The Penumbra of Thalidomide

The need for reform of the Licensing of Pharmaceuticals

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Thalidomide

- Drug was patented by Grunenthal in Germany in 1954
- Launched in October 1957 as a sedative, pain killer and anti-emetic suitable for treating morning sickness in pregnancy
- Licensed in UK in 1958 and in much of the rest of the world – but not in USA where FDA refused a license without further studies
- No studies on pregnant animals were then required because it was believed that drugs would not cross the placenta

Thalidomide – the disaster

- Between 1957 and 1961 (when the drug was withdrawn) more than 10,000 children in 46 countries were born with deformities
- In UK 2000 affected babies of whom 466 survived. Even in US there were cases from clinical trial use
- Phocomelia – absence of limbs most common defect
- This was probably the greatest pharmaceutical disaster ever (though it falls far short of the withdrawal of DDT in1972 which caused millions of deaths from malaria)
- *More recently thalidomide has returned to clinical use for the treatment of leprosy and of myeloma*

Thalidomide – the consequences

- **Immediate**
  Testing for teratogenicity became universal for drugs to be used in pregnancy

  Affected families were paid compensation

  Phocomelia is extremely rare in children not exposed to thalidomide in-utero and a direct causal relationship was clear

- **Subsequent**
  - Procedures for licensing drugs became much more rigorous, lengthy and expensive

  The first European pharmaceutical directive (Directive 65/65/EEC1) was a reaction to the "thalidomide disaster" in the early 1960s. It aimed to establish and maintain a high level of protection for public health. *From Euractiv.com*

  Public tolerance of risk in regard to all prescribed *(as opposed to alternative and herbal)* pharmaceuticals declined sharply to an entirely unrealistic level

The (Unintended) Consequences of the Consequences

- **Drugs have become ruinously expensive**
  It can take more than ten years and cost more than $1billion to bring a new drug to market
- Only large companies with very deep pockets can now afford to take drugs to market.
- In consequence many promising drugs developed by smaller biotech companies remain on their shelves.
- It has become uneconomic to develop drugs for diseases that are not very common (or very rare)
- Litigation against drug companies for harm from side effects has added significantly to drug cost and has lead to drugs being withdrawn for no adequate cause

