

DRUG DEVELOPMENT IN PERSPECTIVE

PHARMACOLOGY TO PHARMACON! SCIENCE TO MAGICAL SUBSTANCE

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The most significant discovery of the 20th
century was...

THE RANDOMISED, DOUBLE BLIND, PLACEBO CONTROLLED CLINICAL TRIAL!

1ST in the early 1950's

1960's: Drug amendments in the USA led to
the modern trial and the coming into-being
of the F.D.A

SOUTH AFRICA: ACT 101, 1965
MCC came into being

Not far behind the USA!

Since then: active participation by SA in International Drug Development Programmes

- SA has done 2 total developments from first-time in man (FIM) to FDA registration:
 - Triptorelin – LHRH – agonist
 - Rifapentine – the last anti-TB drug registered
- Busy with the 3rd :
 - Malaria vaccine
- China and India: NONE !

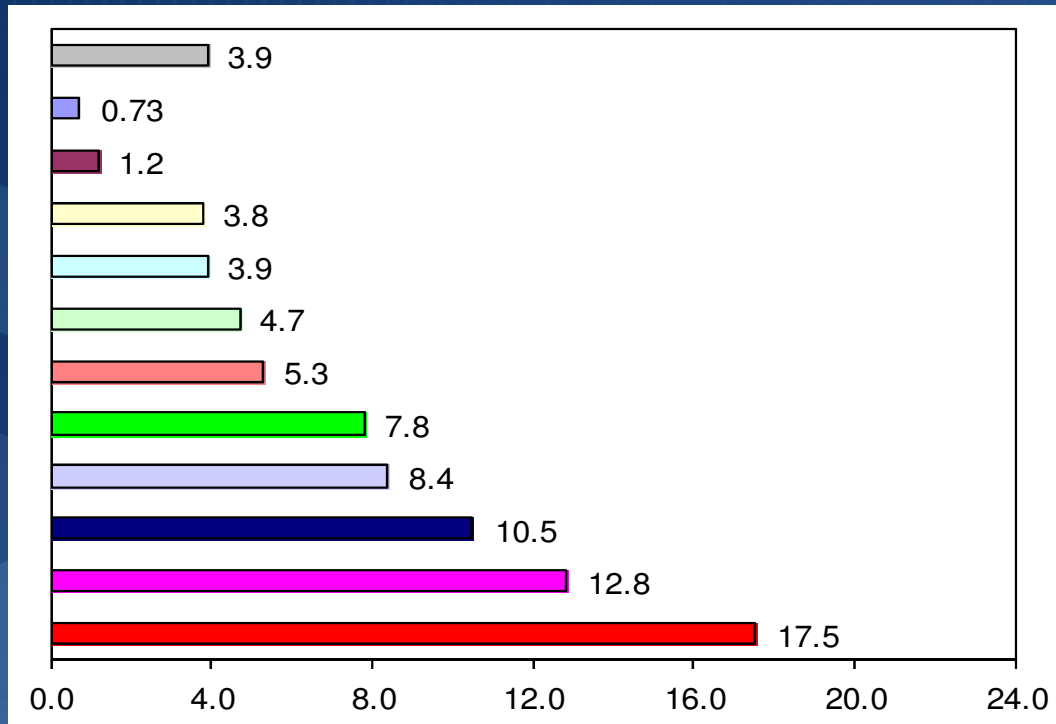
At the moment the international pharmaceutical industry is weathering the perfect storm

- Patent expiries and loss of exclusivity – Exclusivity loss estimated to be around \$11 Bn per annum for 2008 – 2011
- Increasing payor pressure – Health care reforms in the US expected to put further pressure
- Generic competition from emerging markets
- Growing safety concerns - Increasing complexity and data requirements
- Brand Pharma has a perception problem – The Big Evil Pharma
- Increasing earnings pressure from the financial market



