

A world map where the landmasses are dark blue and the oceans are a lighter, darker blue. The map is covered with a dense pattern of small, glowing yellow and green dots, representing city lights or population density. The text is overlaid on the bottom left of the map.

The pharmaceutical industry – who
has just missed the future?

Julian Clark



On the surface it looks good

- Global drug sales will reach \$ 1 trillion in 2014
- 5 – 8% annual global growth
- Price increases in US 8% for 2009
- Big players spend heavily on R&D (>17% revenue)
e.g. \$11 bn per year for Pfizer
- India already second largest by volume, China third largest value market by 2011 surpassed only by US and Japan
- Drugs still less than 10% of total health care costs
- Small molecules 85% of approvals in last 20 years
- Recently, large molecule approvals nearly twice small molecules



Top global markets

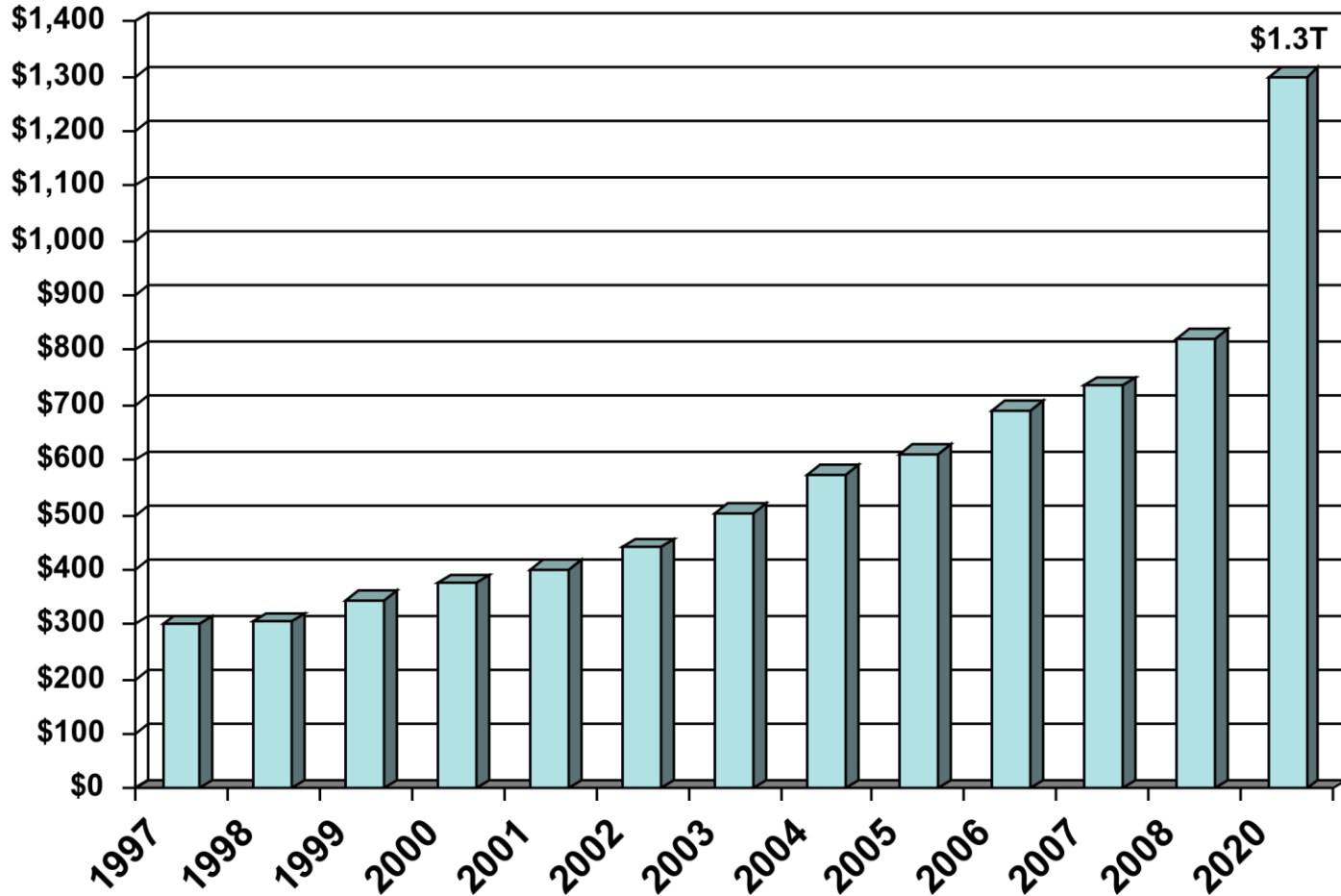
- The US with 41% of sales value continues to dominate the \$719 bn global pharmaceutical market

	Sales \$bn	Share	Change %
US	291.9	40.6	3.2
Japan	73.7	10.2	3.6
France	39.7	5.5	1.4
Germany	38.9	5.4	3.3
Italy	25.1	3.5	4.0
China	22.2	3.1	24.7
Spain	21.4	3.0	6.5
UK	19.8	2.8	4.9
Canada	17.7	2.5	6.1
Brazil	11.6	1.6	12.1
Total	\$561.9	78.2%	4.3%

Sales 12 months to June 2009
IMS Health, MIDAS



Worldwide pharmaceutical sales



\$1.3T



Worldwide consumers of prescription drugs (2010)

	% population growth 1998-2015	Average % GDP growth rate 1995-1999	Pop. brand eligible	
USA	0.7	3.7	309	
France	0.2	2.1	83	
Germany	-0.2	1.5	83	
Italy	-0.3	1.8	58	
Spain	-0.2	3.3	39	
UK	0.0	2.7	60	
China	0.7	8.8	352	(26%)*
Japan	-0.1	1.1	127	
Australia	0.8	4.4	19	
Brazil	1.1	2.2	66	(34%)*
Canada	0.6	3.3	33	
Poland	0.0	5.7	39	
<i>Able to purchase Rx pharmaceuticals</i>			<u>1,240</u>	

*% of population Rx brand eligible



“Pharma is at a pivotal point in its evolution. The dearth of good new compounds in its pipeline is central to all its other problems, including its expenditure, poor financial performance and battered reputation. Moreover,soaring healthcare costs will force Pharma to engage in the dialogue on healthcare funding and work much harder for its dollars.”

