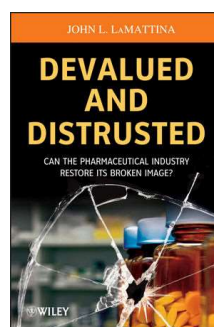
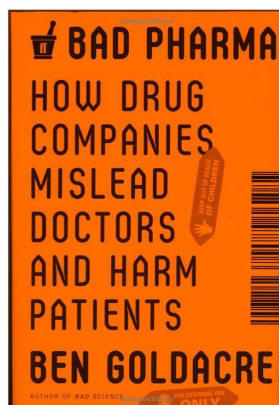
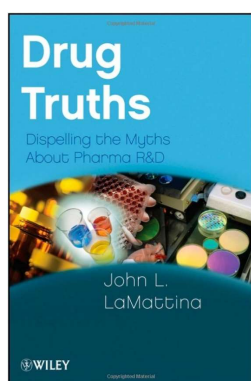


## Rational Drug Design lecture 1

Łukasz Berlicki

### Drug Design

- ▶ „Drug discovery is a **noble profession** but is poorly understood by the public.”



*J. Med. Chem.*, 2013, 56, 5659–5672

## Criticism of pharmaceutical industry

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- ▶ Profit over all
  - ▶ High prices of drugs
  - ▶ Poor access to drugs
  - ▶ Delays in access to generic drugs
  - ▶ Inadequate marketing
  - ▶ Low innovation
  - ▶ Low expenditures for research and development
- 



## New drugs

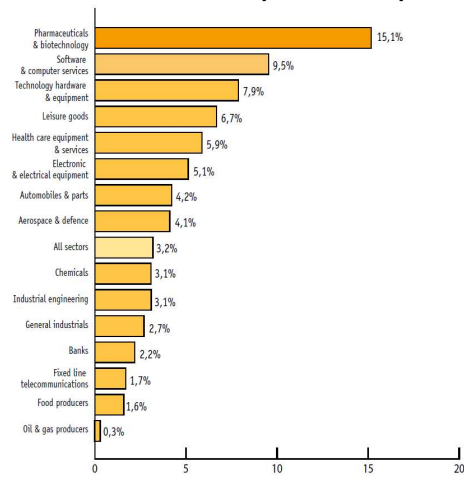
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- ▶ Innovative drug is one of  
**the most technically complicated**  
product on the planet.



## Expenditure

- ▶ Expenditures on research and development as percent of income

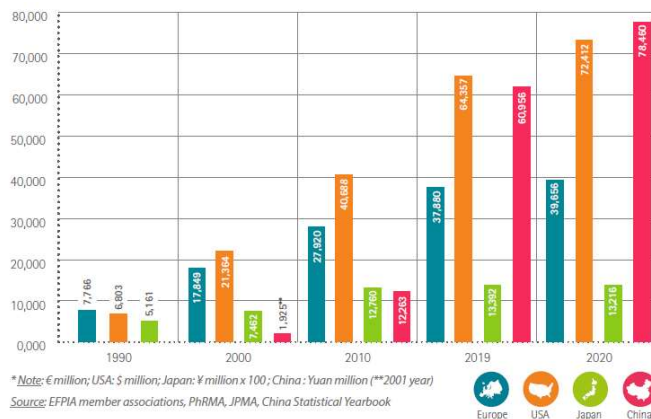


R&D Apple: 3%



## Expenditure

- ▶ Expenditures on research and development in pharmaceutical industry



## Expenditures in Europe

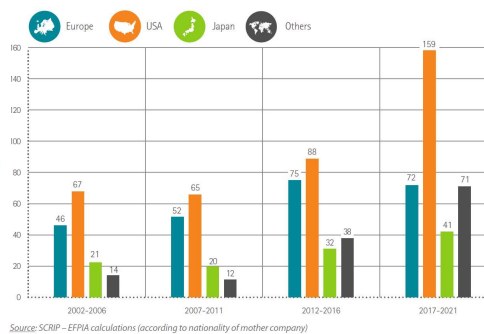
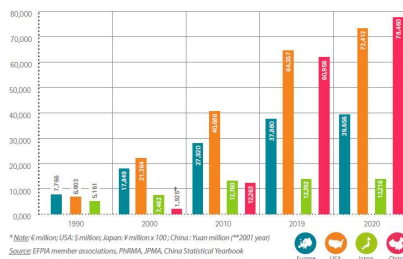
- Expenditures on research and development in European countries

