Drug Value & Market Access Optimization

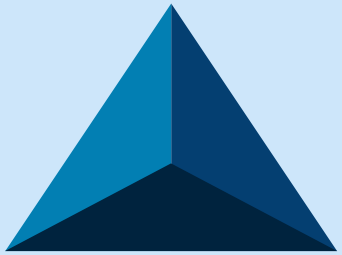
"Finding New & Better Avenues"

From Drug Cost to Payer Valuation

- How to get the best value? -

Report: R&D Excerpts

June 2016



Smart Pharma Consulting

1, rue Houdart de Lamotte – 75015 Paris – France
Tel.: +33 6 11 96 33 78 – Fax: +33 1 45 57 46 59
E-mail: jmpeny@smart-pharma.com – Website: www.smart-pharma.com

Table of contents

The purpose of this report is to provide key information and robust analyses to better optimize drug valuation, from the pharmaceutical companies perspective

Context & Objective

- To slowdown the increase of healthcare expenditure, governments and public or private payers implement a large array of cost-containment mechanisms
- Drugs are particularly affected by these measures, which include:
  - Drug prices control and regulations to favor the prescription of cheaper products like generics and biosimilars
  - Capping of the prescribed volumes
  - Selective reimbursement of drugs (e.g. limitation to a subset of patients or to the most severe cases)
- However, the way these measures are applied does not allow governments and payers to guarantee access to innovation to the largest number of patients
- Thus, governments and payers have no choice but to increase their pressure on drug prices and “force” pharma companies to accept affordable prices

- In this context, the following questions must be raised:
  - What is the value of innovative drugs for the community?
  - What is a fair price for pharmaceutical companies?
- This report reviews:
  - The economic and healthcare environment
  - The R&D cost of drugs
  - The drug pricing strategic approaches of pharma companies, governments and payers
  - The health economic evaluation methods
  - The market access processes in selected countries
  - The best practices in market access
  - The ways to leverage the corporate reputation of pharma companies
- Smart Pharma Consulting proposes new thoughts likely to help pharma companies to optimize the valuation of their drugs

Source: Smart Pharma Consulting analyses

R&D cost of drugs is subject to severe critics due to the absence of recognized valuation methodologies and the lack of independence of the authors of certain studies

What is the R&D cost of new drugs?

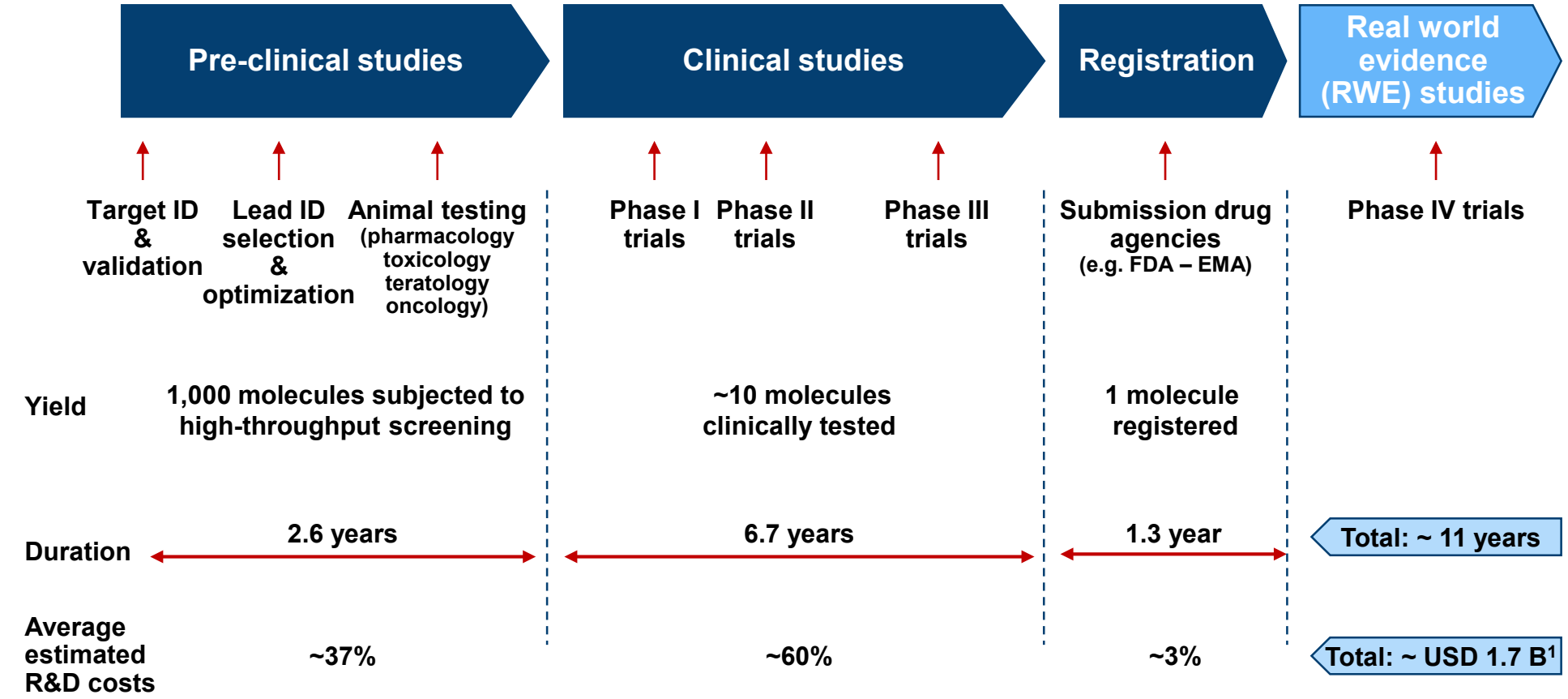
- Prior to reviewing the different approaches to value the price of drugs in Western countries, we propose to **analyze** the **cost** associated to the **research and development** of a **new drug**
- The drug market is often described as "**high risk – high reward**" due to the important level of development failures and to the time required to bring a new product to the market
- Several **studies** have been carried out to **estimate** the **R&D cost** of a new drug, including in addition to the "**out-of-pocket**" costs actually spent in R&D, **multiple factors** such as the **cost of capital**[1], the **failure rates** and the development timelines
- All **these valuations** are **strongly criticized** due to some **methodological problems** and the **lack of independence** of their authors
- Irrespective of these loopholes, the cost to bring a new drug to the market reaches **several USD billion**
- Even if they are often perceived as less important, the manufacturing costs also need to be covered by the price granted by authorities

Source: Smart Pharma Consulting analyses

[1] The cost of the investment in a project which will only generate revenues years later

The current R&D process has a low success rate, with less than 10% of the compounds entering Phase I clinical studies that will reach the market