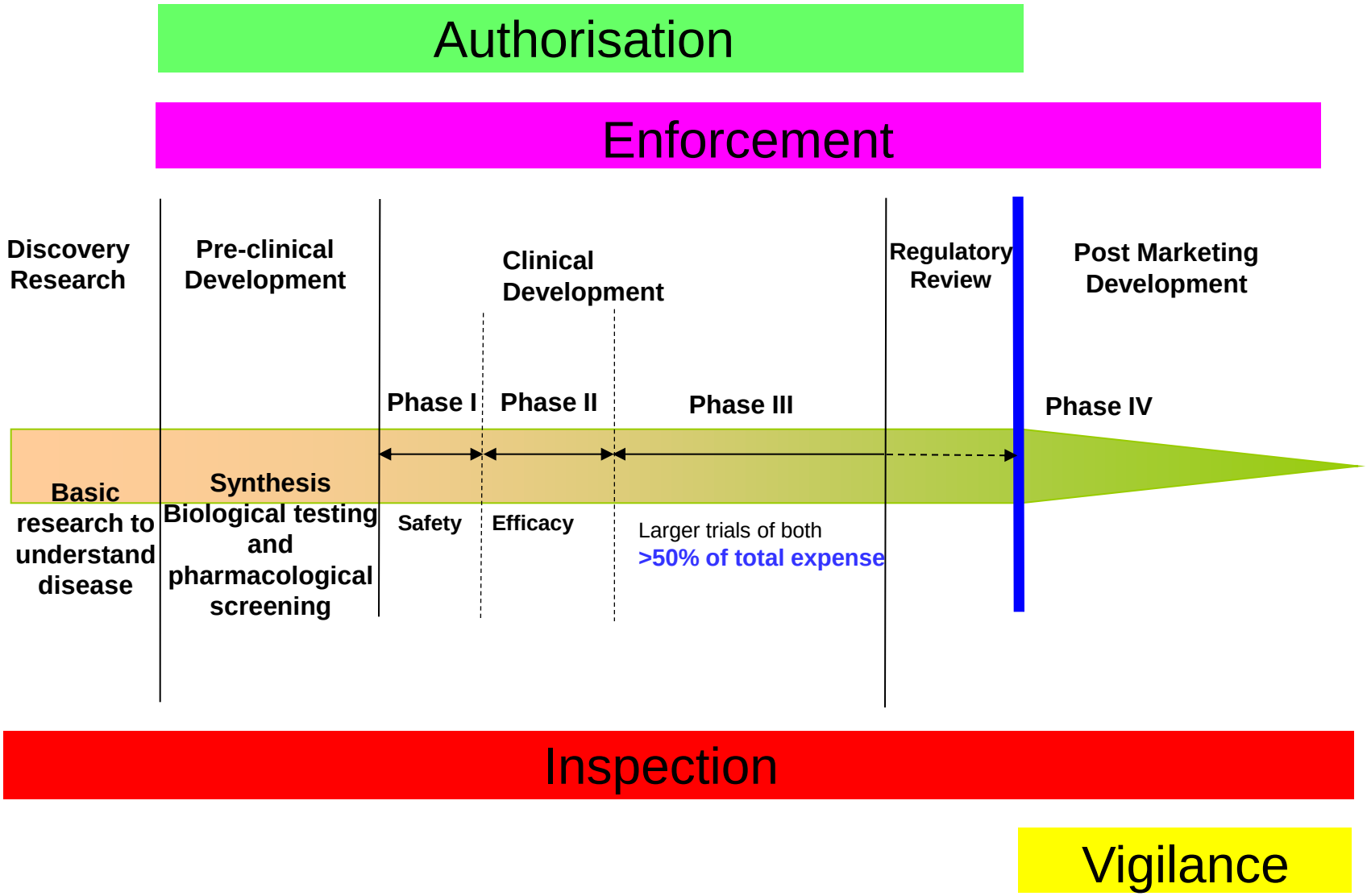
Drug Development Process

- *Applies to prescribed drugs; alternative and herbal medicines largely exempt*
- Ensures purity and consistency of drug
- Studies of drug metabolism and clearance
- Animal studies of safety and efficacy
- Safety studies in man
- Efficacy studies in man
- ***Necessity for all these is not in dispute***

The Named Patient Exemption

- ***The Medicines for Human Use (Marketing Authorisations Etc.) Regulations 1994 [SI 1994/3144]*** *Schedule 1 exempts from the need for a marketing authorisation a relevant medicinal product which is supplied to fill a "special need" and in response to a bona fide unsolicited order, formulated in accordance with the specification of a doctor, dentist or supplementary prescriber and for use by his individual patients on his direct responsibility*
- Allows a doctor in good standing, acting in good faith and with therapeutic intent to treat his own patients (who have given their informed consent) with a compound, including those produced by his own laboratory, without any regulatory approval.
- This has been the route by which much academic translational research has been initiated.
- It vitally needs protecting from interference by European Commission or by anyone else.