EFPIA 2020	€ million	€ million
Austria	283	n.a
Belgium	4,964	n.a
Bulgaria	91	n.a
Croatia	40	642
Cyprus	85	126
Czech Rep.	72	431
Denmark	1,486	90
Estonia	n.a	69
Finland	258	706
France	4,451	35
Germany	7,813	334
Greece	102	1,161
Hungary	298	1,104
Iceland	n.a	7,380
Ireland	305	71
Italy	1,620	5,639
<b>TOTAL</b>		<b>39,656</b>



## Number of new compounds

- In spite of increasing expenditure, the number of new compounds is NOT increasing.

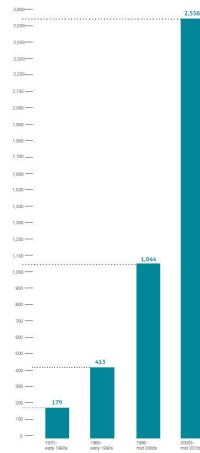


## Expense of introduction of new drug

- ▶ Expense of introduction of new drug is constantly increasing.

2.5 billion USD

New drug **HASTO BE** better than all others present on the market.



## The process of drug development

- ▶ Identification of molecular **TARGET**  
biomolecule is important for disease
- ▶ Identification of active molecule (**HIT**)  
new compound interacts with molecular target
- ▶ Optimization of active molecule (**LEAD**)  
new compound is active and bioavailable
- ▶ Preclinical tests  
compound is safe and effective for animals
- ▶ Clinical tests  
compound is safe and effective for human

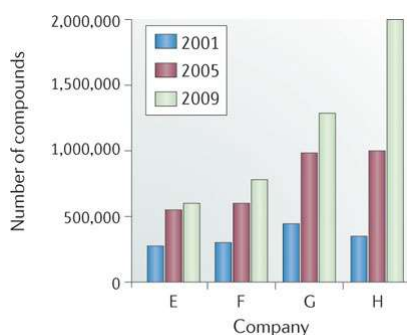
## Molecular target identification

- ▶ There is ca. 1500 active compounds, which acts on 324 molecular targets.
- ▶ It was estimated on the basis of genome analysis that 600-1500 proteins can be **druggable targets**.
- ▶ 25% of known drugs do not have known molecular targets and/or mode of action!



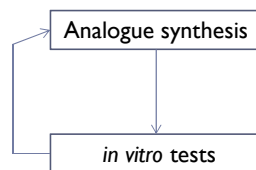
## Hit identification

- ▶ High-throughput screening, HTS
- ▶ Structure-based methods; the biggest database of molecular structures contains ca. 1 billion of molecules.



## Optimization

- ▶ Activity
- ▶ Bioavailability
- ▶ Toxicity



## Preclinical and clinical studies

Preclinical studies – toxicity and effectiveness on animals

**Clinical studies** – on humans

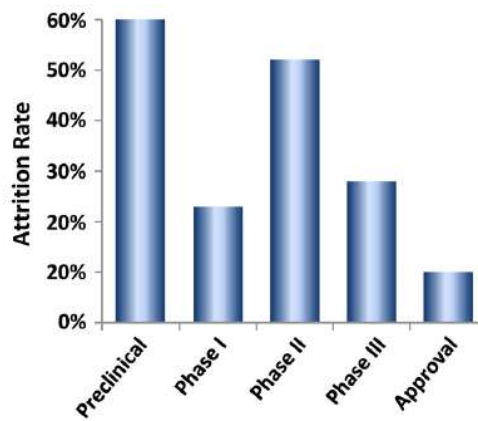
**Phase I** – on small group (20-80), estimation of safety, range of doses and side effects