The conventional R&D process



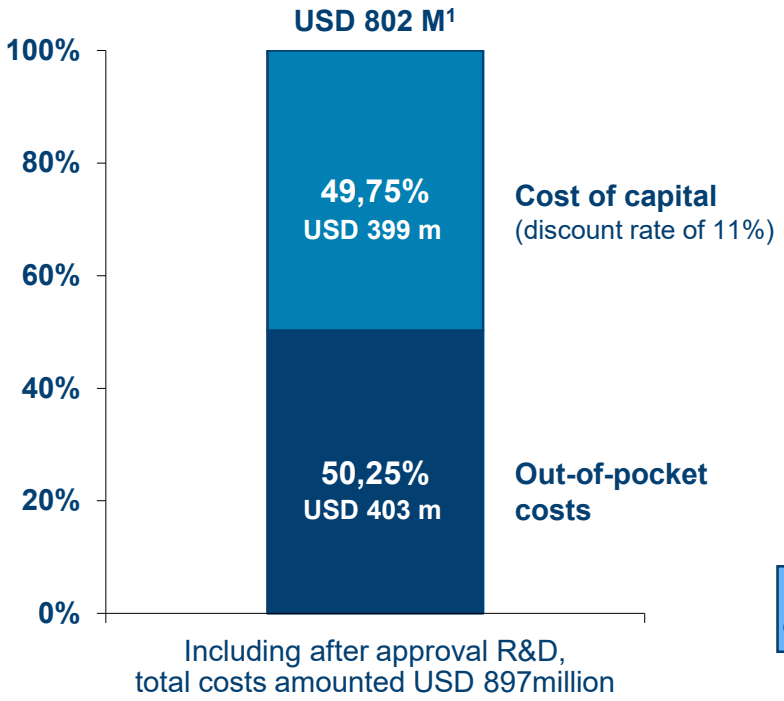
Sources: IBM Consulting 2002 – LEEM – Pharmaprojects, IMS Health – R&D Focus – DiMasi & Al (2014) – Smart Pharma Consulting estimates

[1] Average of estimated studies published with mid-analysis point after 1990

In a 2000 study, DiMasi estimated the out-of-pocket costs per approved new drug at USD 403 million and the fully capitalized total cost at USD 802 million

R&D costs estimates for drugs (2000) (1/3)

Estimated capitalized cost per approved new drug (pre-tax)



- The cost of 68 (including 1 vaccine, 2 monoclonal antibodies, 4 recombinant proteins) randomly selected drugs from 10 pharmaceutical companies have been analyzed[2]
- The compounds chosen were all self-originated (i.e. exclusion of in-licensed compounds) and first tested in humans from 1983 to 1994
- Out-of-pocket costs were capitalized at a real discount rate of 11% until the date of marketing approval (~10.6 years)
- Costs of failure have been allocated to those of marketed new products
- Out-of-pocket and capitalized preclinical costs were estimated at USD 121 M and USD 335 M, respectively
- Out-of-pocket and capitalized clinical costs were estimated at USD 282 M and USD 467 M, respectively

Loopholes of the study

- Source of data coming from drug manufacturers
- Tufts Center is partly funded by pharmaceutical companies
- No consideration of public research grants and of tax reimbursements
- Only NME[3] included (not line extension as new indications, formulations, etc.)

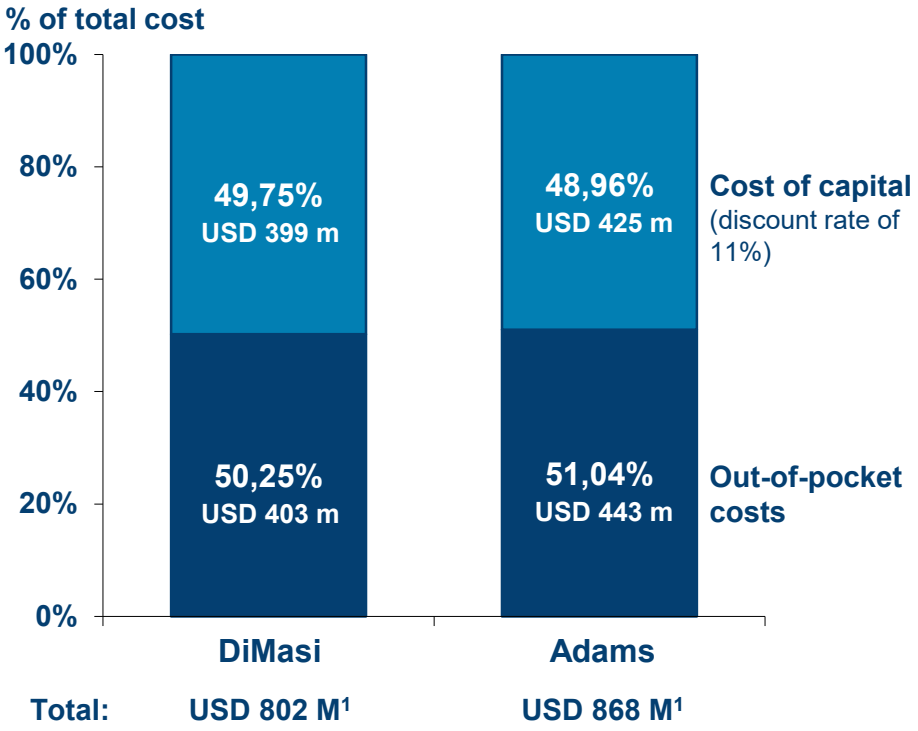
Source: DiMasi JA & al, 2003. J. Health Economics

[1] Capitalized costs in 2000 dollars – [2] From Tufts Center for the Study of Drug Development (CSDD) proprietary databases – [3] New molecular entity

Average R&D estimated costs of a new drug by Adams were slightly higher than the results obtained by DiMasi with the same methodology but a different database

R&D costs estimates for drugs (2000) (2/3)

Estimated capitalized cost per approved new drug (pre-tax)



- The adopted method was identical to the one used by DiMasi (2003):
  - The out-of-pocket money spent for developing a new drug = the estimated average cost of each phase of development x the probability of getting to the phase
  - The time cost (opportunity cost) was estimated using the average duration of each step
  - A discount rate of 11% was used
- Instead of using the proprietary Tufts Center for Study of Drug Development (CSDD) database, Adams used publicly available Pharmaprojects database which is based on press releases, academic presentations, etc.
- Capitalized preclinical costs were estimated at USD 335 M for DiMasi and USD 381 M for Adams
- Capitalized clinical costs were estimated at USD 467 M for DiMasi and USD 487 M for Adams

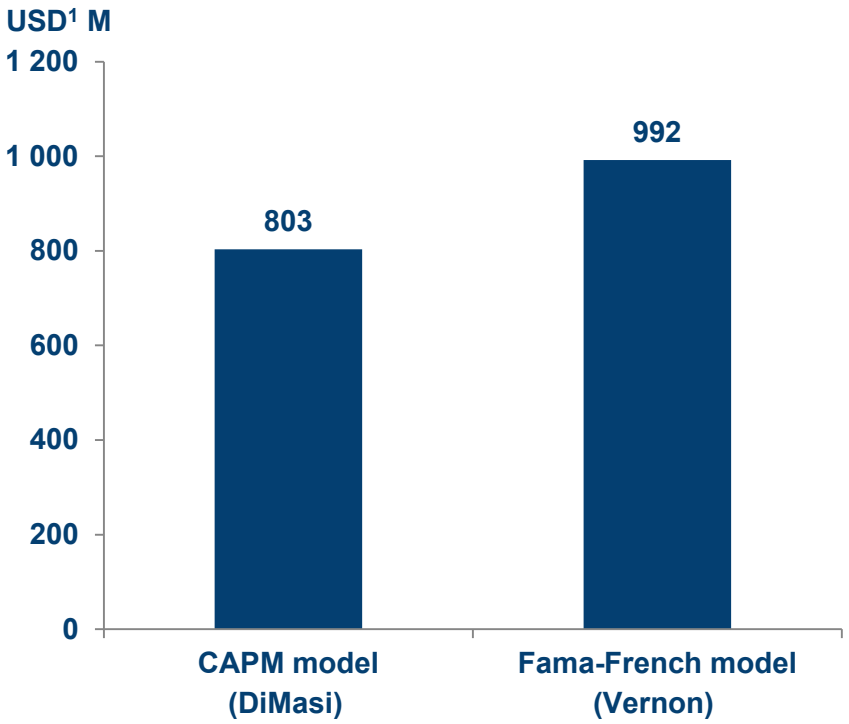
Sources: Adams CP & al, 2006. Health Affairs – DiMasi JA et al, 2003. J. Health Economics