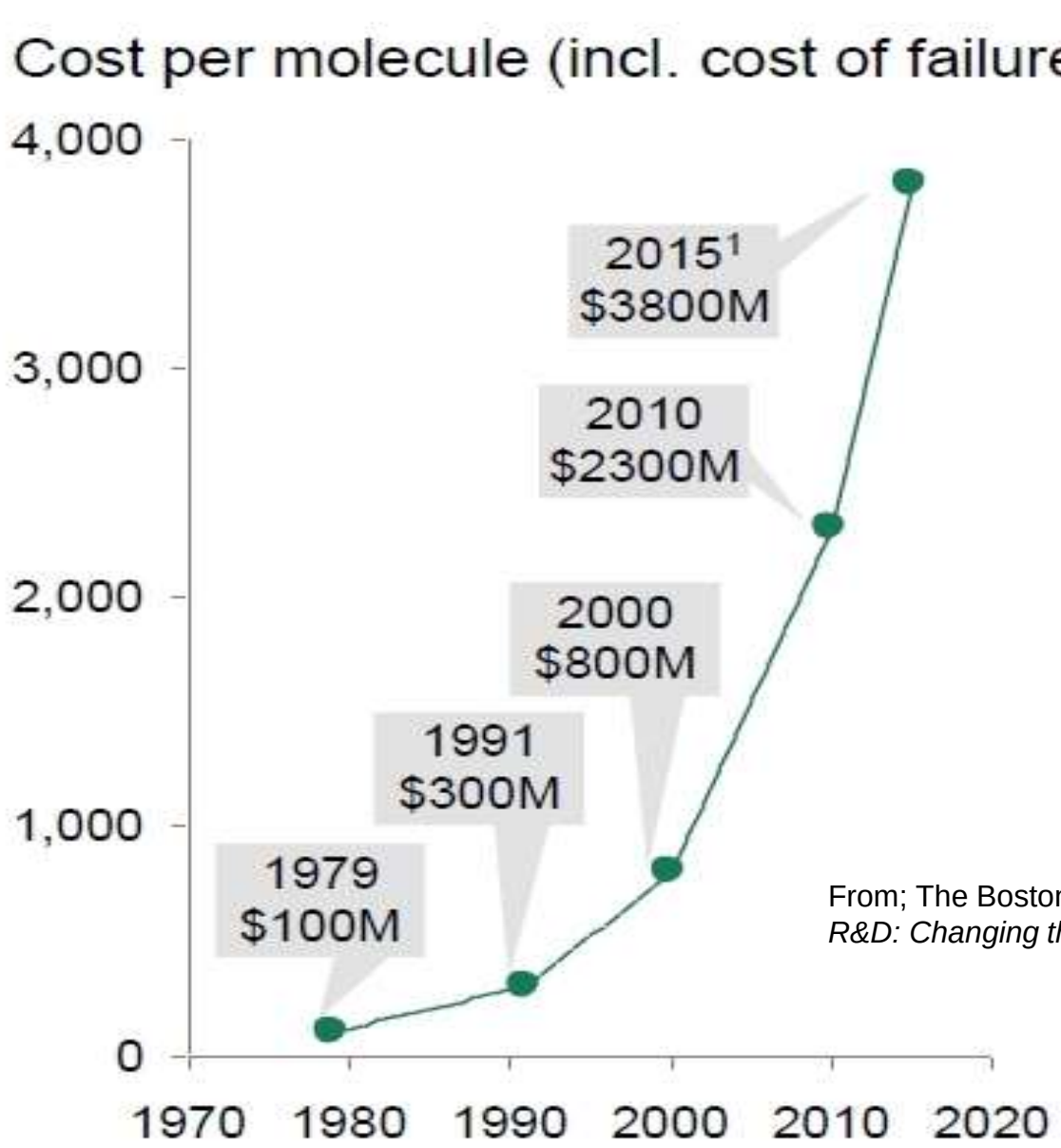
Drug development process



By courtesy of Sir Kent Woods at MHRA

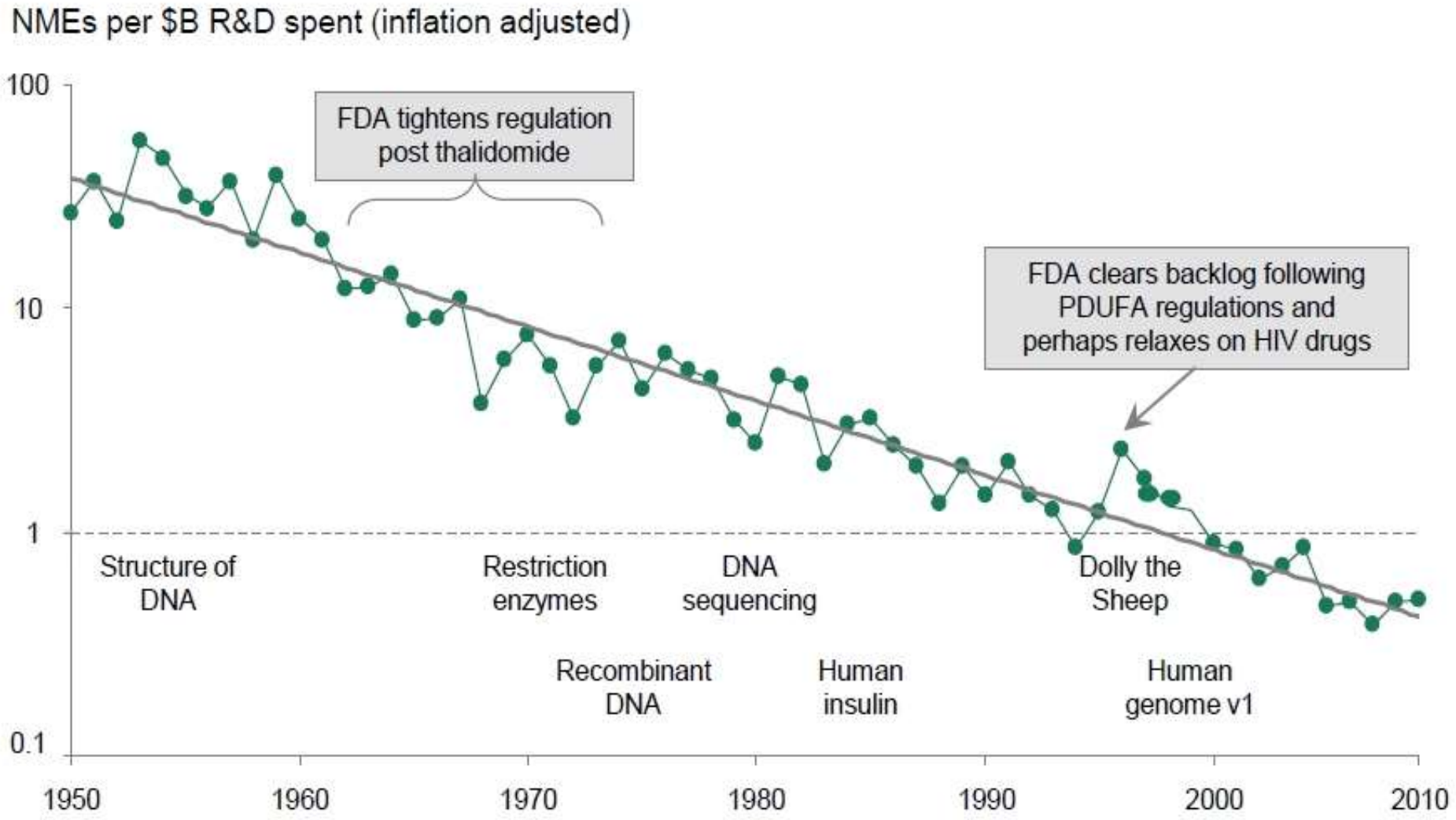
Drug Trials after Licensing

- Prospective randomised trials to improve efficacy of drug use; to test combinations of drugs; and to extend the range of indications go on for many years after drugs are first licensed
- In cancer therapy such trials have lead to substantial improvements in outcomes from existing drugs
- It is NOT suggested that this process be changed



From; The Boston Consulting Group, *Life Sciences R&D: Changing the innovation equation in India,* 2011

Reduction in R&D Productivity



From Bernstein Research, *The Long View: Pharma R&D productivity – When the cures fail it makes sense to check the diagnosis,* September 30, 2010