(PWC)



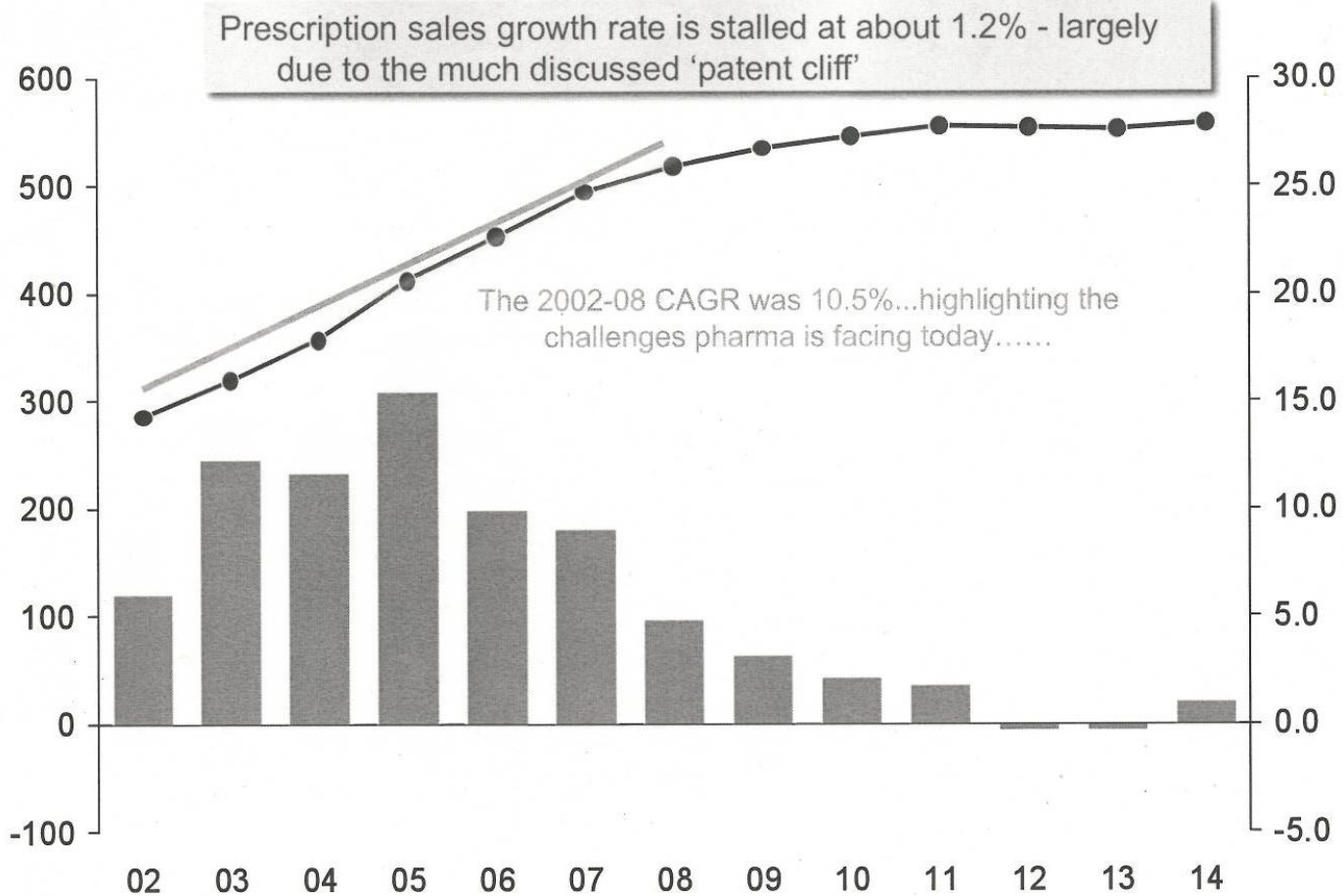
But all is not well

- Boards make decisions with little long term benefit
- Management operates with increasing inefficiency and declining productivity
- Senior position holders with medical, science and global backgrounds are increasingly rare
- We have an industry set for major consolidation
 - c.f. agrichem, automobiles, computers, petrochemicals, electronics



Rapidly declining growth

Prescription pharma sales (\$bn)



Year-on-year growth rate (%)

Source: Datamonitor. Pharmaceutical Company Outlook to 2014. Dec 2009



Let's start by revisiting history



Eight factors are dramatically changing the industry

- Changing markets
- The reality of biology
- Poor productivity
- Pricing and healthcare costs
- Patent expiration cliff
- The rise of generics
- Manufacturing problems
- Risk, litigation and behaviour



The markets have moved

- Overdependence on “traditional targets” and the US market
- Audience changing as healthcare policy makers and payers increasingly control the prescribing decision
- Focus on performance and value for money
- Increasing risk aversion of regulators
- Emerging markets have arrived – esp. China
- Aging population and burden of chronic disease is soaring
- Morbidities are transferring
- Blurring healthcare boundaries (diagnostic, hospital, primary, self medication)