[1] Capitalized costs in 2000 dollars

According to the method used to estimate the cost of capital, R&D costs associated with an approved new drug vary from USD 803 to USD 992 million

R&D costs estimates for drugs (2000) (3/3)

Estimated capitalized cost per approved new drug (pre-tax)



- The following methodological components were identical to the ones adopted by DiMasi estimates:
  - The out-of-pocket money spent for developing a new drug = the estimated average cost of each phase of development x the probability of getting to the phase
  - The time cost (opportunity cost) was estimated using the average duration of each step
  - The database (Tufts Center for Study of Drug Development database) was also the same
- By using a different method to estimate the cost of capital (COC) the results obtained by Vernon differ significantly from DiMasi:
  - 11.02% discount rate for the capital asset pricing model (CAPM) used by DiMasi which is a single factor model
  - 14.36% discount rate for the Fama-French three factor model

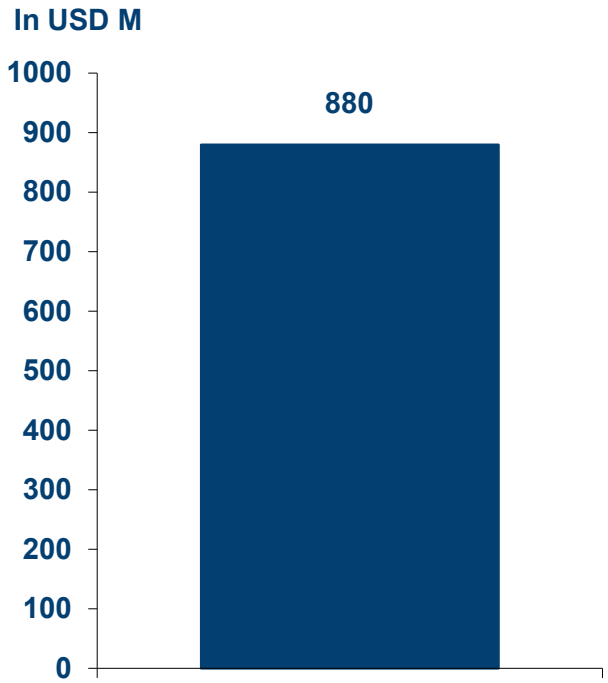
Sources: Vernon J & al, 2009. Health Economics – DiMasi JA & al, 2003. J. Health Economics

[1] Capitalized costs in 2000 dollars

According to the survey carried out by the Boston Consulting Group in 2001, R&D costs required for a successful drug launch were in the range of USD 880 million

R&D costs estimates for drugs (2001)

Estimated capitalized cost per approved new drug



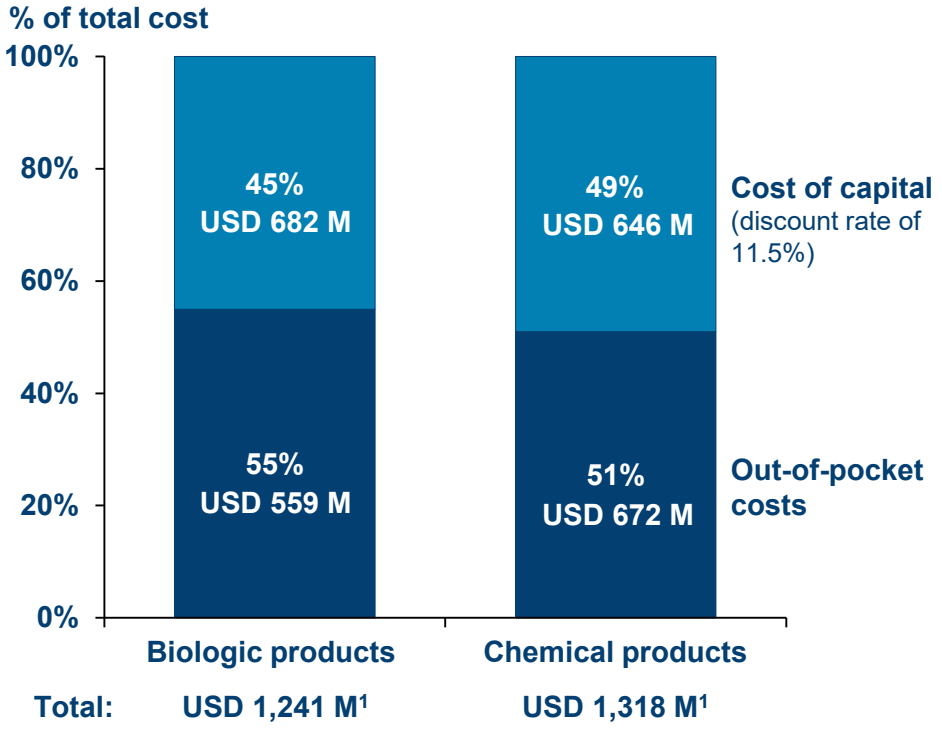
- Estimates are based on an extensive program of discussions in an effort to compile accurate figures for all the main activities in the R&D process
- This bottom-up model is based on the time, the cost and the likely success rate for each step of the R&D process
- This R&D cost model:
  - Is based on primary research (more than 100 discussions with 50 companies and academic institutions)
  - Analyzes the discovery phase in details
  - Is activity-based and flexible
- R&D costs vary according to factors such as therapeutic areas and target classes

Source: BCG analysis, 2001

No significant differences have been observed between the R&D cost of biologic and chemical products (small molecule chemical entities)

R&D costs for biological & chemical products (2005)

Estimated capitalized cost per approved new drug (pre-tax)



