development of a new device in an existing application*."
- "*Incremental* [sequential or follow-on] *innovations ... are improvements ... on existing innovations*." Examples: Reformulations or me-too drugs
- "*Radical* [major, stand-alone discontinuous] *innovations … [are] innovations that represent something completely new and different*." Example: First-in-class drugs
- "*NME is a new drug product that contain active moieties that have not been approved by FDA previously, either as a single ingredient drug or as part of a combination product*" [http://www.fda.gov/drugs/developmentapprovalprocess/druginnovation/default.htm]

Source: Cohen FJ (2005) Nature Reviews Drug Discovery 4: 78-84

Rewardable Innovation

- An innovation must be novel and useful
- Usefulness can come from:
  - Benefit in a condition with no existing effective treatment
  - Improvement in the treatment of a condition that does not have consistently satisfactory treatment
  - Safer treatment
  - More cost-effective treatment
  - More convenient treatment
- Rewardable innovation is defined as "*a medical product that provides … something novel, with the potential or proven ability to yield … a treatment not previously available or clinically significant improvement in treatment … at an acceptable cost*."

Source: Aronson JK et al. (2012) Nature Reviews Drug Discovery 11: 253-254

Rewardable Innovation

- A highly innovative product may result from a new target or a mechanism-of-action, from improved identification of patients who are likely to benefit or from a novel application of an existing drug
- A moderately innovative product may result from a new class of compound, fewer adverse reactions or drug-drug interactions, or a novel method of synthesis
- A slightly innovative product may result from improved pharmacokinetics or improved formulations
- A non-health-related innovation may result from a improved production method

Source: Aronson JK et al. (2012) Nature Reviews Drug Discovery 11: 253-254

Impact of Incremental Innovations

- Simply counting NMEs may underestimate the innovation potential of pharmaceutical R&D
  - Not all NMEs provide blockbuster potential
  - Incremental innovations are an important source of revenues and profits as they provide fewer technical risks at reduced costs
- Between 1990-2003 FDA approved 1,174 NDAs (New Drug Applications), of which 34% were NMEs (New Molecular Entities) and 66% were non-NMEs (new formulations, dosages, indications)[1]
- Incremental innovation generate significant economic and health benefits[2]
  - Improved patient compliance
  - Improved pharmacokinetics
  - Reduced adverse effects
  - Ability to effectively treat a new patient population

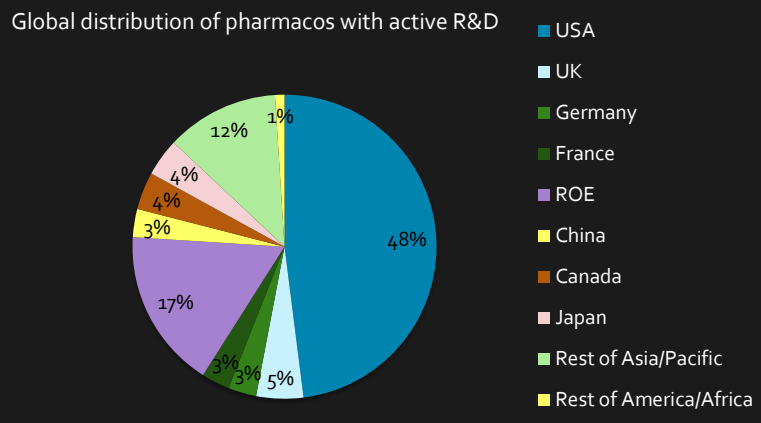
[1]Cohen FJ (2005) Nature Reviews Drug Discovery 4: 78-84; [2]Berndt ER et al. (2006) Pharmacoeconomics 24(2): 69-86

Impact of Incremental Innovations

- First-in-class or best-in-class drugs are important for the success of pharmacos
- Many pharmacos are pursuing the same disease areas, working with the same targets, following the same rationals and providing similar innovations, which is not suitable in todays payers‘ climate
- The development of blockbuster drugs is becoming increasingly complex, as the development of a superior product in an area where a previous highly efficacious blockbuster went off patent is very difficult