**Phase II** – on medium group (100-300), estimation of effectiveness and safety

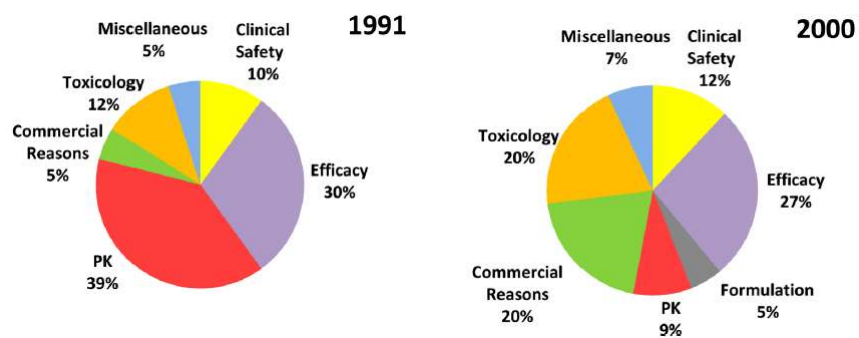
**Phase III** – large group (1000-3000), confirmation of effectiveness, monitoring of side effects, comparison with other therapies

**Phase IV** – studies after introduction on market.

## Preclinical and clinical studies



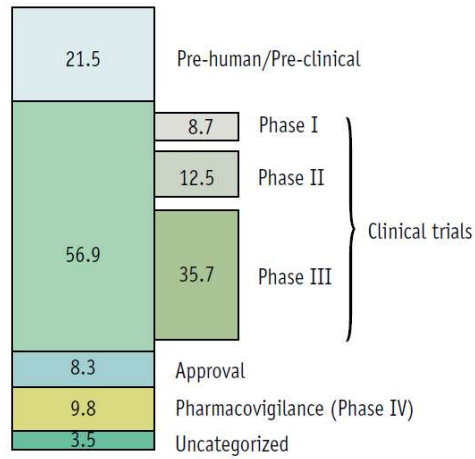
## Clinical studies



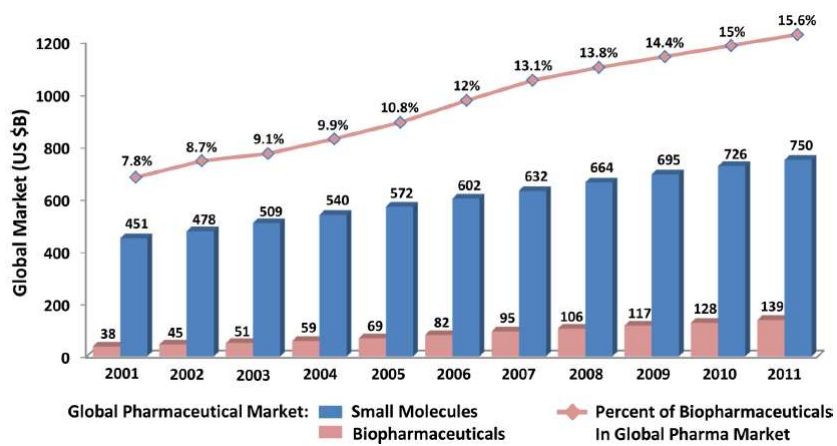


## Distribution of expenditure

▶ Clinical studies cost is the highest



## Incomes



## Incomes of Top10 companies (bln USD)

2021	Company	2020
81.3 ▲	Pfizer	41.8
53.5 ▲	Abbvie	42.9
52.1 ▲	J & J	45.6
51.5 ▲	Novartis	48.7
48.5 ▲	Roche	47.2
46.4 ▲	BMS	42.5
43.0 ▲	Merck	36.9
41.4 ▲	Sanofi	37.6
36.5 ▲	AstraZeneca	25.9
33.1 ▲	GSK	32.6