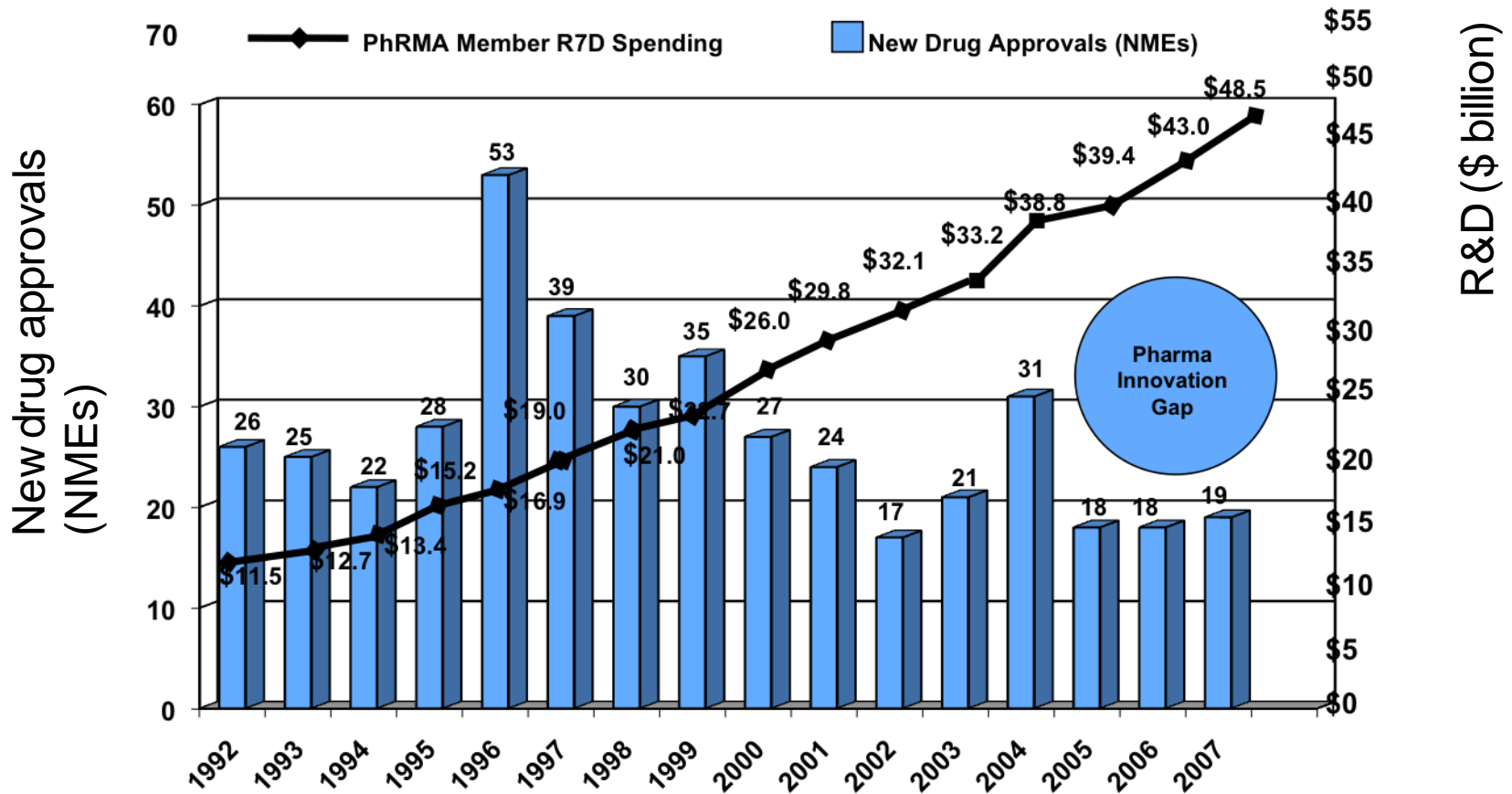


Biology remains complex

- Only just beginning to understand what we don't understand
- Reductionism and systems approaches required
- Not just target validation – validate the patient
 - Genetics and epigenetics
- Targeted and co-therapies
- Understanding mutations and resistance
 - Infection
 - Cancer therapy



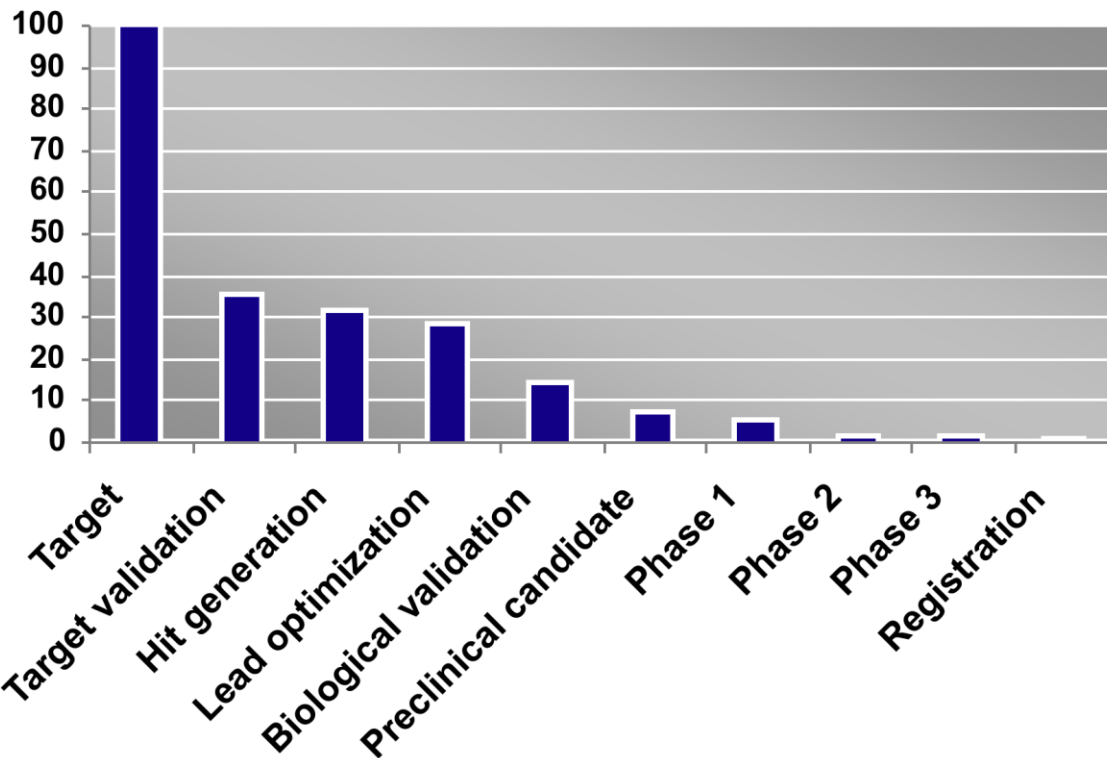
The innovation gap widens





High project attrition rates with two critical early stages

Upstream  Downstream



- Cumulative probability (%) of success at each stage in the process continues to show high attrition
- Critical to get it right “upstream” - “fail early, fail cheap”
- Focus on target and lead optimisation to mitigate risk



Poor productivity

- Spend
 - Corporate R&D from 15 to 17.1% of sales (1995 - 2005)
 - Corporate sales/marketing from 29 to 33% (1995 - 2005)
- Return on R&D
 - Only 1/3 of launched products return more than costs
 - More than 80% of investment is wasted
- Valuation
 - Between 2000 and 2005 the 14 largest companies lost \$ 500 bn in value – before the major patent cliff, before the GFC – future valuations for the same companies have dropped by \$1 trillion (Bradfield)



- Innovation

- Only 1/3 approvals are first or second in class, most “me too”

“... 50% of the pharmaceutical industry’s R&D expenditure is spent on drugs that add nothing significant to physicians’ armamentarium for fighting disease”