Biologic products

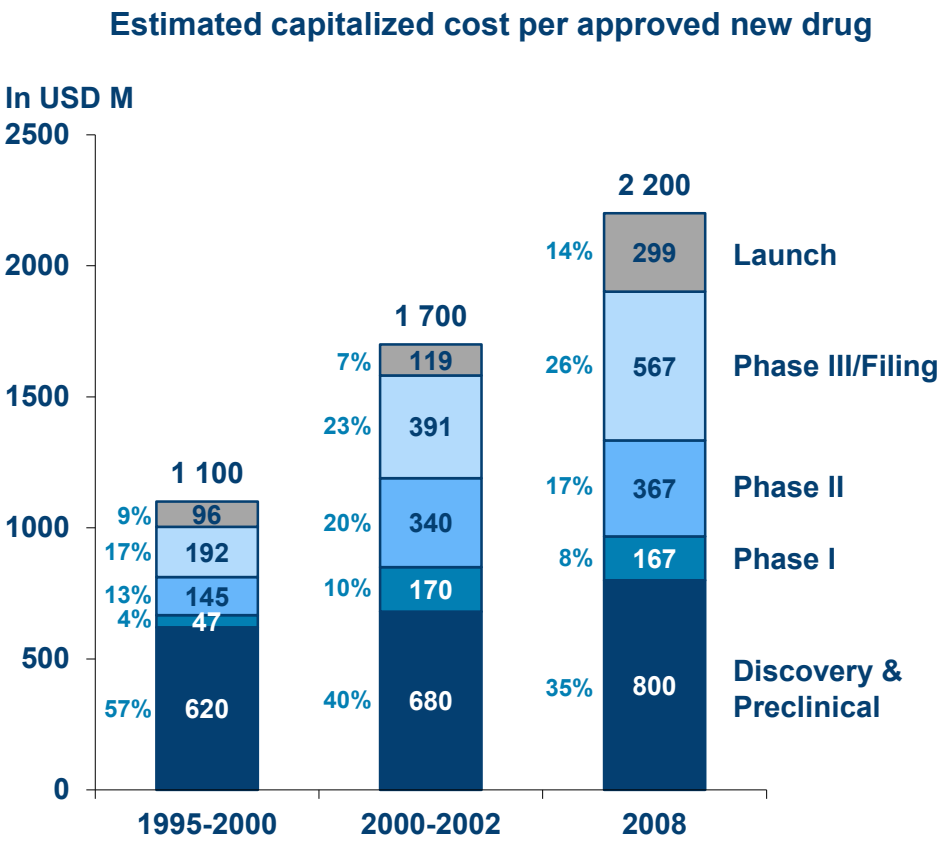
- The costs of 17 investigational biologic products (9 recombinant proteins and 8 monoclonal antibodies) from 4 pharmaceutical companies were analyzed based on 2005 data
- Costs of compound failures were included
- Out-of-pocket costs were capitalized at a real discount rate of 11.5% until the date of marketing approval (~12.5 years)
- Development time costs of failed projects were allocated to those of marketed new products
- Out-of-pocket and capitalized preclinical costs were estimated at USD 198 M and USD 615 M, respectively
- Out-of-pocket and capitalized clinical costs were estimated at USD 361 M and USD 626 M, respectively

Source: DiMasi JA & al, 2007. Manage. Decis. Econ

[1] Capitalized costs in 2005 dollars

According to the economic model developed by Bain & Co, R&D costs required for one successful drug launch were estimated at USD 2.2 billion in 2008

R&D costs estimates for drugs (1995 – 2008)



- When the costs of failed prospective drugs are factored in, the cost for discovering, developing and launching a single new drug has doubled from the 1995-2000 period to 2008, to reach USD 2.2 billion (including both direct and indirect costs)
- The increase results from (between the 1995-2000 and the 2000-2002 periods):
  - A drop in cumulative success rates from 14% to 8%
  - An increase in research, development and launch costs of nearly 50% for each of these steps
- Productivity declines for self-developed products have made in-licensing more attractive

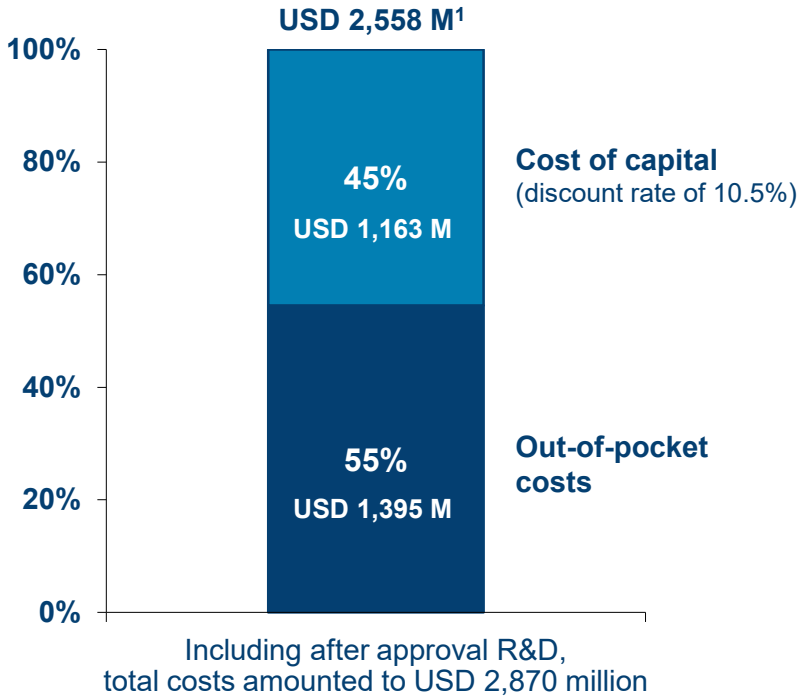
Sources: Gilbert L & al, 2003. In Vivo – O'Hagab P and Farkas C, 2009. Bain & Co

%: Percentage of total costs

The latest estimates by author DiMasi concluded in an important out-of-pocket spending growth while cost of capital discount rate was decreased by one point of percentage

R&D costs estimates for drugs (2014)

Estimated capitalized cost per approved new drug (pre-tax)



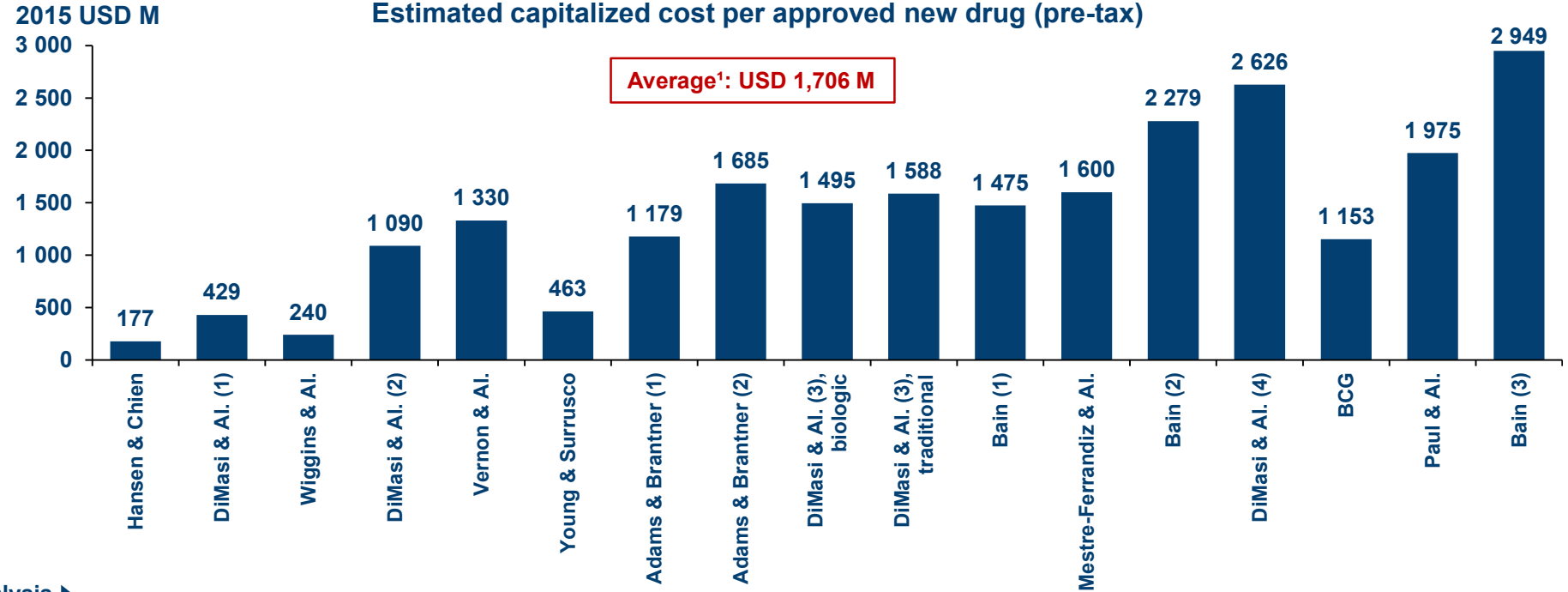
- DiMasi followed a similar methodology compared with its previous estimates on drugs costs (based on 106 new chemical and biologic drugs first tested in humans between 1995 and 2007)
- The database was also the same: Tufts Center for the Study of Drug Development proprietary database
- The cost of capital applied to out-of-pocket costs (10.5%) was decreased compared with previous analysis
- Out-of-pocket and capitalized preclinical costs were estimated at USD 430 M and USD 1098 M, respectively
- Out-of-pocket and capitalized clinical costs were estimated at USD 965 M and USD 1460 M, respectively
- Results showed an important increase of out-of-pocket costs compared with previous estimates. The CAGR of out-of-pocket R&D was estimated per period as follows:
  - 1970s to 1980s: +7.0%
  - 1980s to 1990s: +7.6%
  - 1990s to early 2010s: +9.3%