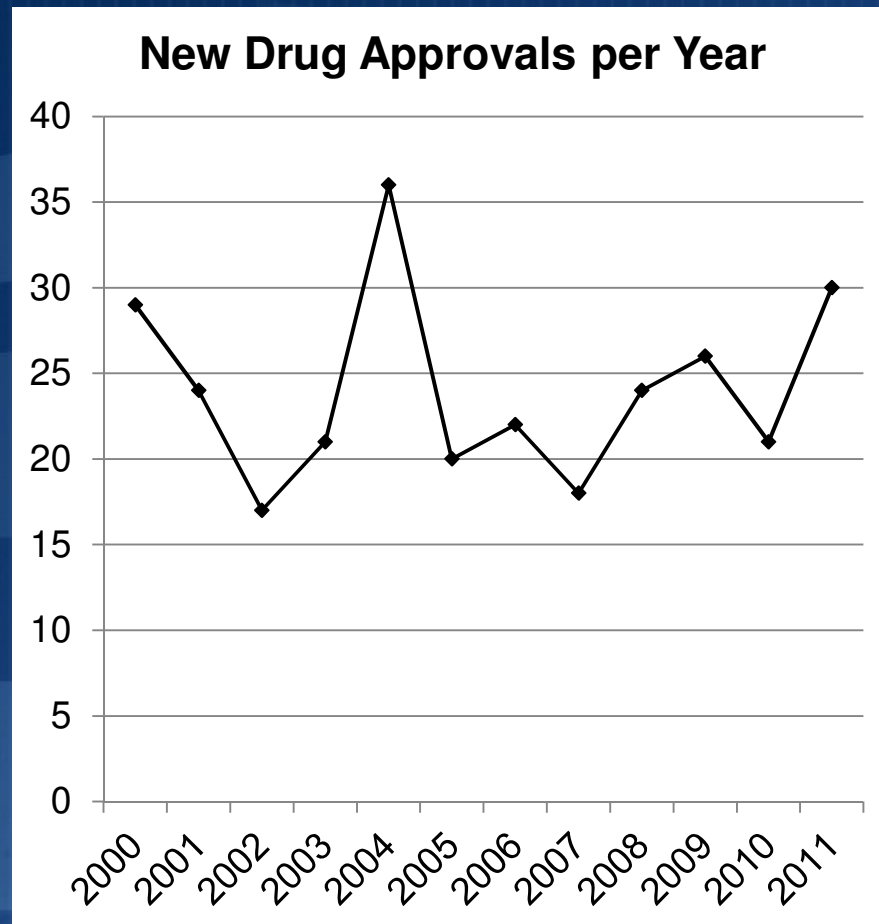
R&D per cent of sales

- All Industries ex. Drugs & Medicine
- Paper & Forest Products
- Metals & Mining
- Aerospace & Defense
- Automotive
- Leisure Timer Products
- Electrical & Electronics
- Office Equipment & Services
- Electrical & Electronics
- Computer Software & Services
- Drugs & Medicine
- Research-based Pharmaceuticals



Research-based pharmaceutical companies' based on ethical pharmaceutical sales and ethical pharmaceutical R&D only, as tabulated by PhRMA. 'Drugs and medicine' category based on total R&D and sales for all products of companies within the drugs and medicine sector, tabulated by Standard & Poor's Compustat, a McGraw-Hill Division.

Productivity crisis



- Phase II clog in development pipeline
- Number of molecules entering Phase III development expected to decline
- Increasing complexity and study durations
- Industry consolidation and portfolio rationalization

In 2005, Goldman Sachs analyzed the pipeline of 17 large pharma firms and estimated that there ~180 drugs at various stages of development, targeting the market before 2009. After applying normal industry attrition rates, the output comes to <20 per annum, roughly one molecule per firm...

Source: FDA – NMEs Approved by CDER (2011)

High attrition rates

In spite of Industry's best efforts, Cumulative success rates are still low

	Pre-Clinical	Phase I	Phase II	Phase III/ File	Launch
1995 - 2000	8	6	3	2	1
		75%	37.5%	25%	12.5%
2000 - 2003	13	9	5	2	1
		68.23%	38.46%	15.38%	7.69%
2004-2010	16	11	7	2	1
		69%	43.47%	14.35%	6.31%

With increasing payor pressures and shorter exclusivity periods,
Pharma innovation is becoming unattractive to investors