Source: Berndt ER et al. (2006) Pharmacoeconomics 24(2): 69-86, DiMasi JA (2003) Journal of Health Economics 22: 151-185

76% of pharmacos with active R&D come from Europe and US



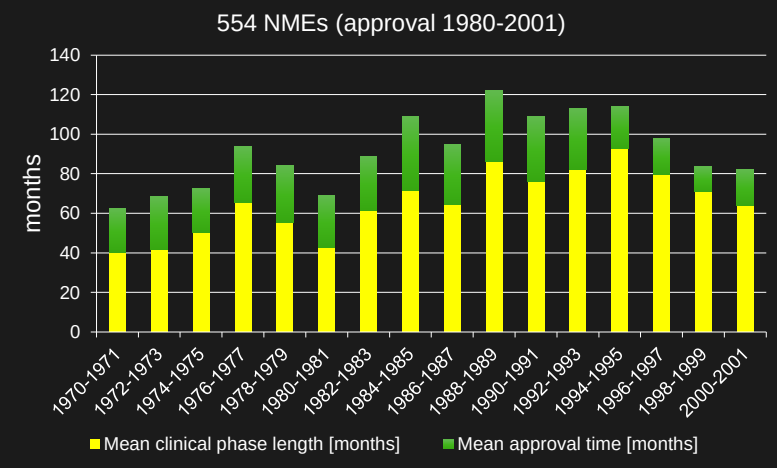
Source: Citeline (2014) Pharma R&D Annual Review (http://www.citeline.com/wp-content/uploads/Citeline_2014_RD_Annual_Review1.pdf)

Lack of efficacy is still the main reason for compound failure

- Between 2007-2010, 83 compounds failed in Phase III or during the submission process
  - 66% insufficient efficacy
  - 32% not better than placebo
  - 5% not better than active control
  - 29% no real benefits as add-on therapies
- Between 2011-2012, 56% of total failures in Phase II and III resulted from lack of efficacy

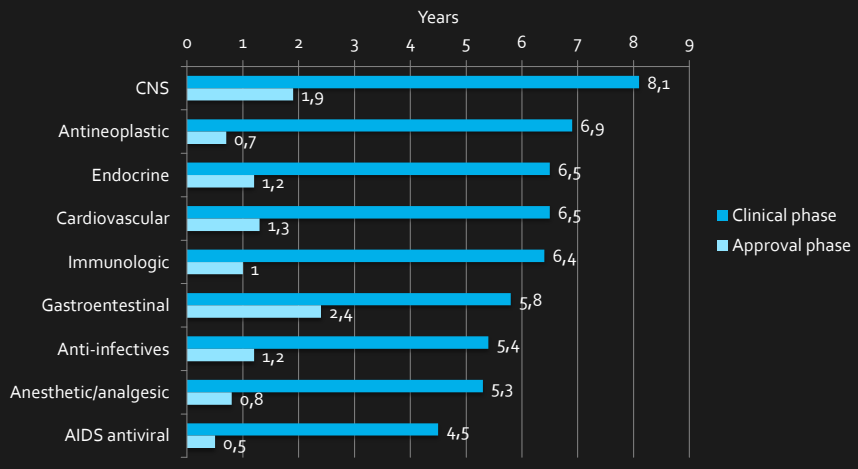
Source: Arrowsmith J (2011) Nature Reviews Drug Discovery 10: 1, Arrowsmith J and Miller P (2013) Nature Reviews Drug Discovery 12: 569

Mean clinical phase and approval time from 60 to 80 months



Data derived from: Reichert JM (2003) Nature Reviews Drug Discovery 2: 695-702; 504 NDAs, 50 BLAs

