Biotechnology revolution: The industry perspective

Corvinus University of Budapest

Disclaimer

The views and opinions expressed in the following PowerPoint Slides are those of the individual presenter and should not be attributed to, or considered as reflecting the position of MERCK or its management

Manufacturer’s challenges and manufacturing costs

Challenges in the 2nd wave of biosimilars

Estimation of Costs of Developing a New Drug

Fixed Costs – Conservative Approach as in Literature

- Clinical trials
- Capital costs
- Manufacturing

Grabowski et al; Manage. Decis. Econ. 28: 439–451 (2007)

Actual Costs

- **R**eference **P**roduct – RP

Zarxio		Neupogen						
A00675111G	V200001	1009162	1025275	1020167	1024506	1029572	N0792AB	N1178AB
000657409G	V201002	1014928	1025872	1021955	1024772	1029837	N0839AA	N1179AB
000675011G	V201102	1020649	1026358	1024050	1025051	1029838	N0875AA	N1204AJ
030806	V201001	1021957	1026361	1000197	1025222	1032557	N0911AA	N1213AH
040906	V201101	1023892	1026689	1000539	1026494	1036993	N0996AD	
050906	V200201	1025269	1027991	1001143	1026519	1031133A	N0999AF	
111007		1027491	1031121	1003784	1026606	1032549A	N1005AA	
050409		1027493	1021952	1003865	1026690	N0512AA	N1014AB	
150210		1035682	1025277	1003937	1027142	N0527AA	N1062AA	
140210		1036971	1028687	1004154	1028082	N0577AA	N1113AG	
220810		1038184	1012002	1018725	1028497	N0586AA	N1114AA	
		P104490	1013453	1023368	1029228	N0715AF	N1114AJ	
		1022878	1017557	1023377	1029442	N0715AH	N1144AE	

Zarxio™ (filgrastim); Sandoz, a Novartis Company; Presentation to the Oncologic Drugs Advisory Committee; January 7, 2015

Actual Costs

- **R**eference **P**roduct – RP
- **I**ntellectual **P**roperty - IP

Actual Costs

- **R**eference **P**roduct – RP
- **I**ntellectual **P**roperty - IP
- **C**hemistry **M**anufacturing **C**ontrols - CMC Programme

Actual Costs

- **R**eference **P**roduct – RP
- **I**ntellectual **P**roperty - IP
- **C**hemistry **M**anufacturing **C**ontrols - CMC Programme
- Manufacture

Titers and Yields - key benchmarks that manufacturers use to determine operational efficiency and improvements in bioprocessing

- **Titer**: the amount of protein in grams produced in each liter of bioreactor fluid. If the titer doubles, only half as much fluid volume needs to be purified or half as many lots/batches are needed to produce the same amount of product - a very important measure of the efficiency of a product's manufacturing, and related manufacturing costs

- **Yield**: measured as percent of mass (grams) of purified product obtained vs. mass (grams) at the start of purification - a measure of the efficiency a manufacturer has achieved in the downstream purification and filtration operations

- A major problem is that titer and yield data for commercial biopharmaceutical products are rarely published. Thus, most of the titer and yield data come from individuals' notes and recollections from conference presentations, posters, and discussions with colleagues.

Rader et al; Bioprocessing; WINTER 2014/2015 • Volume 13/ Issue 4 • ISSN 1538-8786

Actual Costs

- **R**eference **P**roduct – RP
- **I**ntellectual **P**roperty - IP
- **C**hemistry **M**anufacturing **C**ontrols - CMC Programme
- Manufacture
- Preclinical Programme

Actual Costs

- **R**eference **P**roduct – RP
- **I**ntellectual **P**roperty - IP
- **C**hemistry **M**anufacturing **C**ontrols - CMC Programme
- Manufacture
- Preclinical Programme
- Regulatory