KGHM, \$3,100

## Companies

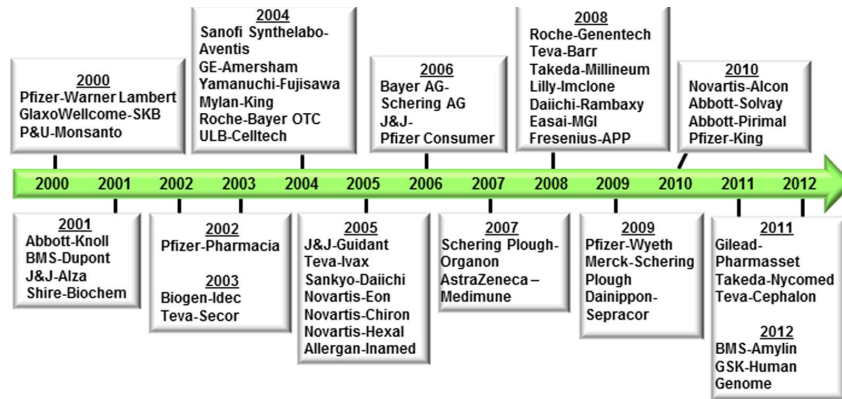
1998

Abbott Labs	G. D. Searle	Procter & Gamble
Am. Cyanamid	Glaxo	Rhone Poulenc
A. H. Robins	Hoechst	Rorer
Astra	Hoffmann-LaRoche	R. P. Scherer
BASF	ICI	Roussel
Beecham	J & J	Sandoz
Boehringer	Knoll	Schering-Plough
Boots	Eli Lilly	Smith Kline
Bristol-Myers	Marion Labs	Squibb
Carter-Wallace	Merck	Sterling
Ciba Geigy	Merrell Dow	Upjohn
Connaught	Monsanto	Warner-Lambert
DuPont	Pfizer	Wellcome
Fisons Corp	Pharmacia	Zeneca

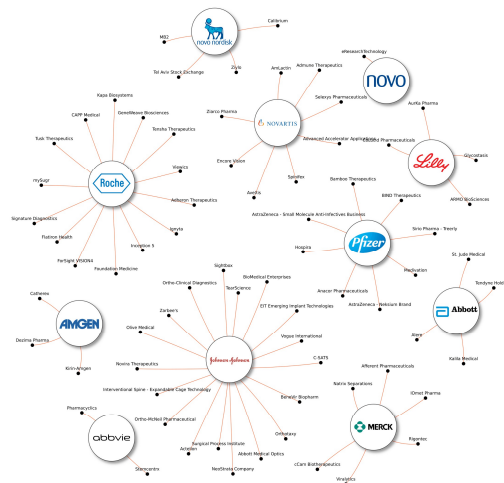
2011

Abbott Labs	Eli Lilly
Astra-Zeneca	Merck
Boehringer	Novartis
Bristol-Myers Squibb	Pfizer
GlaxoSmithKline	Sanofi-Aventis
Johnson & Johnson	