Poor productivity

- The attrition cost is exemplified by the large number of failed Ph III trials – when the loss in time and money is greatest
- Investing in failure - on average there is a 70% chance of failure from start of Ph III to IND/BLA
- Of Ph III failures:
 - 31% due to safety
 - 50% lack of efficacy

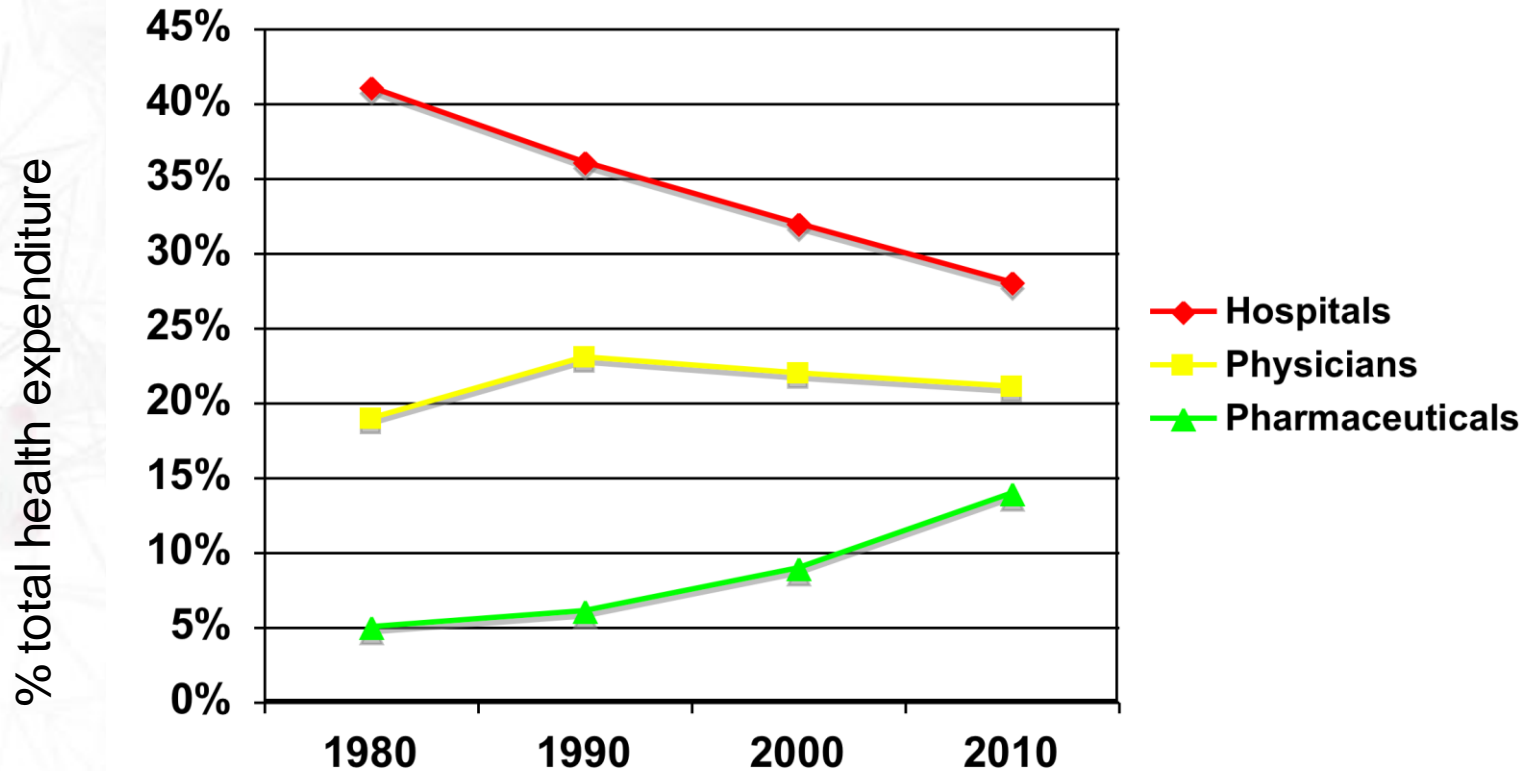


Poor productivity: two recent examples

- Efficacy
 - GSK herpes vaccine fails in Ph III trial (09/2010) involving 8,300 women across 50 sites
 - Effect “not substantially different from zero”
 - *“GSK has made the decision not to pursue further worldwide development of Simplirix”*
- Safety
 - Lilly Alzheimer’s drug fails in Ph III trial (09/2010) involving 2,600 subjects
 - The drug (semagacestat) actually made subjects worse
 - What went wrong? The target is expressed in many tissues. Was this to be expected?