Source: DiMasi & Al., 2014

[1] Capitalized costs in 2014 dollars

If there is an important variation between estimates due to the different methodologies (cost of capital, etc.), there is also a clear increasing trend of R&D costs per new drug

Evolution of R&D costs (1/2)



	Hansen & Chien	DiMasi & Al. (1)	Wiggins & Al.	DiMasi & Al. (2)	Vernon & Al.	Young & Surrusco	Adams & Brantner (1)	Adams & Brantner (2)	DiMasi & Al. (3), biologic	DiMasi & Al. (3), traditional	Bain (1)	Mestre-Ferrandiz & Al.	Bain (2)	DiMasi & Al. (4)	BCG	Paul & Al.	Bain (3)
Mid-analysis year[2]	1969	1976	1978	1989	1989	1995	1996	1996	1997	1997	1998	2000	2001	2001	2001	2002	2008
Publication date	1979	1991	1987	2003	2009	2001	2006	2010	2007	2007	2009	2012	2009	2014	2001	2010	2009
Cost of capital used	8.0%	9.0%	8.0%	11.0%	14.4%	9.0%	11.0%	11.0%	11.5%	11.5%	N/A	N/A	N/A	10.5%	N/A	11.0%	N/A

Note: For the sake of comparability, all values are adjusted to USD 2015 prices using data of the US GDP implicit price deflator from the US. Bureau of Economic Analysis. The GDP implicit deflator shows the rate of price change in the economy as a whole, being the ratio of GDP in current local currency to GDP in constant local currency

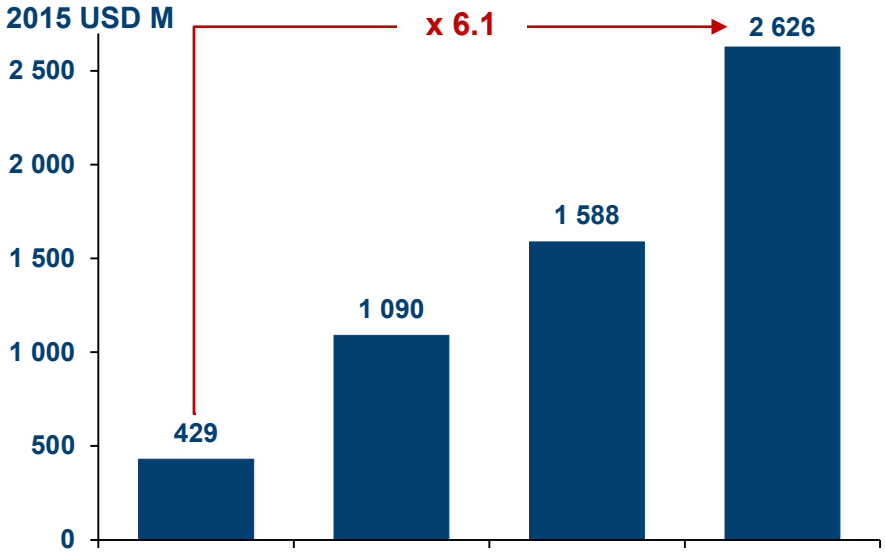
Sources: Authors publications – "The cost of drug development: A systematic review", Steve Morgan & Al

[1] Average of estimates with mid-analysis point after 1990 –
[2] Products with first testing in humans over the analyzed period

The analysis of four studies carried out with the same methodology, shows that the development cost of new drugs has more than sextupled over the last three decades

Evolution of R&D costs (2/2)

Estimated capitalized cost per approved new drug (pre-tax)



	DiMasi (1)	DiMasi (2)	DiMasi (3)	DiMasi (4)
Mid-analysis year[1]	1976	1989	1997	2001
Publication date	1991	2003	2007	2014
Cost of capital used	9.0%	11.0%	11.5%	10.5%

- The evolution of the capitalized R&D costs per approved new drug, after neutralization of the inflation, can be mainly explained by:
  - The growth of the out-of-pocket costs, especially the growth of clinical trials spending: x10.8 between the 1991 and the 2014 estimates (vs. preclinical spending which grew less: x3.9)
  - The decrease of the success rates to reach approval from phase I, ranging from 23% in the first 1991 estimates to 12% in the 2014 estimates
  - The overall increase of the used cost of capital, even if, in the 2014 estimates, a 10.5% cost of capital was used, in decrease of 1 point of percentage from the previous estimates. These assumptions of cost of capital seem overestimated compared with available data from NYU Stern School of Business for biotech products (9.2%, based on 411 firms) and for traditional pharma (7.7%, based on 157 firms)

Note: For the sake of comparability, all values are adjusted to USD 2015 prices using data of the US GDP implicit price deflator from the US. Bureau of Economic Analysis. The GDP implicit deflator shows the rate of price change in the economy as a whole, being the ratio of GDP in current local currency to GDP in constant local currency

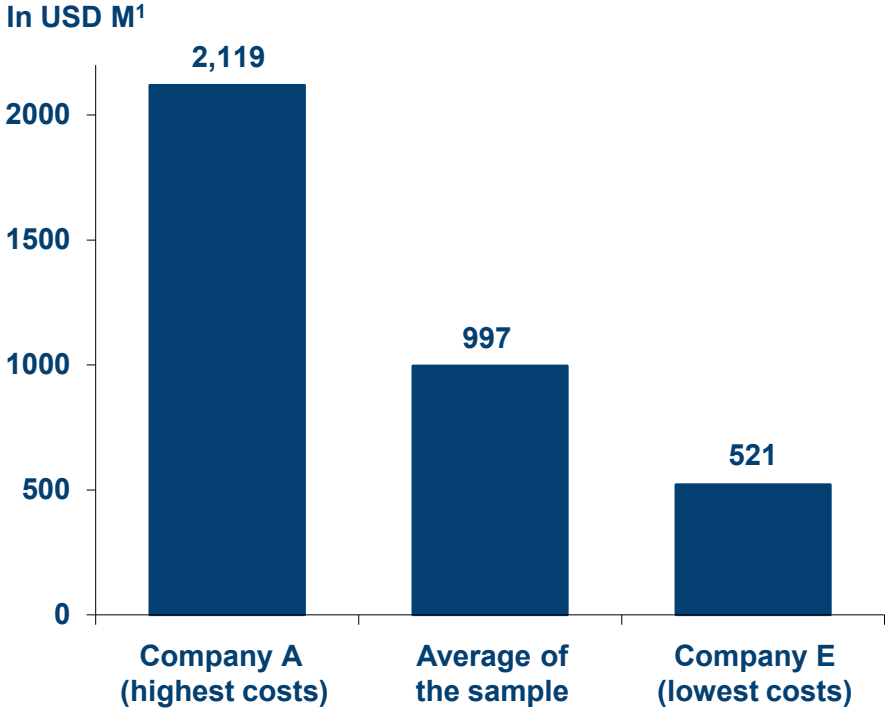
Sources: DiMasi (1991) – DiMasi et al. (2003) – DiMasi, Grabowski (2007) – DiMasi (2014) – Cost of Capital - NYU Stern School of Business, January 2016