## Merging of companies



## Merging of companies

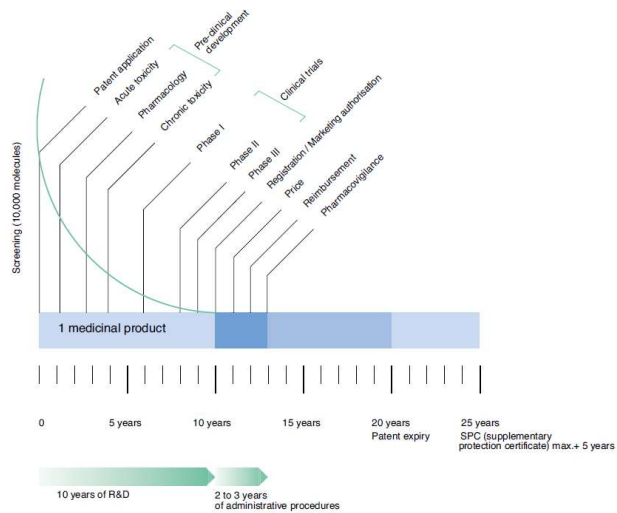


## Top10 drugs - Blockbusters

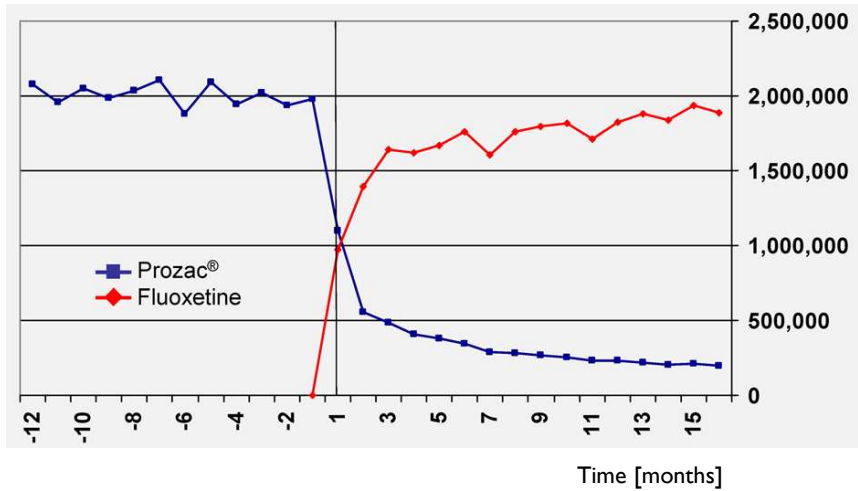
### TOP PHARMA DRUGS BY SALES IN 2021 (USD Bn)



## Timeline of new drug introduction



## Patent cliff



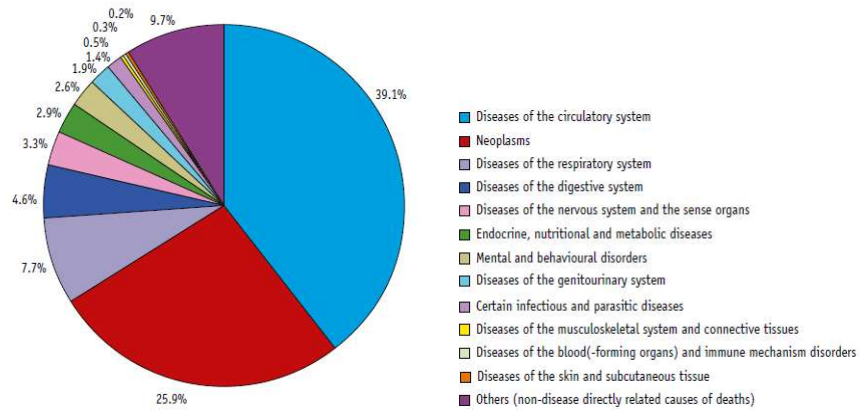
## Drugs which lose patent protection

- ▶ Loss of patent protection can cause significant decrease of company incomes

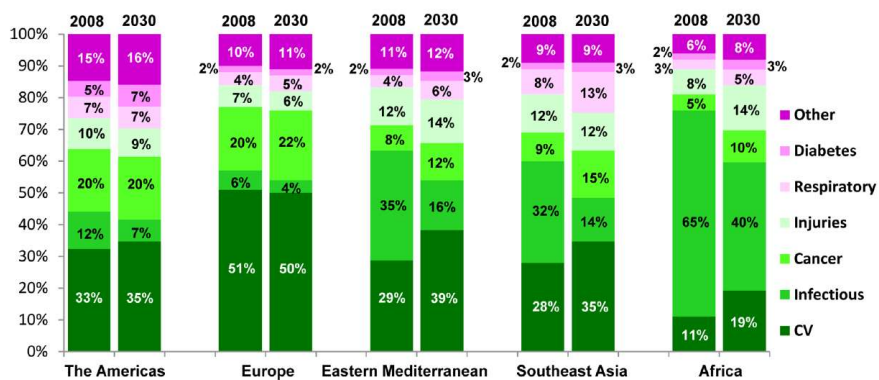
Year	Drug	Income [billion \$]	Company
2011	Actos®	4.6	Takeda
2011	Zyprexa®	5.0	Eli Lilly
2011	Lipitor®	12	Pfizer
2012	Levaquin®	1.4	Janssen
2012	Lexapro®	3.5	Forest
2012	Seroquel®	5.6	AstraZeneca
2012	Plavix®	9.1	BMS <sup>c</sup> / Sanofi
2012	Singulair®	5.4	Merck
2012	Diovan®	6.1	Novartis
2013	Cymbalta®	3.5	Eli Lilly
2013	OxyContin®	2.4	Purdue
2013	Zometa®	1.5	Novartis
2014	Nexium®	5.0	AstraZeneca
2014	Celebrex®	2.7	Prizer
2014	Sandostatin®	1.3	Novartis
2015	Abilify®	4.6	BMS <sup>c</sup>
2015	Gleevec®	4.3	Novartis
2016	Crestor®	6.1	AstraZeneca