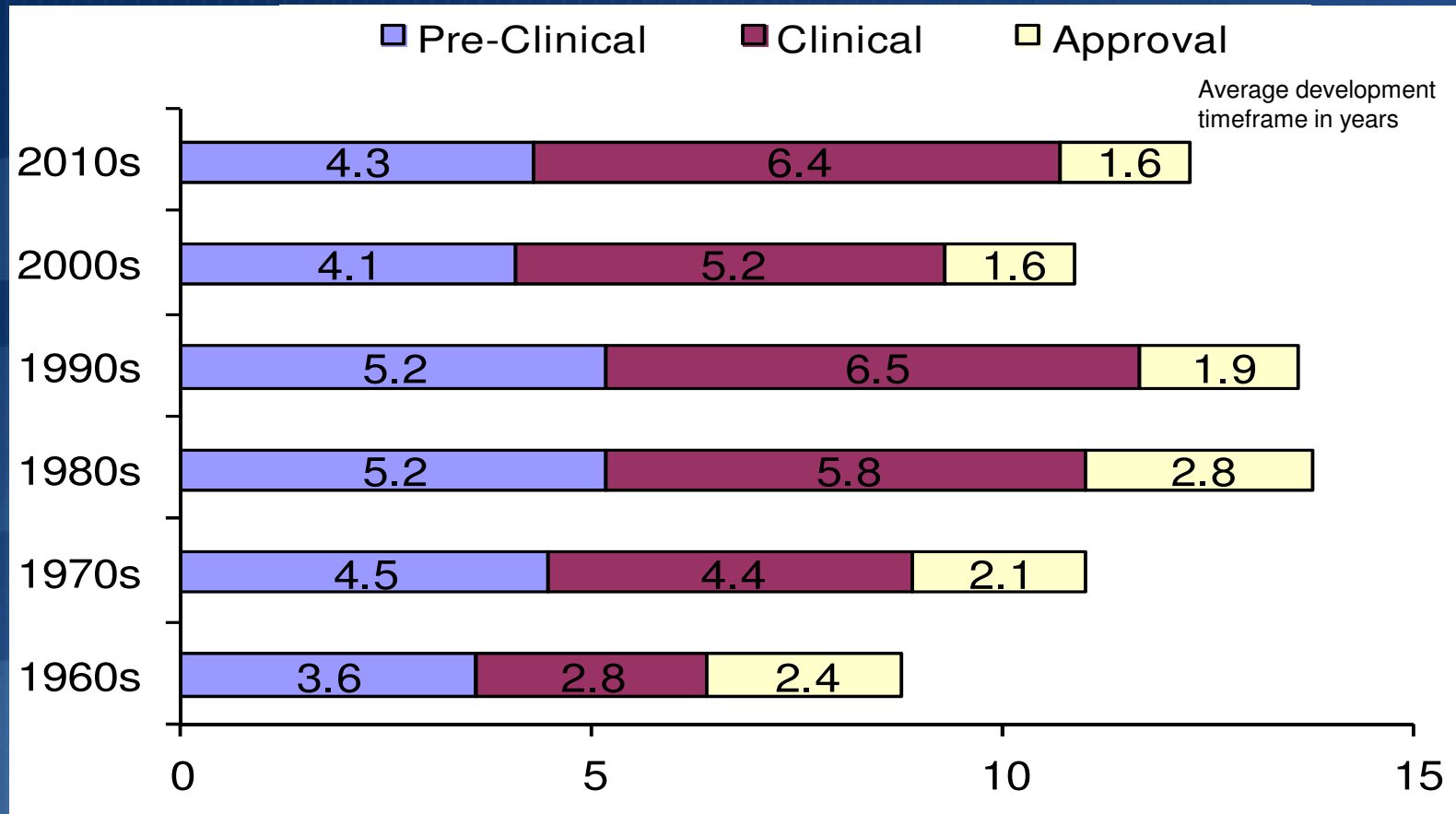
Example of a phase III failure: The Torcetrapib Mystery

“Pfizer spent more than \$900 million testing its experiment heart pill, torcetrapib. But in December 2006 a 15,000 – patient study revealed that this chemical increased death rates (93 vs 58), forcing Pfizer to suddenly drop the project”

“What went wrong”

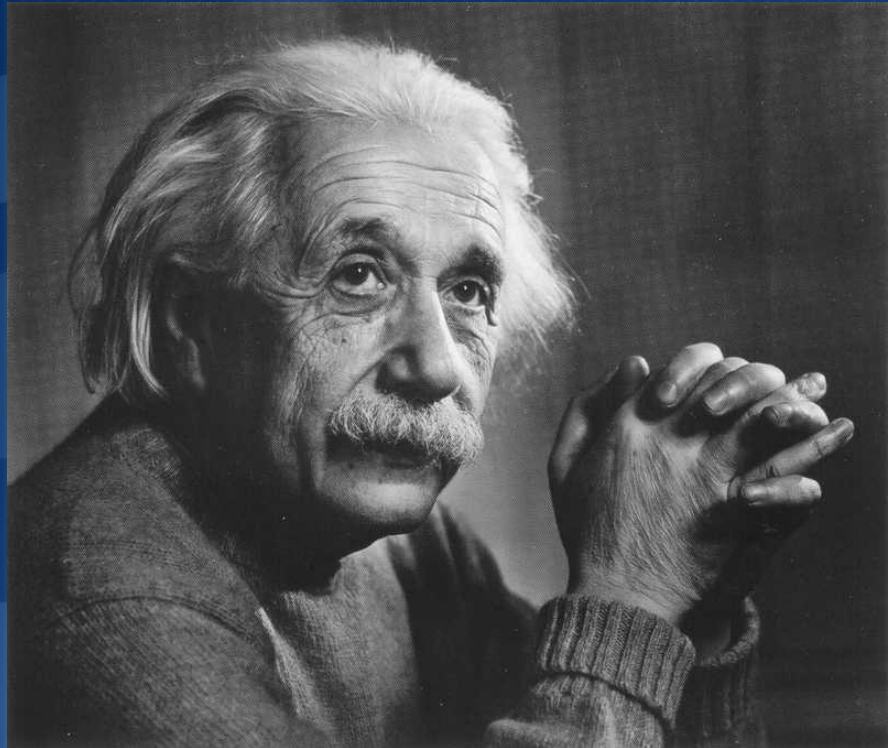
“Why torcetrapib failed is the biggest mystery facing the \$260 billion global pharmaceutical industry”

And long cycle times



... In spite of the considerable improvement in the early 2000s, the average development cycle continues to cross a decade...