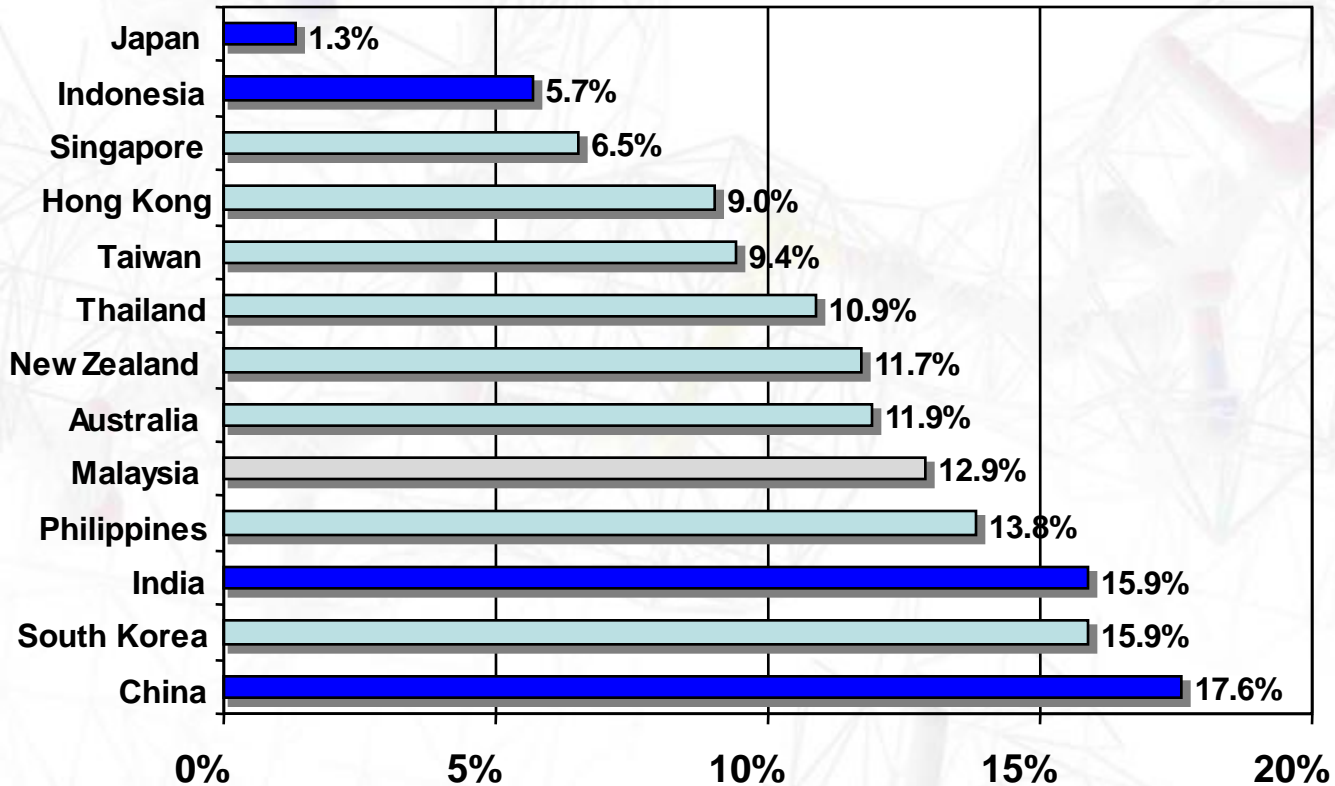
US healthcare expenditure by category



- Positive impact of day surgery and managed care
- Rising cost of “biotech” drugs



Asian healthcare spending growth rate



- China, South Korea and India will continue to be major drivers of global growth in healthcare spending
- Can they afford this growth?



Consequence of healthcare cost increases

- Potentially bankrupt system in the US by 2015
- Reimbursement increasingly driven by medical and economic outcomes with clear thresholds (e.g. NICE in the UK)
- Proliferation and redistribution of healthcare outcomes information – careful with the “spin”
- Emphasis on generics and “bio-similars”



Consequences of healthcare costs increases

- Targeted use of medicines and increased expectations from “personalised” medicine
- Increased focus on quality of life rather than longevity
- Return to palliative care and social support
- Emphasis on prevention/mitigation
- Major ramifications for pharma and biotech



Drug price backlash

- High drug prices are attracting increasing attention and bear little relationship to type of drug
- How to prioritise insurer's resources (NHS, PBS, private, etc)?
- National Institute for Clinical Excellence (NICE, UK) guidelines
 - Do not recommend treatments that cost more than \$58,300 per QALY (*Herceptin* has a price of \$34,000 per QALY)
 - Recent cancer drugs have cost \$135,000 - 325,000 per QALY and been declined
- What if no other treatment?



The most expensive drugs

Drug	Indication	Annual cost US\$	Company
Soliris (eculizumab)	Paroxysmal nocturnal hemoglobinuria*	\$409,500	Alexion Pharmaceuticals
Elaprase (idursulfase)	Hunter's syndrome	\$375,000	Shire Pharmaceuticals
Naglazyme (galsulfase)	Maroteaux-Lamy syndrome	\$365,000	BioMarin Pharmaceuticals
Cinryze (C1 esterase inhibitor)	Hereditary angiodema	\$350,000	ViroPharma
Myozyme (alglucosidase alpha)	Pompe disease	\$300,000	Genzyme
Arcalyst (rilonacept)	Cryopyrin-associated periodic syndromes	\$250,000	Regeneron
Fabrazyme (agalsidase beta)	Fabry disease	\$200,000	Genzyme
Cerezyme (imiglucerase)	Gaucher disease	\$200,000	Genzyme
Aldurazyme (laronidase)	Hurler syndrome	\$200,000	Genzyme, BioMarin Pharmaceutical