## Causes of death

- ▶ Diseases of circulatory system and neoplasms are major causes of death



## Causes of death - continents

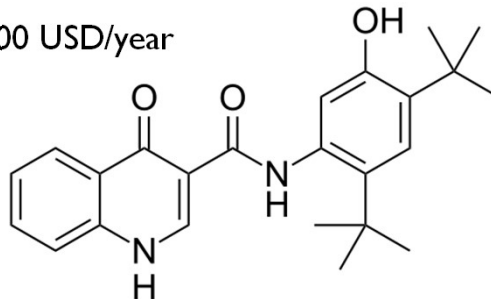


## Main areas of biggest pharma companies

company	therapeutic areas of focus
Pfizer	oncology, pain, diabetes, AD, inflammation, psychoses
Merck	cardiovascular, diabetes/endocrinology, neuroscience/ophthalmology, oncology, respiratory/immunology, infectious disease
Novartis	hypertension, metabolism, virology/anti-infectives, neuroscience, oncology, ophthalmology, respiratory, transplantation
GlaxoSmithKline	cardiovascular/metabolic, inflammation, infectious disease, neuroscience, oncology, ophthalmology, respiratory
Eli Lilly	neuroscience, urology, cardiovascular, autoimmunity, musculoskeletal, diabetes, oncology
Abbott	chronic kidney disease, multiple sclerosis, antivirals, oncology, women's health, immunology, neuroscience/pain
BMS	cardiovascular, immunology, metabolics, oncology, virology, neuroscience
AstraZeneca	cardiovascular, anti-infectives, oncology, gastrointestinal, neuroscience, respiratory/inflammation
Takeda	cardiovascular, metabolic, neuroscience, respiratory/immunology, oncology
Johnson and Johnson	cardiovascular/metabolic, immunology, anti-infectives, neuroscience/pain, oncology

## Drugs for rare diseases

- ▶ Kalydeco (Vertex), drug against some types of cystic fibrosis
- ▶ Ca. 30 000 cases in USA
- ▶ Cost of therapy 300 000 USD/year