Actual Costs

- **R**eference **P**roduct – RP
- **I**ntellectual **P**roperty - IP
- **C**hemistry **M**anufacturing **C**ontrols - CMC Programme
- Manufacture
- Preclinical Programme
- Regulatory
- Clinical Programme

Actual Costs

- **R**eference **P**roduct – RP
- **I**ntellectual **P**roperty - IP
- **C**hemistry **M**anufacturing **C**ontrols - CMC Programme
- Manufacture
- Preclinical Programme
- Regulatory
- Clinical Programme
- RMP including PAC/PASS and Ph IV

Actual Costs

- **R**eference **P**roduct – RP
- **I**ntellectual **P**roperty - IP
- **C**hemistry **M**anufacturing **C**ontrols - CMC Programme
- Manufacture
- Preclinical Programme
- Regulatory
- Clinical Programme
- RMP including PAC/PASS and Ph IV
- Commercialisation

Different payer archetypes exist across Europe – Important for Commercialization

- **Tender model:** Payers implement strict tendering schemes with the objective of achieving the lowest cost for a therapy class. Maximum uptake could be achieved when a national single win tender for coverage of the entire therapy area is implemented. E.g. Poland, Norway and Hungary to some degree, although volume exclusivity is not guaranteed to the winner of the blind-bidding process.

Different payer archetypes exist across Europe – Important for Commercialization

- **Tender model:** Payers implement strict tendering schemes with the objective of achieving the lowest cost for a therapy class. Maximum uptake could be achieved when a national single win tender for coverage of the entire therapy area is implemented. E.g. Poland, Norway and Hungary to some degree, although volume exclusivity is not guaranteed to the winner of the blind-bidding process.

- **Hospital or plan purchasing:** Typically used where national purchasing does not occur and relies on the ability of hospitals or plans to negotiate with competing manufacturers of biologics. Discounts from list price can be achieved, particularly when negotiating is done at a regional level. E.g. Italy, Spain, Germany and UK.

Different payer archetypes exist across Europe – Important for Commercialization

- **Tender model:** Payers implement strict tendering schemes with the objective of achieving the lowest cost for a therapy class. Maximum uptake could be achieved when a national single win tender for coverage of the entire therapy area is implemented. E.g. Poland, Norway and Hungary to some degree, although volume exclusivity is not guaranteed to the winner of the blind-bidding process.

- **Hospital or plan purchasing:** Typically used where national purchasing does not occur and relies on the ability of hospitals or plans to negotiate with competing manufacturers of biologics. Discounts from list price can be achieved, particularly when negotiating is done at a regional level. E.g. Italy, Spain, Germany and UK.

- **Competition driven free market:** Little to no direct involvement by the payer in setting or negotiating prices. Instead, manufacturers are free to set their own price - below a specific level - and free market competition forces set the final price for the drugs. E.g. Belgium, Finland and Switzerland.

Assessing biosimilar Uptake and Competition in EU Markets IMS Institute for Healthcare Informatics October 2014

Estimation of Costs of Developing a New Drug

??????????????????????????????

Estimation of Costs of Developing a New Drug

??????????????????????????????

However, don’t believe in the 2,6 Billion story

Since several years the same figures for Drug Development costs for a New are Drug copy/pasted based on data from the same source:

TUFTS Center and DiMasi et al,

Joseph A. DiMasi being Director of Economic Analysis, Tufts Center for the Study of Drug Development , Tufts University School of Medicine

2003: 803 Million US - *Dimasi JA, Hansen RW, Grabowski HG. The price of innovation: new estimates of drug development costs. J Health Econ. 2003;22:151–85.*

2014: 2.6 Billion US - *How the Tufts Center for the Study of Drug Development pegged the cost of a new drug at $2.6 billion. Boston: Tufts Center for the Study of Drug Development, November 18, 2014 (http://csdd.tufts.edu/files/uploads/cost_study_backgrounder.pdf)*