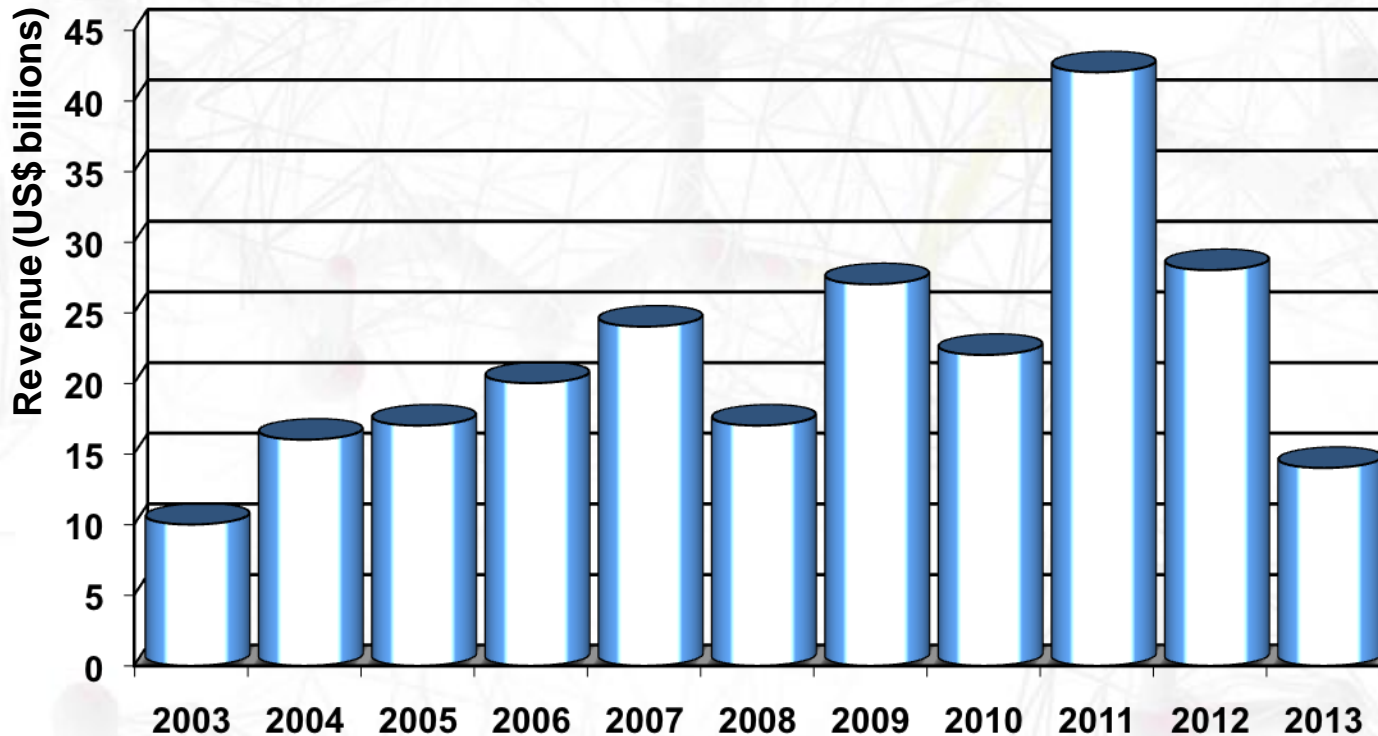


Drug price backlash example

- *Folotyn* approval by FDA for peripheral T-cell lymphoma (5,600 cases in US per year)
- It is Allos' first and only drug - price \$30,000/ month
 - cf *Erbix* \$10,000/month, *Avastin* \$8,800/month, *Arzerra* \$16,300/month, *Clolar* (Genzyme) costs \$34,000 per week
- On average a few extra months of life - 27% of 109 patients experienced a reduction in tumour size which lasted a median of 9 months, 12% had reduction in size that lasted more than 14 weeks
- Who pays? If the kids - then “no”; if the public - then “yes”!



Major patent expiries



- Revenues for top 8 territories
- Between 2006 and 2011, 103 drugs go off patent
- Between 2009 and 2013 a major proportion of \$133 bn will be lost

Biggest impact on AstraZeneca, Lilly, BMS, Pfizer and Merck



The generics challenge

- Traditional pharma “minds” do not understand generics – intellectual denial but very difficult
- Innovator loss of sales 80% in first six months but fierce competition between generic suppliers
- A successful generic player must be first out on midnight of patent expiry
- Strong political promotion - healthcare costs
- Growing at 15% with rapid global concentration – Teva has 17% global value market share and is now the 15th largest pharma company
- Current market \$72 bn in US and 76% of volume



Manufacturing problems

- The dreaded “483” is on the increase due to better surveillance by the FDA, profit pressures and increased management risk taking
- Example: J&J “phantom recall” of McNeil OTC products (53 million bottles)
 - CEO before congressional committee
 - \$100 m investment in new facilities and equipment
 - More than \$1 bn at risk before reputation
- Example: Genzyme’s chronic problems with contamination and plant closure (Fabrazyme) benefit Shire (Replagal) and will probably lead to takeover by Sanofi
- Example: Gilead major warning
- Example: Ranbaxy major warning
- Example: BMS ongoing problems in Puerto Rico

US product recalls:

1,742 in 2009
426 in 2008

One rogue company
but recalls still 50%
increase



Recent law suit examples

- GSK has paid \$1 bn to settle Paxil cases and reserved a further \$3 bn
 - \$380 m for suicide and suicide attempts
 - \$200 m for addiction and birth defects
 - \$400 m for antitrust, fraud and design claims
 - 600 birth defect claims outstanding
 - Only 12 suicide suits outstanding
- DOJ crackdown highly publicised
 - Pharma corruption - bribes, kickbacks, cartel etc
 - Healthcare fraud - defrauding insurers and providers
 - Advertising misconduct and claims
 - Settlement fines for Pfizer (\$2.3 bn), Novartis (\$423 mn), Lilly, AstraZeneca,



Recent law suit examples

- Merck had spent more than \$1 bn in legal fees by 2007 and reserved more than \$5 bn to settle Vioxx claims
- Novartis \$250 mn sex bias ruling to improve personnel policies and punitive damages to 5,600 employees.
- Big pharma has spent \$ millions in Europe to try and change DTC law – it is a European legislative priority and complete waste in the face of community standards
- Trouble brewing for Actelion – neglected to report deaths of more than 3,500 patients on two of its hypertension drugs



- Merck transferred patents on *Zocor* and *Mevacort* to its own Bermuda company and licensed back - \$2.3 bn moved out of the US
- Schering Plough caught with a similar strategy with Ireland and fined \$437 m
- IRS has flagged extensive investigation of the industry, especially with expansion into developing markets:
 - Transfer pricing
 - Tax evasion
 - (Bribes)



Guess what?

- Industry image is at an all time low
 - from once being one of the most respected industries
- Contributes to:
 - Government pressure
 - Flight of capital
 - Flight of people



Case study: Lilly

- Losing patent protection in the next seven years on drugs that accounted for 74% of sales in 2009
- Highest ratio of research to revenue 19.8% 2009 or \$4.3 bn/year
- Only one new product in last five years (*Effient* - sales \$60 m in 2009) - no new drug until 2013
- Purchased ImClone Systems or \$6.5 bn in 2008
- Revenues to shrink to \$18-19 bn from 23 bn
- Strongly attached to Indianapolis since 1876



- CEO Lechleiter's strategy:
 - No mega merger, remain focused on in-house R&D
 - Development Center of Excellence (2009) breaking up divisions into five categories
 - Move into cancer from strength in CNS (*Prozac, Zyprexa, Cymbalta*)
 - \$1 bn/ year expense cut (incl 5,500 job cuts in 2009)
 - Seek revenue generating late stage opportunities
 - Looked at more than 1,000 deals
- Borrowed time - there will be strong pressure to acquire or merge



Strategic responses: the “flock”

- Mergers and acquisitions
- Downsizing
- Out-sourcing
- In-licensing
- Emerging markets

It is extremely rare that companies provide the business and economic metrics, numbers and statistics that shape their decisions



Biotechnology M&A activity

- 1,171 M&A deals worth \$295 bn in last 10 years
- Only 18% of targets were revenue producing
- Top 25 targets valued at \$1.6 bn, 28% in Europe
 - Roche – Genentech (\$47 bn)
 - AstraZeneca – MedImmune (\$15 bn)
 - GSK – almorexant (\$3.3 bn), HuMaxCD20 (\$2.1 bn), antiinfectives (\$1.9 bn), ID Biomedical (\$1.6 bn)
 - Amgen – Immunex (\$11.1 bn), Abgenix (\$2.7 bn)
 - Lilly – ImClone (\$6.5 bn), Icos (\$2.3 bn)
 - Genzyme – Bayer oncology (\$2.8 bn), mipomersen (\$1.9 bn)