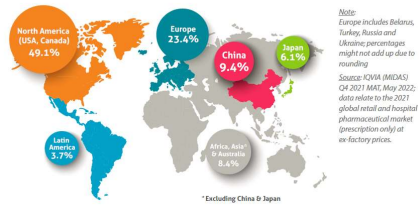
# New drugs

## ► Sales of new drugs according to region

GEOGRAPHICAL BREAKDOWN (BY MAIN MARKETS) OF SALES OF NEW MEDICINES LAUNCHED DURING THE PERIOD 2016-2021

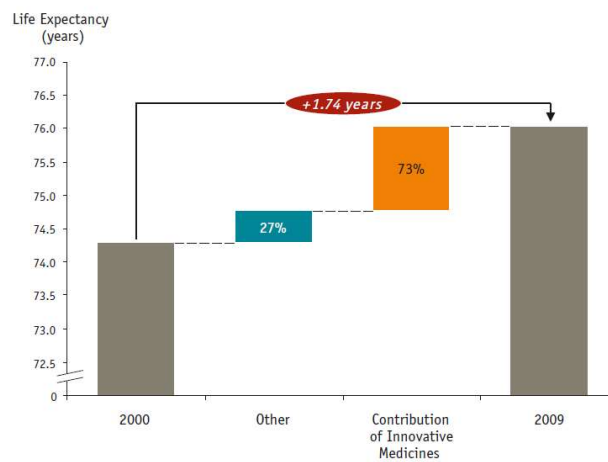


BREAKDOWN OF THE WORLD PHARMACEUTICAL MARKET - 2021 SALES



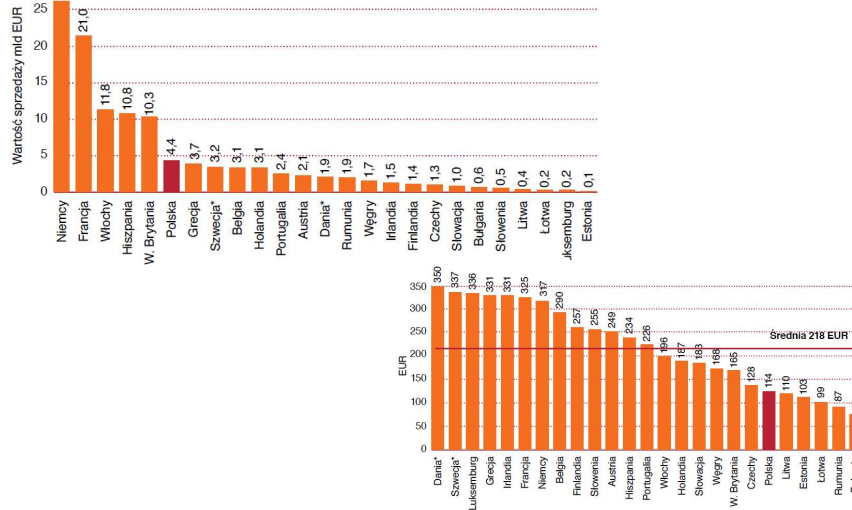
# Life expectancy

## ► New drugs increases life expectancy significantly

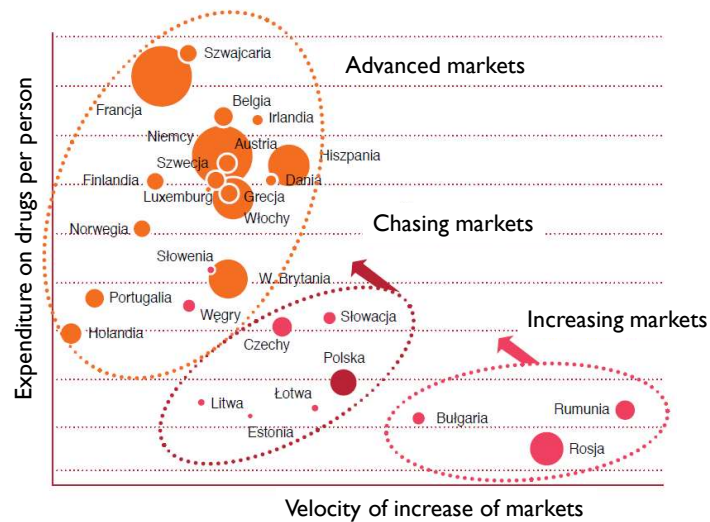




## Pharmaceutical industry in Poland

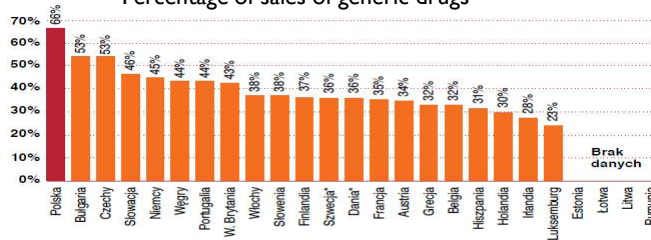


## Pharmaceutical markets in Europe

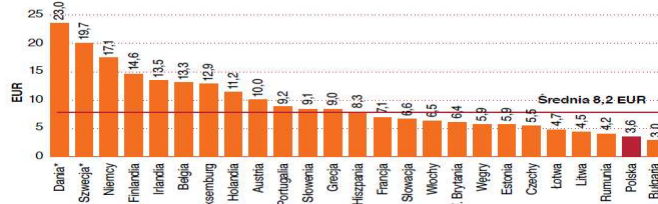


## Generic drugs

Percentage of sales of generic drugs

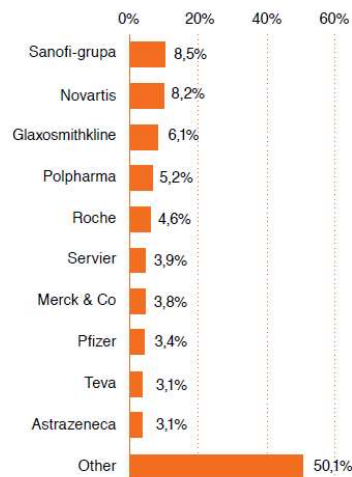


Mean price per drug

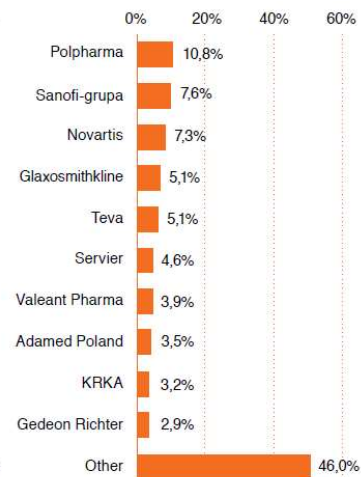


## Top10 companies in Poland

by value



by number of drugs



## Top10 korporacji farmaceutycznych

No	Type	Name	Sales (mln PLN)	No of products
1	Oryginalna	SANOFI-GRUPA	1 140	131
2	Oryginalna	NOVARTIS	1 004	232
3	Oryginalna	GLAXOSMITHKLINE	834	121
4	Generyczna	POLPHARMA	716	104
5	Oryginalna	SERVIER	627	69
6	Generyczna	KRKA	489	62
7	Oryginalna	MERCK & CO	478	73
8	Generyczna	TEVA	463	167
9	Generyczna	ADAMED POLAND	456	60
10	Oryginalna	ASTRAZENECA	436	30