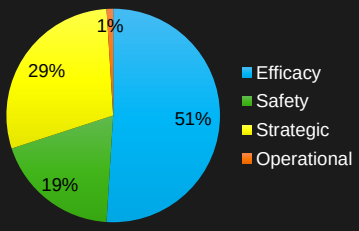
FDA Drug Approval Times



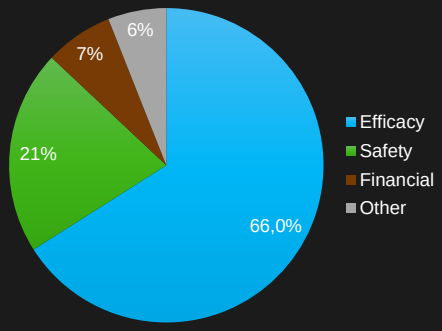
Source: Kaitin KI and DiMasi JA (2011) Clinical Pharmacology and Therapeutics 89(2): 183-188

Trends in attrition rates in 2011-2012

Phase II failures[2]



Phase III and submission failures[2]



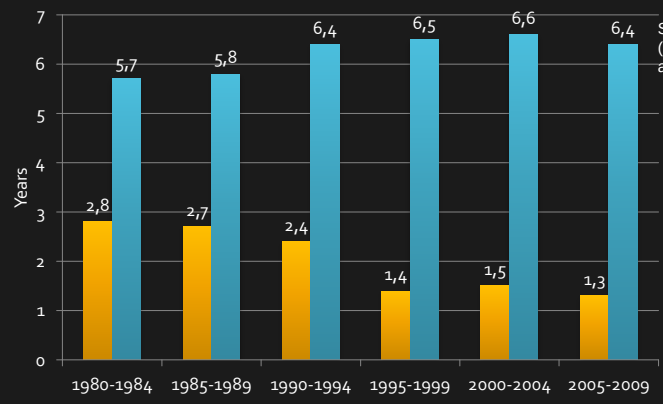
Source: Arrowsmith J and Miller P (2013) Nature Reviews Drug Discovery 12: 569

Costs of Innovation (1987)

Phase	Mean Duration [months]	Mean Phase Costs [USD millions]	Capitalized Costs [USD millions]*
Preclinical	42.6	65.5	155.6
Phase I	15.5	9.3	17.8
Phase II	24.3	12.9	21.4
Phase III	36.0	20.2	27.1
Long-term animal studies	33.6	5.3	8.2
Other animal studies	33.6	0.4	0.7
Total		113.6	230.8

Data derived from: DiMasi JA (1991) Journal of Health Economics 10: 107-142
*23% success rate in clinical phases, 9% discount rate

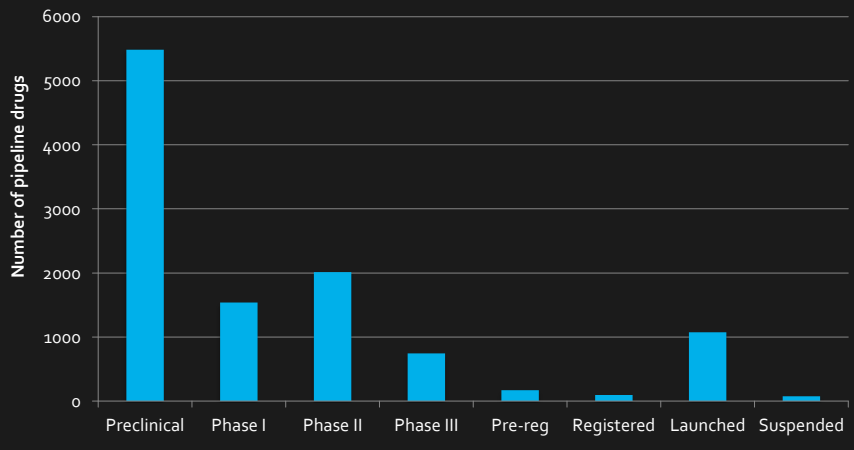
New drug approvals today are associated with R&D expenditure that were invested many years ago ...