The $2.6 Billion Pill — Methodologic and Policy Considerations – Data Source

- The raw numbers on which the analysis is based are not available for transparent review
- The analysis was based on data that 10 unnamed drug makers provided on 106 unnamed investigational compounds that they had “self originated”
- The study included both products that made it to market and a much larger number that did not - since we cannot know which compounds were studied, it is hard to evaluate the key assumption that more than 80% of new compounds are abandoned at some point during their development — a key driver of the findings

Jerry Avorn, n engl j med 372;20 nejm.org may 14, 2015

The $2.6 Billion Pill — Methodologic and Policy Considerations

- Nearly half the cost of drug development was accounted for by the cost of capital - $1.2 billion was ascribed to this cost of capital, with only $1.4 billion attributed to funds actually spent on research

- These capital costs were assessed at 10.6% per year, compounded

- The highest cost was that of the failure of compounds earlier in development because of unanticipated problems with safety, lack of efficacy, or both - this expensive weakest link points not to costly regulatory delay but to the limits of companies' ability to efficiently choose compounds for development and to identify adverse effects or limited efficacy earlier in the development process.

Jerry Avorn, n engl j med 372;20 nejm.org may 14, 2015

The $2.6 Billion Pill — Methodologic and Policy Considerations

- The study does not take into account the large public subsidies provided to pharmaceutical companies in the form of research-and-development tax credits or substantial funded research at non-profit, university- affiliated centers - without knowing which drugs were included in the Tufts analysis, there is no way to know how many of the “self-originated” products also built on underlying basic science research whose costs were borne by the public

- Furthermore, some of the most important recent new medications were not developed by large drug manufacturers but were acquired through purchase of the biotech firms that discovered them.

- These, in turn, are often spinoffs based on the discoveries of NIH funded university research laboratories.

Jerry Avorn, n engl j med 372;20 nejm.org may 14, 2015

Sofosbuvir - Sovaldi

- Sofosbuvir - developed under the leadership of a Professor of biochemistry at Emory University
- He set up Pharmasset Inc. in 2004 as his business to develop Sofosbuvir and hold the patents
- U.S. Government heavily funded the research, with major grants from the National Institutes of Health (NIH) and support from the Veterans Administration
- Pharmasset raised around $45 million in a 2007 IPO and used those funds and others to supplement the R&D
- According to the company's SEC filings, the total Pharmasset R&D on Sofosbuvir up through 2011 totalled around $62.4 million
- By the fall of 2011, Sofosbuvir was ready for Ph II clinical trials, carried out between October 2011 and April 2012 by the NIH, which published the results in the Journal of the American Medical Association in 2013

Sofosbuvir - Sovaldi

- In January 2012 Gilead paid $11.2 billion to purchase Pharmasett and the Professor pocketed an estimated $440 million for his shares in Pharmasett

- Ph III trials were carried out in 2013 paid by Gilead, at a cost of perhaps $50-$100 million for a two-month trial that covered around one thousand patients (exact costs the of the Ph III not disclosed by the company)

- It is estimated that private investors spent perhaps $300 million in R&D outlays for Sofosbuvir over the course of a decade, and perhaps well below that sum. Those R&D outlays were likely recouped in a few weeks of sales in 2014

- The total private-sector outlays on R&D were perhaps $300 million, and almost surely under $500 million.

Sofosbuvir - Sovaldi

- Introduced in the US - $84,000 for a 12-week/$7,000 per week/$1,000 per pill

- In the first year of marketing, Sovaldi and Harvoni did $12.4 billion of market sales in 2014, which is more in just one year than the $11.2 billion price that Gilead paid to buy Sofosbuvir

- The total expense is even higher because the full regimen requires that the drug be used in combination with at least one other antiviral medicine

- It would cost a total of $226.8 billion to treat the estimated 2.7 million people living with chronic hepatitis C infection in the US (Centers for Disease Control and Prevention)

- Currently, the lowest available tiered price is $900 for a three-month treatment course in the poorest countries and in some additional developing countries, such as Egypt and India