What can be done about it – What would Einstein do?



“The significant problems we face today cannot be solved at the same level of thinking we were at when we created them”

Albert Einstein

FDA: Six priority public health challenges in 2004/ 6

- Biomarker development
- Streamlining CT's
- Bioinformatics
- Manufacturing
- Antibiotics and countermeasures to combat emerging INF and BIOTERRORISM
- Dev. Therapies for children and adolescents

New science is changing healthcare...

Structural Biology	Rational design of new medicines
Genetics, genomics and proteomics	Better targeting of medicines
Metabonomics	Better diagnosis and monitoring
Vaccines and immunomodulation	Prevention and monitoring of infectious diseases
Point of care diagnostics	Faster diagnosis and enhanced involvement of the patient
Bionics	Organ replacement and enhancement
Cell and tissue engineering	Regenerative medicine
Imaging	Better diagnosis and precision treatment
Micro-electronic devices	Sensing and monitoring; increased independence for individuals
Minimally invasive and robotic surgery	Enhanced precision and reduction in unwanted drama

New science is changing
health care ...
Pharmacology is changing drug
development!

Pharmacology is changing drug development

- Emerging world of PERSONALISED MEDICINE
- Increased use of BIOMARKERS
- Predictive BIO-SIMULATION
- INNOVATIVE STUDY DESIGNS
- CREATIVE PROCESS DELIVERY

PERSONALISED MEDICINE

- Meticulous patient selection
 - Polymorphisms increase new disease targets
 - Radical differences
 - Differences in drug metabolism
- Greater efficacy, reduced adverse events
- Variation in response to treatment linked to genes:
 - Genotype identification kit
 - Therapeutic kit: diagnostic kit plus medication!

Drug development: The high-Tech Clinical Trial

- Pharmacogenomics will...
 - Reduce number of patients in clinical trials
 - Shorten time-to-market
 - 13.3 years $\wedge \approx 10$ years
 - Shorten development time
 - 4-7 years $\wedge \approx 2-4$ years
 - Reduce cost of drug development
 - \$1.3 billion $\wedge \approx$ \$200 million

BIOMARKERS

- Possibility to replace a distant clinical endpoint with more proximal surrogate end point
- Early elimination of unviable/ unsafe candidates
- Of great value in optimal/ efficient trial design
- Technology for biomarker discovery & validation from genomic/ proteomic data are maturing

PREDICTIVE BIO-SIMULATION

- Use of virtual patients
- Helps to interpret pre-clinical outputs in the context of human physiology
- Increased predictability of clinical outcomes
- Optimal designs of trial protocols
- Used in identification of appropriate surrogate endpoints and biomarkers

INNOVATIVE STUDY DESIGNS

- Non-inferiority trials
- Enrichment designs
- Adaptive trial designs
- Analysis of multiple end-points
- Measuring disease-related symptoms & patient reported outcomes
- Dose-response relationships in oncology

CREATIVE PROCESS DELIVERY

- Electronic data capturers
- eMedical records (her)
- Access to patients
 - Disease epidemiology
 - Protocol defined patients
 - Trial-orientated patient populations

What role can South-Africa play?

- Focus where we have a competitive edge:
 - Primate research
 - Access to patients
- Take leadership in research ethics
 - Accreditation in place
 - Site insist & audits

- A DRUG DEVELOPMENT-FRIENDLY regulatory authority
 - 28 day CTA-exemption
 - Rational and Scientific adverse event monitoring
 - Clinical pathway priorities
- Government financial support
 - Tax incentives
 - Clinical research in
 - HIV/ AIDS
 - MALARIA
 - TB
 - Research human recourses

RESEARCH: CLINICIANS

- Pre-requisites:
 - Inquisitive mind
 - Creative thinking
 - Innovative spirit
 - Critical evaluation
 - Good judgement
- Training required
 - Research ethics
 - Good Clinical Practice (GCP-ICH)
 - Therapeutic area

WHAT CAN YOU DO?

- Help create a research culture at UP Medical school !
- Get the right training!
- Publish before graduating!
- Lead, don't follow !
- Give, don't just take/ get!

Thank You



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