[1] Products with first testing in humans over the analyzed period

The huge variations in the average estimated R&D capitalized costs within the largest companies are strongly driven by the probability for drugs to reach to market

Variations in R&D costs estimates according to companies (2000)

Estimated capitalized cost per approved new drug (pre-tax)
(Sample of 11 companies amongst the largest worldwide in 2001)



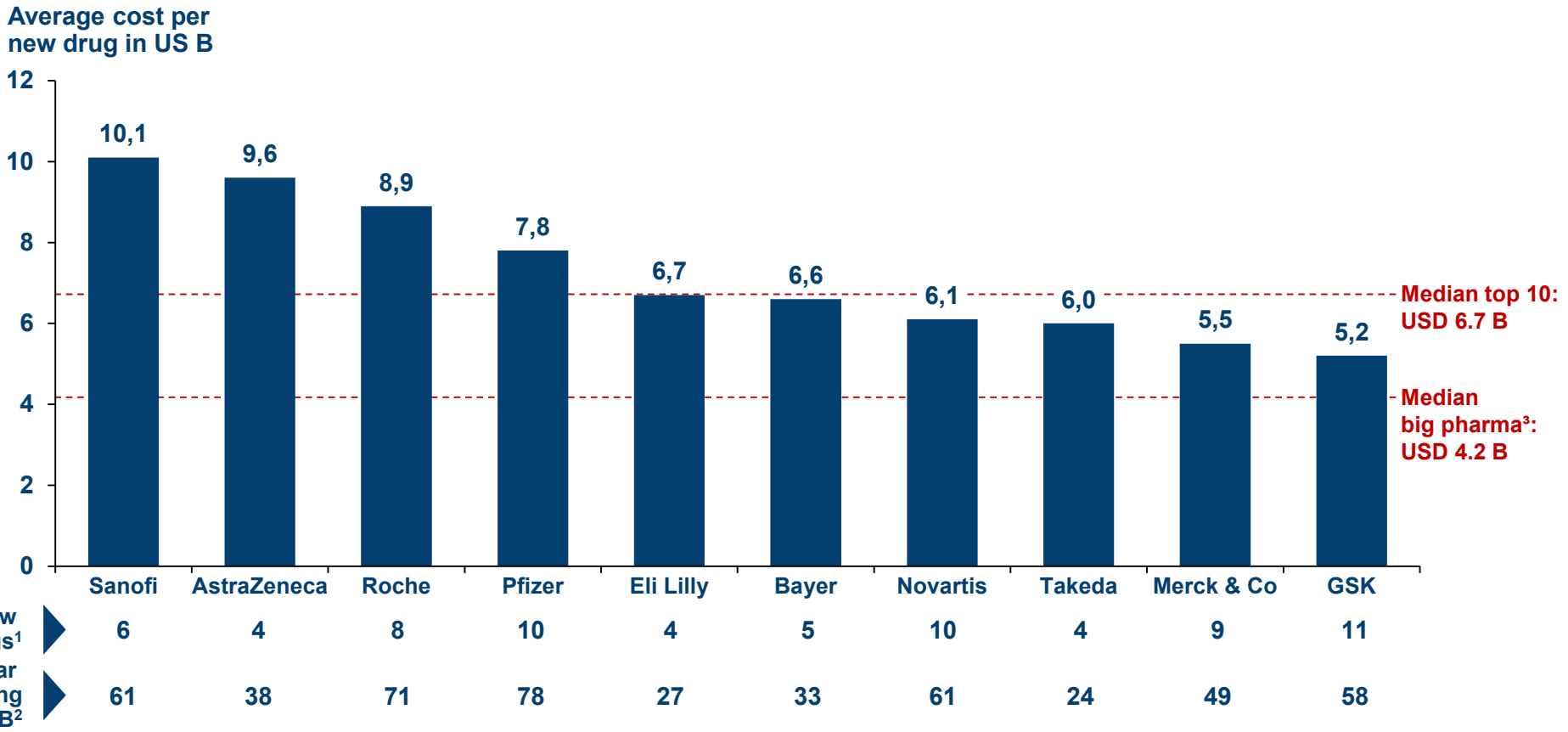
- It has been argued that larger companies have economies of scale and scope that might be associated with lower development costs *(Henderson et al, 1996, Rand J. Economics)*
- However, the results of this study do not support the conclusion that R&D capitalized costs are related to the size of the company
- Drugs from companies that had the largest number of drugs in development had an average capitalized cost of USD 992 M vs. USD 868 M for the average drug (i.e. + USD 124 M)
- Company A, showing the highest R&D costs (USD 2,119 M) had 92 drugs in development while company E, showing the lowest R&D costs (USD 521 M) had 34
- Some costs may also be attributable to strategic decisions of companies (e.g. high risk/high return vs. low risk/low return)
- The probability that a drug from company A goes from Phase I to market is 7% vs. 58% for company E

Source: Adams CP et al, 2006. health Affairs

[1] Capitalized costs in 2000 dollars

The overall cost per new drug differs significantly amongst top 10 pharma companies, with Sanofi spending twice as much as Merck & Co or GSK per launched product