Year	Value \$ bn	Number
2009	48	193
2008	94	148
2007	42	145
2006	36	115
2005	23	113
2004	7	96
2003	17	128
2002	3	96
2001	20	85
2000	5	52
Total	295	1,171



Pharma M&A activity

- 1,345 deals worth \$691 bn in last 10 years
- Virtually all targets revenue generating
 - Glaxo – SmithKline Beecham (\$74 bn)
 - Pfizer – Wyeth (\$68 bn), Pharmacia (\$56 bn)
 - Sanofi – Aventis (\$65 bn)
 - Merck – Schering Plough (\$41 bn)
 - Bayer – Schering (\$22 bn)
 - J&J – Pfizer Consumer (\$16.6 bn), ALZA (\$12.3 bn)
 - Teva – Barr (\$9.0 bn), Ivax (\$8.0 bn)
 - Abbott – Solvay (\$7.6 bn), Knoll (\$7.0 bn)

Year	Value \$ bn	Number
2009	147	140
2008	41	140
2007	72	180
2006	75	138
2005	47	128
2004	95	171
2003	24	173
2002	66	147
2001	28	87
2000	97	41
Total	691	1,345



M&A – what's left short term?

- Likely Genzyme by Sanofi Aventis, Crucell by J&J
- Other candidates:
 - Celgene (\$20 bn)
 - Allergan (\$20 bn)
 - Biogen Idec (\$14 bn)
 - Shire (\$10 bn)
 - Lilly
 - AstraZeneca
 - Novo Nordisk
 - BMS
- All merged companies lost market share from 3% (GSK) to 39% (Aventis), all with a worsening of productivity
 - By using capital in acquisitions companies have removed a credit rating cushion - rating for entire industry has fallen



Down sizing or “resizing”

- Over 300,000 pharma and biotech jobs eliminated over the past three years
- Cuts in all areas but especially sales and R&D
- Drivers:
 - Rationalisation to secure short term profit
 - Decline of the sales force model
 - Moving to Asia and outsourcing
 - “Punishment” for lack of R&D productivity
- Expect a major psychological impact in the face of absent leadership and alternatives



Down sizing or “resizing”

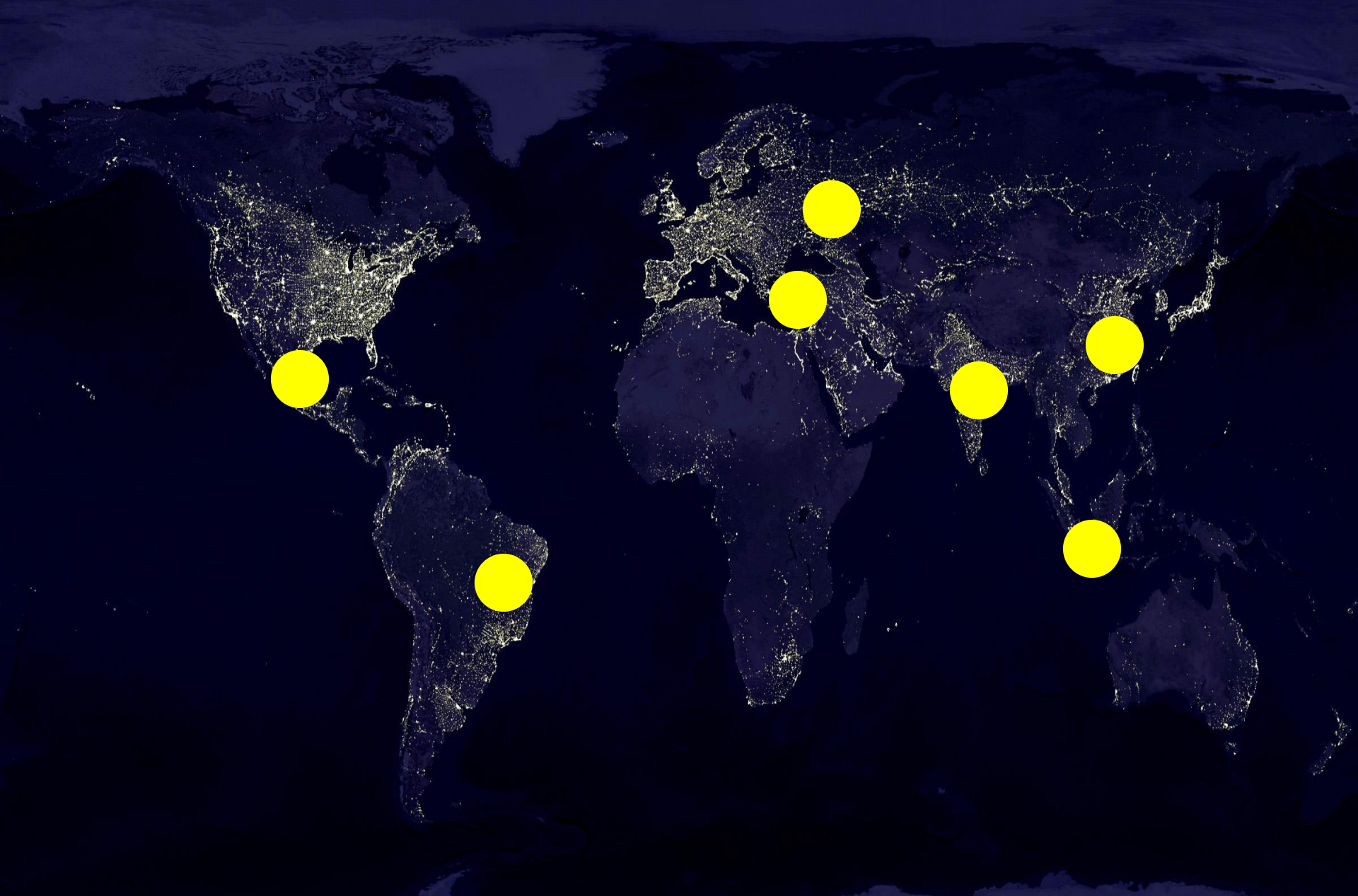
- Case – serial cuts: AstraZeneca has had total cuts of 25,000 jobs (nearly 20%) within a decade
- Case – acquisition: Abbott cut 3,000 Solvay jobs (30% of Solvay) immediately after integration
- Case- merger: Pfizer/Wyeth are eliminating 15% of R&D people and 35% of R&D space
- Case – benefits: BMS have a salary freeze for 2010 against a 6% sales increase in 2009 and already 7,000 jobs recently eliminated
- Case – structure: Sanofi Aventis cuts management levels from 11 to 6