## Placement of pharma industry in Poland



## Employment

### ▶ Number of persons employed in pharmaceutical industry in Europe

EFPIA 2011	Units		
Austria	11,175	Lithuania	1,370
Belgium	32,167	Malta	445
Bulgaria	9,300	Netherlands	15,000
Croatia	6,000	Norway	4,000
Cyprus	1,140	Poland	31,000
Czech Republic	2,300	Portugal	8,502
Denmark	20,223	Romania	22,000
Estonia	400	Serbia	n.a.
Finland	5,436	Slovakia	3,000
France	103,900	Slovenia	12,200
Germany	105,435	Spain	37,971
Greece	13,700	Sweden	13,185
Hungary	22,600	Switzerland	38,561
Ireland	24,000	Turkey	25,000
Italy	65,000	United Kingdom	65,000
Latvia	n.a.	<b>Total</b>	<b>700,010</b>

## „Great place to work”

1. DHL Express
2. **AbbVie**
3. Hilton
4. Hilti
5. Salesforce
6. Specsavers
7. Stryker
8. Sopra Steria
9. Teleperformance
10. Cisco
11. **Bristol-Myers Squibb**
12. **Chiesi Group**
13. Cadence
14. Fronius
15. Deloitte
16. SC Johnson
17. Grohe
18. Adobe
19. Admiral Group plc
20. Groupe SEB
21. Atos
22. Insight
23. **Ipsen**
24. Liberty Mutual
25. **Biogen**

## Summary

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- ▶ Introduction of new drug on market is expensive (1-1.5 billion USD) and long (10-20 years),
- ▶ Expenditures on research and development in pharmaceutical industry are high.
- ▶ Poland is large pharmaceutical market but expenditures on R&D are relatively small.