Biggest R&D spenders per new drug – Top 10 big pharma companies

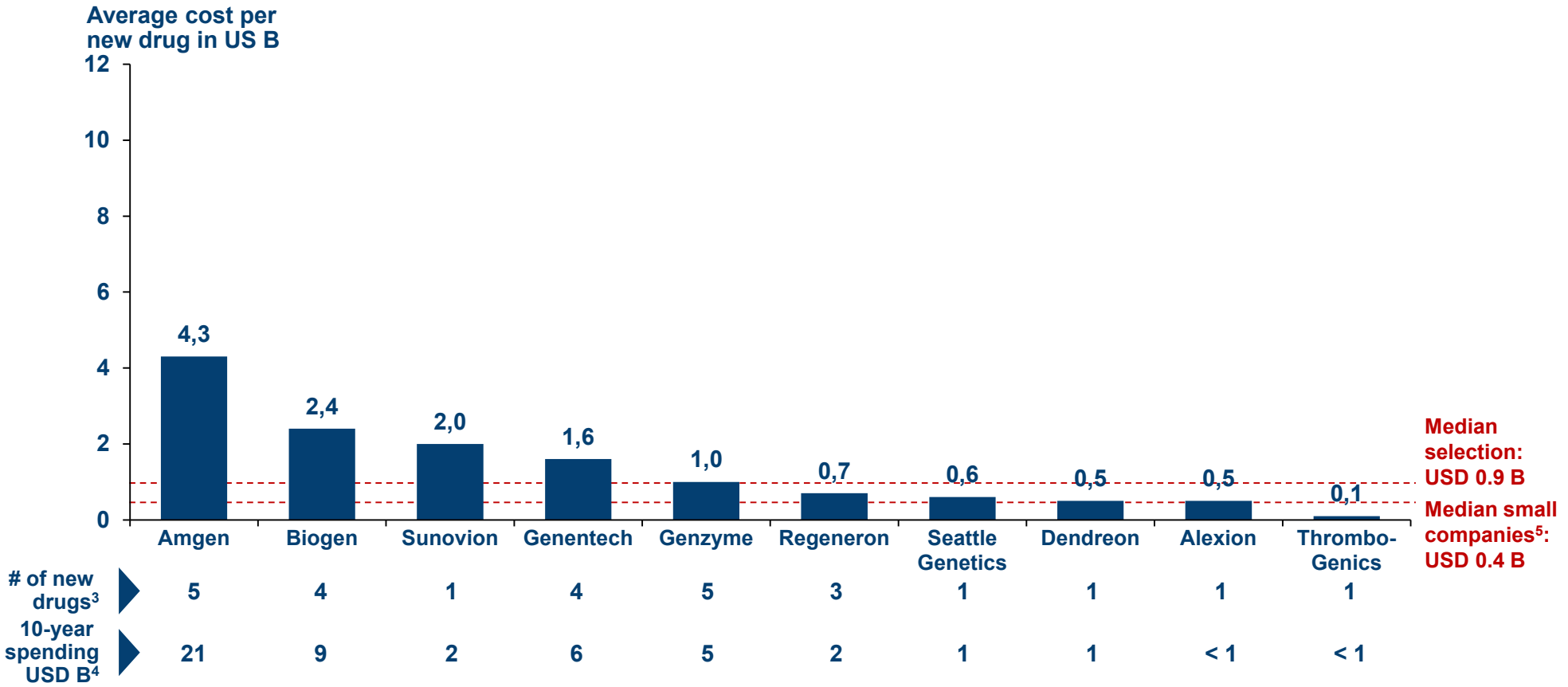


Source: Forbes August 2013 after Innothink Center for Research in Biomedical Innovation

¹ Cumulated over the 2003-2012 period – ² Period preceding new drugs approval – ³ Companies that have launched 4 products or more over the period
Note: Abbott has been excluded for including medical devices sales. Wyeth and Schering-Plough have been excluded for being merged with Pfizer and Merck & Co respectively

Biotech companies, which spend much less than big pharma companies in R&D and focus on a limited number of projects, show a cost per new drug 4.7 times lower[1]

Biggest R&D spenders per new drug – Selection of 10 biotech companies[2]



Source: Forbes August 2013 after Innothink Center for Research in Biomedical Innovation

[1] USD 4.2 B, median spending of big pharma companies / USD 0.9 B, median for biotech companies = 4.7 – [2] Defined as companies that are mainly focused on biologic products – [3] Cumulated over the 2003-2012 period – [4] Period preceding new drugs approval – [5] Companies that have launched 1 product over the period

Forbes analysis might have major flaws but it allows to compare the R&D cost to develop a new drug between different profiles of pharma companies

Comment on Forbes drugs development cost estimates

Methodology

- The imprecise analysis performed by Forbes takes into account the 10 years of R&D spending by a selection of 98 companies filing to the USA Security and Exchange Commission and reported to the number of NMEs approved over the period, with a 1 year offset

Loopholes of the study

- The analysis performed by Forbes has numerous flaws, admitted by the author himself:
  - The analysis may include costs that are not directly related to drugs approval, such as safety monitoring spending (post-marketing) for big pharma companies
  - Costs of development related to other activities, like medical devices (such as Abbott or J&J) may be included for several companies
  - Numbers have not been inflation-adjusted

Results of the study

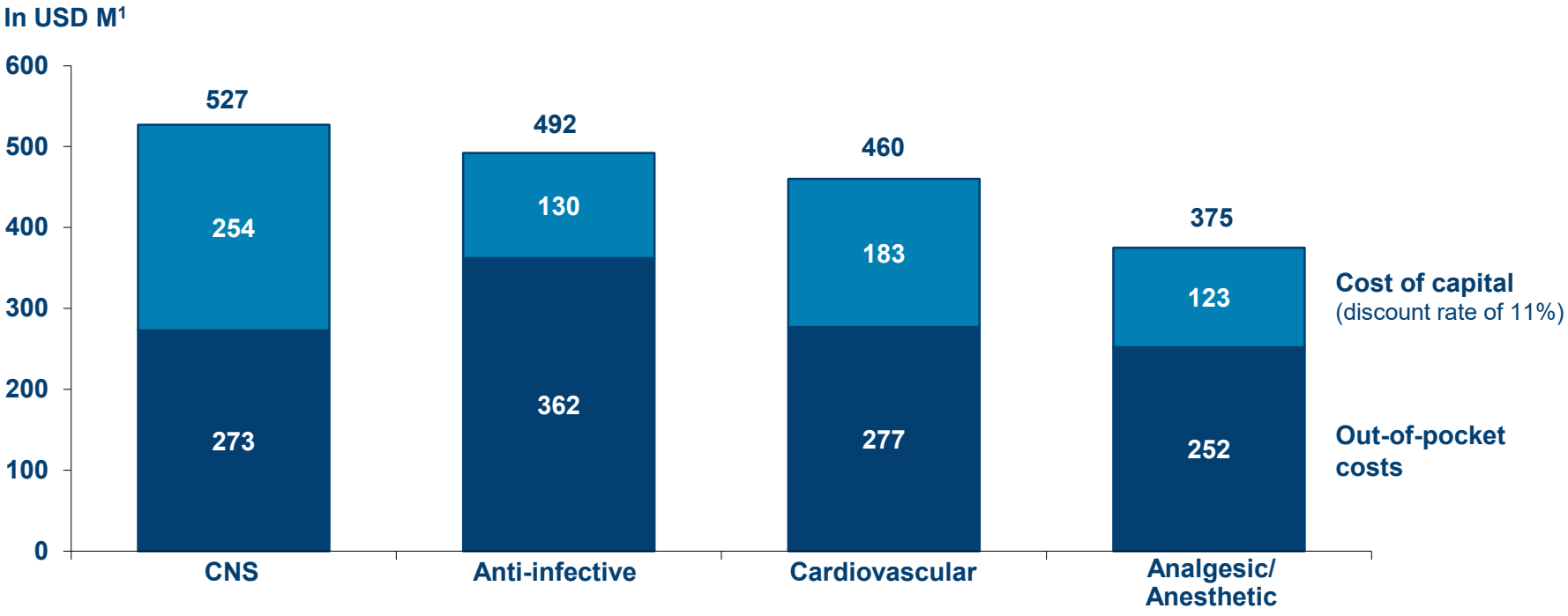
- Knowing the weaknesses of the study, results might still be interesting since they allow to compare companies and show:
  - That the success of big pharmas R&D may vary widely from a company to another
  - That companies focused on one or a small number of research projects, such as most biotech companies, spend less for each drug launched compared to big pharmas, which might be explained by:
    1. Partnerships between these small biotech companies and big pharmas that carry out most of the development costs
    2. The fact that small companies that failed to develop their product are not represented (only the successful ones are represented)