Source: Kaitin KI and DiMasi JA (2011) Clinical Pharmacology and Therapeutics 89(2): 183-188

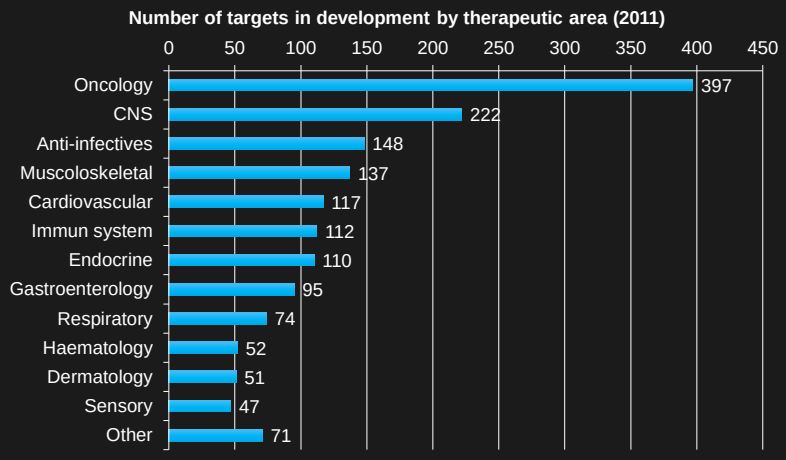
„*Shorter FDA approval times since mid 1990s were associated with the Implementation of the Prescription Drug Use Fee Act of 1992*“ [DiMasi et al. (2003) Journal of Health Economics 23: 151-185]

Total Size of R&D Pipeline by Development Phase (2014)



Source: Citeline (2013) Pharma R&D Annual Review (http://www.citeline.com/wp-content/uploads/Citeline_2013_RD_Annual_Review1.pdf)

26% of all drug targets are in the field of oncology



Berggren R et al. (2012) Nature Reviews Drug Discovery 11: 435-436

How many NMEs are required for large pharma?

2002 sales	Anticipated sales from current products in 2012	Annual real growth rate	Sales gap for new products to fill in 2012	Estimated number of NCEs required to fill the gap (over ten years)	Year 2012 required NCE output
USD 45 billion	USD 30 billion	5%	USD 43.5 billion	75-90	9.5-11
USD 30 billion	USD 20 billion	5%	USD 29 billion	50-60	6.5-7.5
USD 20 billion	USD 13.3 billion	5%	USD 19.3 billion	33-40	4.3-5
USD 15 billion	USD 10 billion	5%	USD 14.5 billion	25-30	3.25-3.75
USD 10 billion	USD 6.67 billion	5%	USD 9.67 billion	16.5-20	2.15-2.25

[1]Munos B (2009) Nature Reviews Drug Discovery 8: 958, [2]Kola I and Landis J (2004) Nature Reviews Drug Discovery 3: 711

Pharmacos have reduced their R&D personnel

	Company	Date	Notes
1	Novartis	Jan. 2012	2.000 US sales jobs
2	Sanofi	Imminent	Up to 2.000 French jobs
3	Pfizer	2005	Still another 12.100 of planned 60.000 jobs to be cut
4	Roche	June 2012	Nutley site closed, 1.000 R&D jobs cut
5	GlaxoSmithKline	n.a.	Ongoing restructering, no specific job target announced
6	Merck & Co.	July 2011	12-13% workforce reduction in addition to earlier cuts following the Schering-Plough merger
7	Johnson & Johnson	Nov. 2009	7.000 – 8.200 jobs
8	Abbott	Jan. 2012	700 manufacturing jobs
9	Bristol-Myers Squibb	n.a.	Ongoing, 295 jobs cut in 2012
10	AstraZeneca	Feb. 2012	7.300 jobs (incl. 2.200 in R&D)

Source: Germann PG et al. (2013) Human Genomics 7: 5