The $2.6 Billion Pill — Methodologic and Policy Considerations

- Since the figure's release, it has been used to justify the cost of several expensive medications and to support longer periods of marketing exclusivity for new drug products

- These arguments are based on the proposition that drug companies (which are major supporters of the Tufts center) must be helped to recoup the huge capital needs required to discover the cures of tomorrow

Jerry Avorn, n engl j med 372;20 nejm.org may 14, 2015

Revised cost estimates, self-originated new chemical entities (million US$, year 2000)

Phase	*DHG 2003 gross costs per approved drug*	*Net mean costs per approved drug (-50% tax savings)*	*Net median costs per approved drug (-50% tax savings)*	*Capitalization factors for different discount rates*			*Net median capitalized cost per approved drug*		
				High (7%)	*Medium (5%)*	*Low (3%)*	*High*	*Medium*	*Low*
Phase I	70.7	35.3	26.2	1.57	1.39	1.22	41.1	36.2	31.9
Phase II	77.6	38.8	28.7	1.45	1.31	1.18	41.6	37.5	33.7
Phase III	126.0	63.0	46.6	1.23	1.16	1.10	57.5	54.2	51.1
Animal	7.6	3.8	2.8	1.48	1.33	1.19	4.2	3.7	3.3
Trial total	281.9	141.0	104.3	1.38	1.26	1.15	144.3	131.7	120.1
Preclinical	120.8	60.4	44.7	1.94	1.61	1.33	86.5	72.0	59.7
Total	402.8	201.4	149.0	1.55	1.37	1.21	230.9	203.7	179.7

Light et al; 2011 The London School of Economics and Political Science, 1745-8552 BioSocieties 1–17; 7 February 2011;

Challenges for the 2nd wave of biosimilars

1st Wave of Biosimilars

Erythropoietin	~3+ Billion
Filgrastim	~1+ Billion
Somatropin	~3+ Billion

1st Wave of Biosimilars

Erythropoietin	~3+ Billion
Filgrastim	~1+ Billion
Somatropin	~3+ Billion

2nd Wave of Biosimilars

Adalimumab	~10.7+ Billion
Avastin	~7+ Billion
Etanercept	~8.4+ Billion
Infliximab	~6.7+ Billion
Rituximab	~7.7+ Billion

1st versus 2nd Wave of Biosimilars – Main Differences

- Higher Complexity of the Compounds

1st versus 2nd Wave of Biosimilars – Main Differences

- Higher Complexity of the Compounds
- Shift from Supportive Care to Disease Treatment

1st versus 2nd Wave of Biosimilars – Main Differences

- Higher Complexity of the Compounds
- Shift from Supportive Care to Disease Treatment
- Increased number of indications

1st versus 2nd Wave of Biosimilars – Main Differences

- Higher Complexity of the Compounds
- Shift from Supportive Care to Disease Treatment
- Increased number of indications
- New/Different Clinical Stakeholders

1st versus 2nd Wave of Biosimilars – Main Differences

- Higher Complexity of the Compounds
- Shift from Supportive Care to Disease Treatment
- Increased number of indications
- New/Different Clinical Stakeholders
- A lot more money involved

1st Wave of Biosimilars

Erythropoietin	~3+ Billion
Filgrastim	~1+ Billion
Somatropin	~3+ Billion

2nd Wave of Biosimilars

Adalimumab	~10.7+ Billion
Avastin	~7+ Billion
Etanercept	~8.4+ Billion
Infliximab	~6.7+ Billion
Rituximab	~7.7+ Billion

1st versus 2nd Wave of Biosimilars – Main Differences

- Higher Complexity of the Compounds
- Shift from Supportive Care to Disease Treatment
- Increased number of indications
- New/Different Clinical Stakeholders
- A lot more money involved
- For some Originators the Drug is essential for their revenues