Source: Forbes August 2013 after Innothink Center for Research in Biomedical Innovation

R&D capitalized costs vary substantially across therapeutic areas due to the differences in development timelines, clinical trials sizes and success rates

R&D costs estimates for drugs by therapeutic area (2000) (1/2)

Estimated capitalized cost per approved new drug (pre-tax)

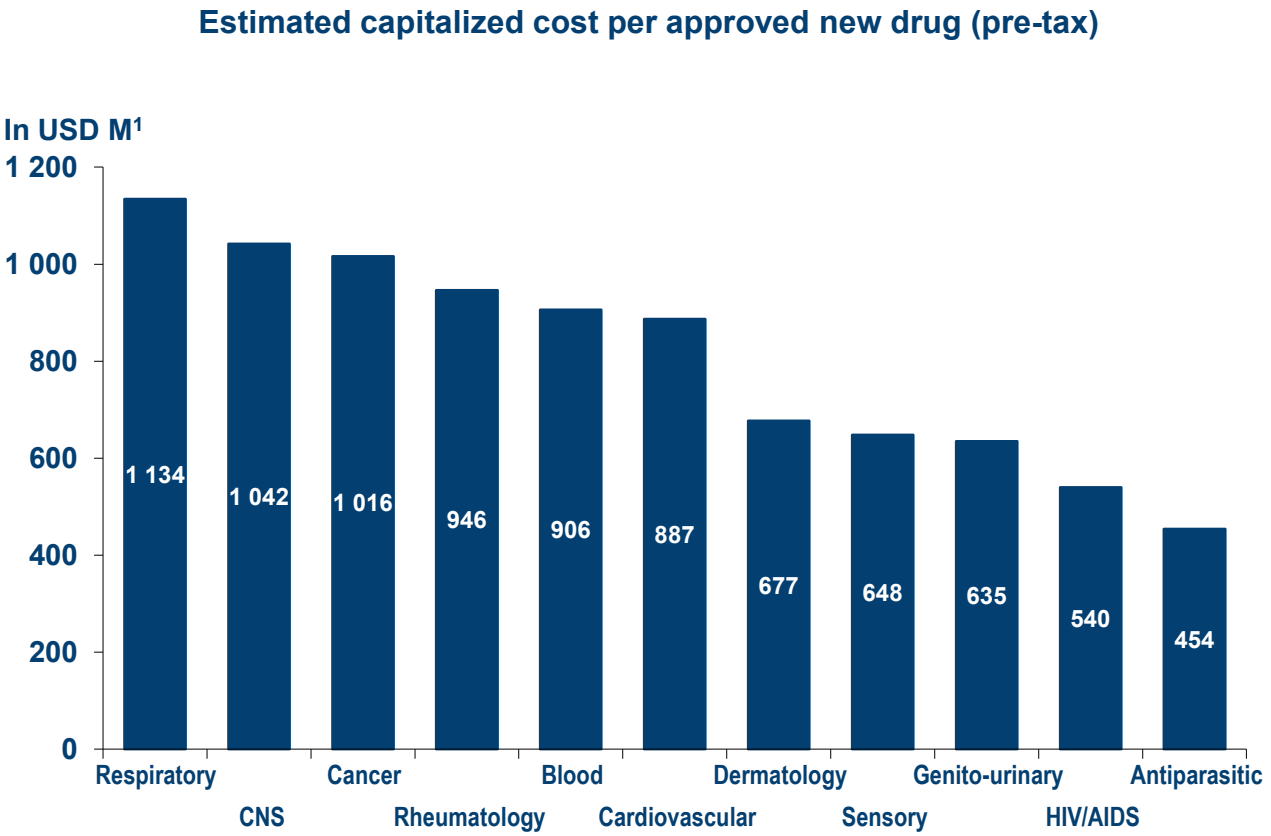


Source: DiMasi et al, 2004, Drug Information Journal

[1] Capitalized costs in 2000 dollars

R&D capitalized costs can vary depending on the therapeutic area, due to the specific regulatory policies which can have a substantive effect on success rate and duration

R&D costs estimates for drugs by therapeutic area (2000) (2/2)



- The difference observed in development costs between disorders is attributable to the variability in:
  - Success rates
  - Durations of each development step
- Higher success rates have been observed for drugs indicated for disorders with higher unmet medical needs (e.g. HIV/AIDS, breast cancer)
- Phase III durations for HIV/AIDS drugs are associated with lower capitalized costs because they are in general allowed to file NDAs[2] without completing large-scale clinical trials, unlike cardiovasculars

Source: Adams CP et al, 2006. health Affairs

[1] Capitalized costs in 2000 dollars – [2] New Drug Applications

The controversies re. the valuation of R&D cost weaken this argument, which is often used by pharma companies to justify the price of their new drugs

Estimated R&D cots of drugs

- The review of the main studies published since 2000 shows that the **average capitalized costs** of a new drug development is estimated at **USD ~1.7 B**
- The average cost of a new drug is **USD ~7 B** for the **top 10** pharma companies and **USD ~ 1 B** for **biotech** companies that are focused on a more limited number of research projects
- The huge **variations** observed from one source to another are due to differences in **methodologies** and **cost assumptions**
- These figures should be **analyzed with caution** because:
  - They include the **cost of drugs having failed** during their development
  - They take into account the **cost of capital** invested (~50% of the total estimated cost)
  - They do **not deduct corporate tax savings** (estimated at ~35% of total R&D costs)
  - They **use means** while medians would be more appropriate because of the huge difference of R&D costs observed according to the pharma companies and the type of products being developed
- The **median cost** of one single successful new drug, **without** considering the associated **opportunity costs** and **with deduction of tax savings**, should amount **USD 0.5-1 B**

Source: Smart Pharma Consulting analyses

[1] For an opportunity cost estimated at 11%. The US government guidelines call for using 3%

Smart Pharma Consulting

Consulting company dedicated to the pharmaceutical sector operating in the complementary domains of strategy, management and organization

Core capabilities

1 Strategy

- **Assessing the attractiveness of markets** (Hospital / retail innovative products - Vaccines - OTC - Generics)
- **Growth strategy**
  - Optimization of marketing / sales investments
  - Development of a company in the hospital market Business
  - Valuation for acquisition
  - Portfolio / franchise assessment
- **Extension of product life cycle performance**
  - Improvement mature products performance
  - Adaptation of price strategy
- **Defense strategies vs. new entrants**
- **Competitive strategies in the hospital market**
- **Strategic partnerships companies / pharmacies**

2 Management

- **Facilitation and structuring of strategic thinking for multidisciplinary product teams**
  - Key challenges identification
  - Strategic options formalization
  - Resource allocation optimization program
- **Training of marketing and market research teams to sales forecast techniques (modeling and scenarios development)**
- **Development and implementation of a "coaching program" for area managers**
  - Sales reps coaching
  - Regional action plans roll-out
- **Development and implementation of a "sales techniques program" for sales forces (STAR[1])**

[1] Sales Techniques Application for Results

3 Organization

- **Rethink of operational units organization**
- **Improvement of sales force effectiveness**
- **Improvement of the distribution channels covering the hospital and retail markets**
- **Development of a strategic planning process**

1, rue Houdart de Lamotte – 75015 Paris – France • Tel.: +33 6 11 96 33 78 • Fax: +33 1 45 57 46 59 • E-mail: jmpeny@smart-pharma.com • Website: www.smart-pharma.com