- Approx 1/3 of R&D is now outsourced
- The demise of the FIPCO (fully integrated pharma company) and the rise of the FINPCO (fully integrated networked pharma company)



- Example: Sanofi Aventis/Covance
 - Outsource \$2.2 bn 10 year contract to lower costs and improve productivity in return for two sites and maintaining employment for 5 years
 - *“The deal will help Sanofi reduce research costs and the time needed to move medicines from the laboratory to patients”*
- Example: Lilly/Covance
 - Outsource \$1.6 bn 10 year contract in return for facility acquisition and services
 - *“Covance has been looking for more predictable revenue by moving away from periodic contracts”*



The ubiquitous “E7 strategy”



The advance of China

(US\$ bn)

2002 Top 10		2005 Top 10		2010 Top 10	
USA	196	USA	262	USA	466
Japan	53	Japan	65	Japan	81
Germany	20	Germany	24	Germany	37
France	19	France	21	France	28
UK	14	UK	16	<u>China</u>	<u>24</u>
Italy	13	Italy	15	UK	24
Spain	9	<u>China</u>	<u>14</u>	Italy	23
Canada	8	Brazil	10	Canada	17
Mexico	8	Canada	10	Spain	16
<u>China</u>	<u>6</u>	Spain	10	Brazil	15
Total	346	Total	447	Total	731



Emerging market risks to be managed

- Low margins – 36% vs 60% in US and 68% in Europe
- Better suited to generics players in short term
- Less patent protection and counterfeits
- Government deals dominate – reduced prices
- Government concerns over pharma “collusion”
- Rapid growth to be managed



Emerging market risks to be managed

- High staff turnover rate (28% in China) and competition for people repatriated to boost domestic industry
- 50% in Brazil, Russia, India, China, Mexico and Turkey - the rest are very fragmented
- Requires considerable cross-cultural skills
- Growth opportunities but will not solve pharma's underlying problems



Engage with generics

- “Big pharma” is belatedly discovering “if you can’t beat them- then join them”
- Novartis has Sandoz as its well established generics unit
- Pfizer will create a generics unit and aims to have a pipeline of 10 -15 products to compete with, e.g. Amgen’s *Epogen* and Sanofi’s *Lovenox*
- Do generic deals, e.g. Pfizer/Watson for *Lipitor*
- Merck acquired a biosimilars operation for \$130 m



- Access skills
- Business to business
- With academia – migrate upstream
- Academia trend from contracts to collaboration
- Increased pooling, collaboration and partnering with biotech

Bayer/Tsinghua University
Pfizer/University College London
AstraZeneca/University of Virginia
University of Dundee/5 pharmas
GSK/Harvard
Boehringer Ingelheim/IMP
Genentech/Abbott/WEHI/
CSL/WEHI
Pfizer/Peter MacCallum
Genentech/UCSF



Move into novel partnerships

- GSK and Pfizer created a novel joint venture
- Pooled all assets in HIV
 - Approved products
 - Pipeline products
- GSK have a 85% share based on revenues of \$3 bn
- Pfizer provide the pipeline
- Protects therapeutic area during company restructuring
- More public-private partnerships to be expected



The first “money back” guarantee and subsidy

- J&J’s cancer drug Velcade was rejected from listing by the NHS (NICE)
- J&J proposed a rebate for the cost of patients who don’t improve “sufficiently” after four cycles
- Cost is \$6,000 per cycle
- A win for the patient and pressure for a predictive biomarker
- Novartis now contributing to patient’s out of pocket expenses for *Gilenya* (multiple sclerosis) which is priced at \$4,000 per month



Productivity case study: Pfizer

- Few big selling products have emerged from Pfizer R&D since Viagra in 1998, despite an unmatched investment in R&D
- Pfizer's mega mergers with Wyeth, Warner Lambert and Pharmacia have produced little synergies.
- *“The company would have preferred more drugs to have come out of its laboratories in recent years”*
- *“People should not look through the eyes of the past but instead focus on the company's pipeline...we are building a coherent organisation, allowing a diversity of approaches”* (Dolsten head R&D)



Organisational change

- Several players are experimenting with organisational changes, attempting to:
 - Encourage open innovation
 - Reduce unit size, increase information sharing
 - Increase disciplinary interactions
- Several different concepts:
 - Disease focused centres
 - Centres of excellence
 - Semi-autonomous units competing for funds
- Examples: Lilly Development Centers of Excellence and GSK Centres of Excellence in Drug Discovery



Critical R&D leadership issues

- Higher quality “shots on goal” – less quantity, greater intellect, validation of patient, not just target
- Revise reward systems for innovation and R&D
- Empower and utilise middle management
- Stronger link between CSO/R&D and CEO/Board
- Encourage organisational experimentation
- Focus on establishing new clinical trial approaches
 - Adaptive clinical trials (e.g. I-Spy-2)

Douglas FL et al (2010) Nature Revs Drug Discovery August 20



The board room challenge

- Decline of scientific/ technical experience at the top
- Enormous wastage in R&D and marketing
- Locked-in thinking perpetuating a status quo that doesn't exist, underpinned by “ethnocentric” over-confidence
- Organising to solve complex, not statistical problems
- Industry has not made a compelling argument for itself or its performance
- Disintermediation and empowered end-users



The board room challenge

- *“...giant research budgets have generated dismal returns. That should be no surprise. Massive cash-rich, bureaucratic organisations with palatial offices are never the best environment for cutting-edge science.”* (Matthew Lynn, Bloomberg)
- The future is not guaranteed for many - who will be the first to exit R&D?



Ultimate drivers of sustainable value

- Integrity
- Quality
- Curiosity
- Culture
- *“Focus on science not swagger”*
- Major opportunities for the intellectually nimble
- Ensure “bioprocessors” are fully integrated into all stages and issues



Thank you!

Julian Clark (jclark@wehi.edu.au)



- Thomson Reuters
- MedTrack/Datamonitor
- Business Insights
- PWC
 - Pharma 2020: Challenging business models – which path will you take?
 - Pharma 2020: Virtual R&D
 - Pharma 2020: The vision