1st versus 2nd Wave of Biosimilars – Main Differences

- Higher Complexity of the Compounds
- Shift from Supportive Care to Disease Treatment
- Increased number of indications
- New/Different Clinical Stakeholders
- A lot more money involved
- For some Originators the Drug is essential for their revenues
- Originators invest far more money in anti Biosimilar campaigning – «Raising Awareness»

2 US Examples for drug prices

CEO WHO RAISED PRICE OF OLD PILL MORE THAN $700 CALLS JOURNALIST A 'MORON' FOR ASKING WHY

Pharmaceutical Companies Buy Rivals' Drugs, Then Jack Up the Prices

5 drugs that underwent monstrous price hikes

Price Hike for Tuberculosis Drug Cycloserine Rolled Back From 2,000% Jump

CEO Martin Shkreli: 4,000 percent drug price hike is 'altruistic,' not greedy

ANGRY OVER DRUG PRICES, MORE STATES PUSH BILLS FOR PHARMA TO DISCLOSE COSTS

Valeant: The company has jacked up prices on 54 meds this year by an industry-leading average of 65.6%, according to a Deutsche Bank analysis.

Last year, it hiked the prices on 62 drugs--by 50%, on average.

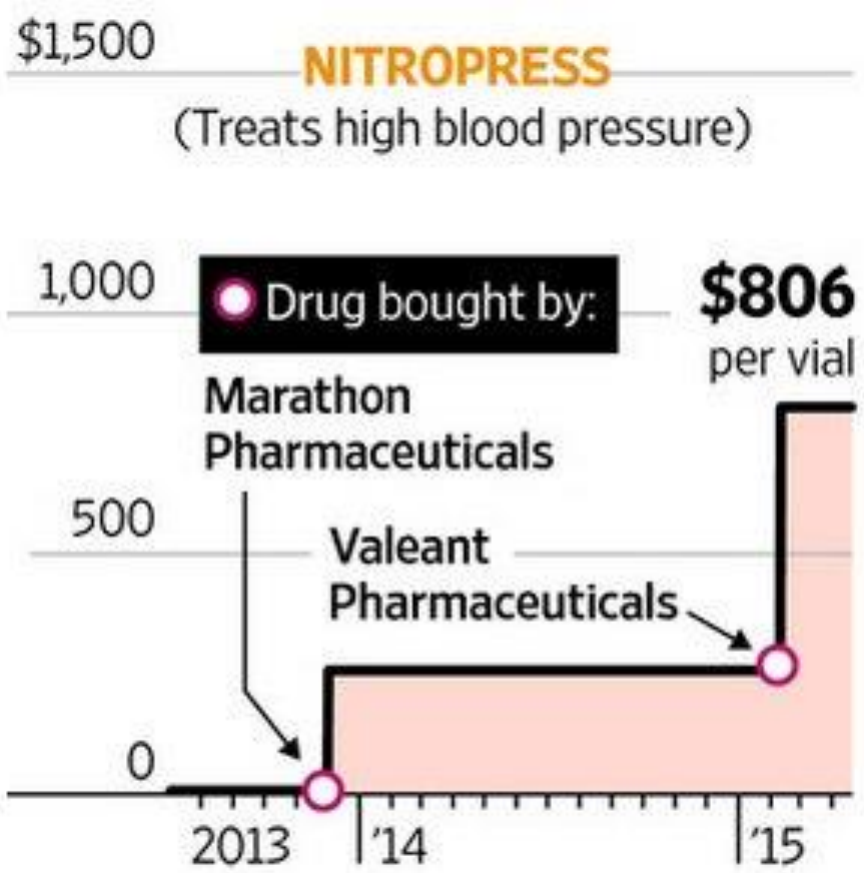
Glumetza is now 550% more expensive than it was on Jan. 1. As of July 31, the drug's list price stood at $10,020 for 90 tablets, up from $896 in January 2013.

Isuprel and Nitropress -- prices Valeant punched up by 536.7% and 236.6%, respectively

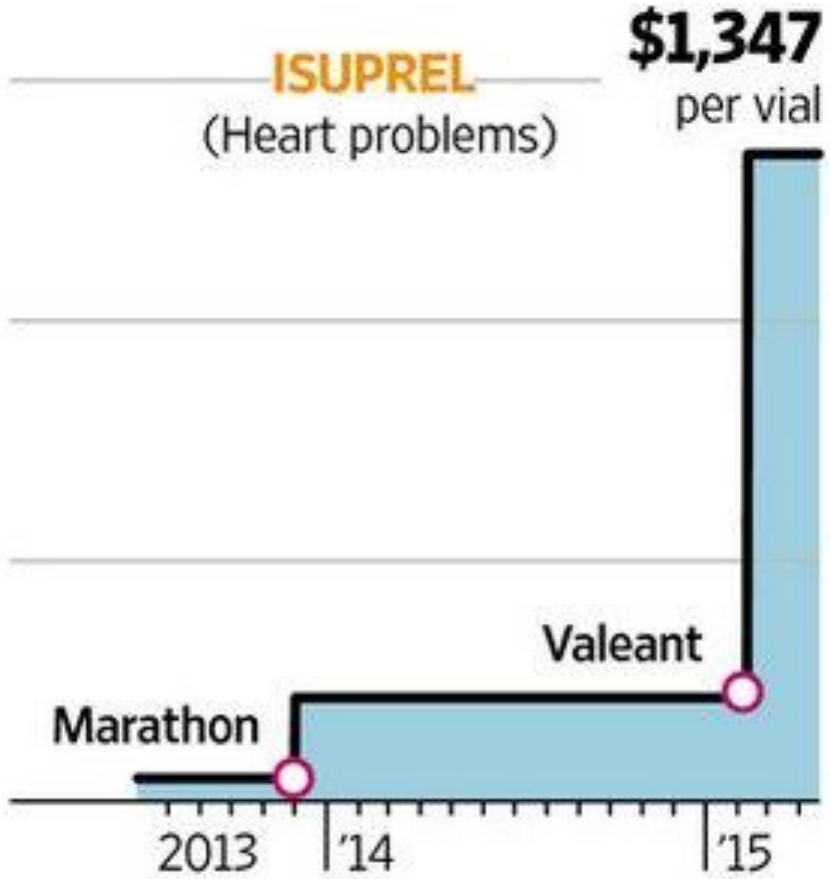
Prices charged by the company for roughly 30 older prescription drugs have risen over the past two and a half years, from as little as 90 percent for a nasal spray to 2,288 percent for ear drops.

Overall, specialty pharma's price increases on branded drugs averaged out to 22%

Most pharmaceutical companies spend an average of 17 percent of their income on research and development, Valeant spends 3 percent (Citron Research)



Source: Truven Health Analytics



The Daraprim/Pyrimethamine story

- Daraprim: a drug that treats toxoplasmosis, a condition that afflicts AIDS patients, among others
- First on the market in 1953
- In countries other than U.S. Daraprim is sold by GSK at around $20 for 30 pills
- GSK sold the rights to market Daraprim in the U.S. in 2010
- Turing Pharmaceuticals acquired the exclusive rights to market Daraprim in August 2015 for $55 million from Impax Laboratories
- Turing increased the price of Daraprim in the U.S. from $13.50 a pill to $750, rise of more than 5,000%
- Turing defended this move, saying they plan to invest in R&D to improve the 62-year-old drug

- Last week, all 18 Democratic members of the House Committee on Oversight and Government Reform sent a letter requesting that Committee Chairman Jason Chaffetz issue Valeant a subpoena.

- They also called for Valeants CEO to testify before the committee, along with Turing Pharma CEO, whose 5000%-plus Daraprim price hike recently ignited the public's fury and brought drug pricing onto the national stage as a hot-button campaign issue.

Köszönöm