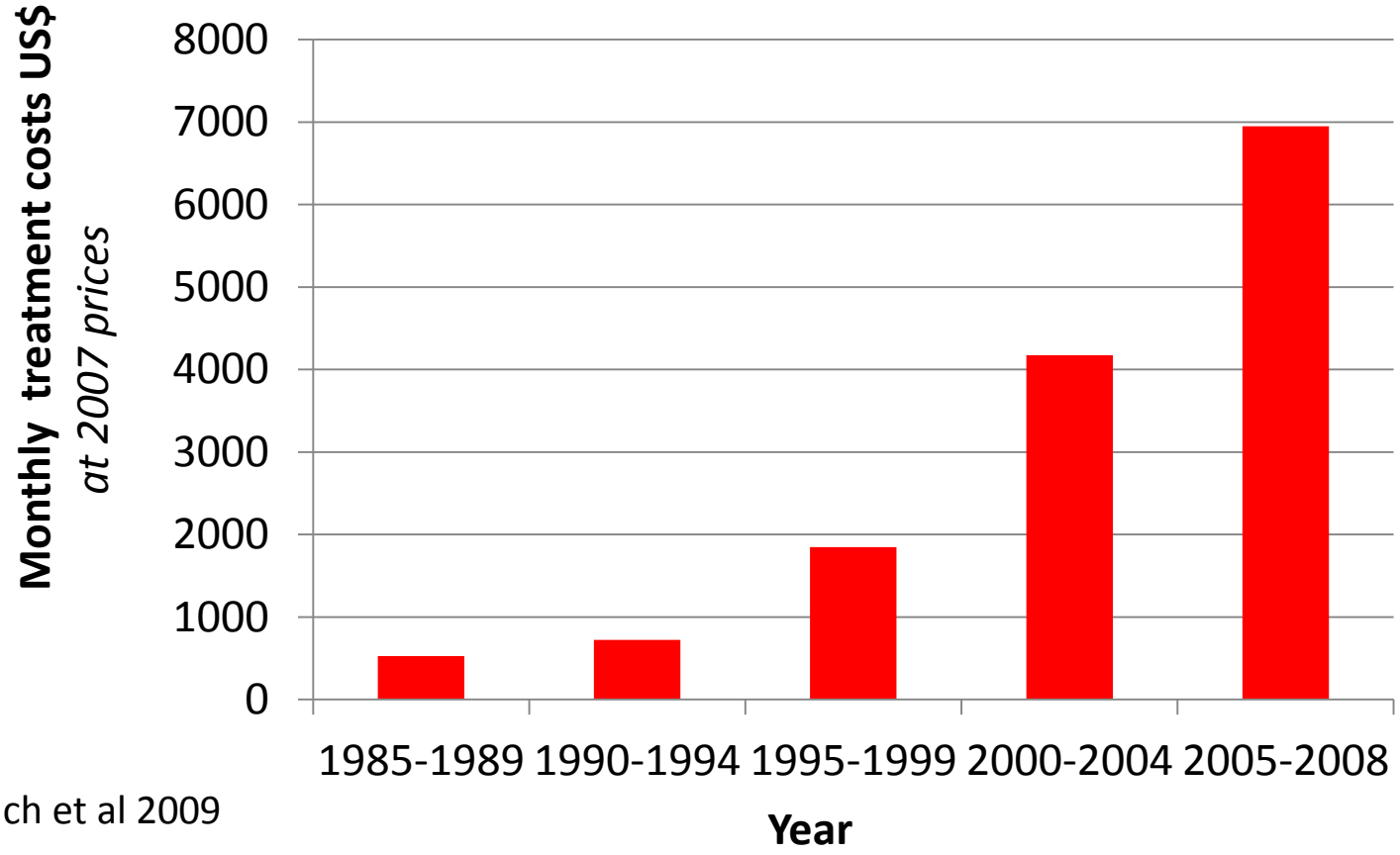
PDUFA – Prescription Drug User Fee Act, 1992

The Cautious Regulator Problem, or the cumulative ratchet-like effect of the regulators' low risk tolerance. Each sin by the industry, or genuine drug misfortune, tightens the ratchet. Few events loosen the ratchet.

Fear of Congress drives FDA caution
To a lesser extent fear of the tabloid press drives MHRA

Median Monthly Costs

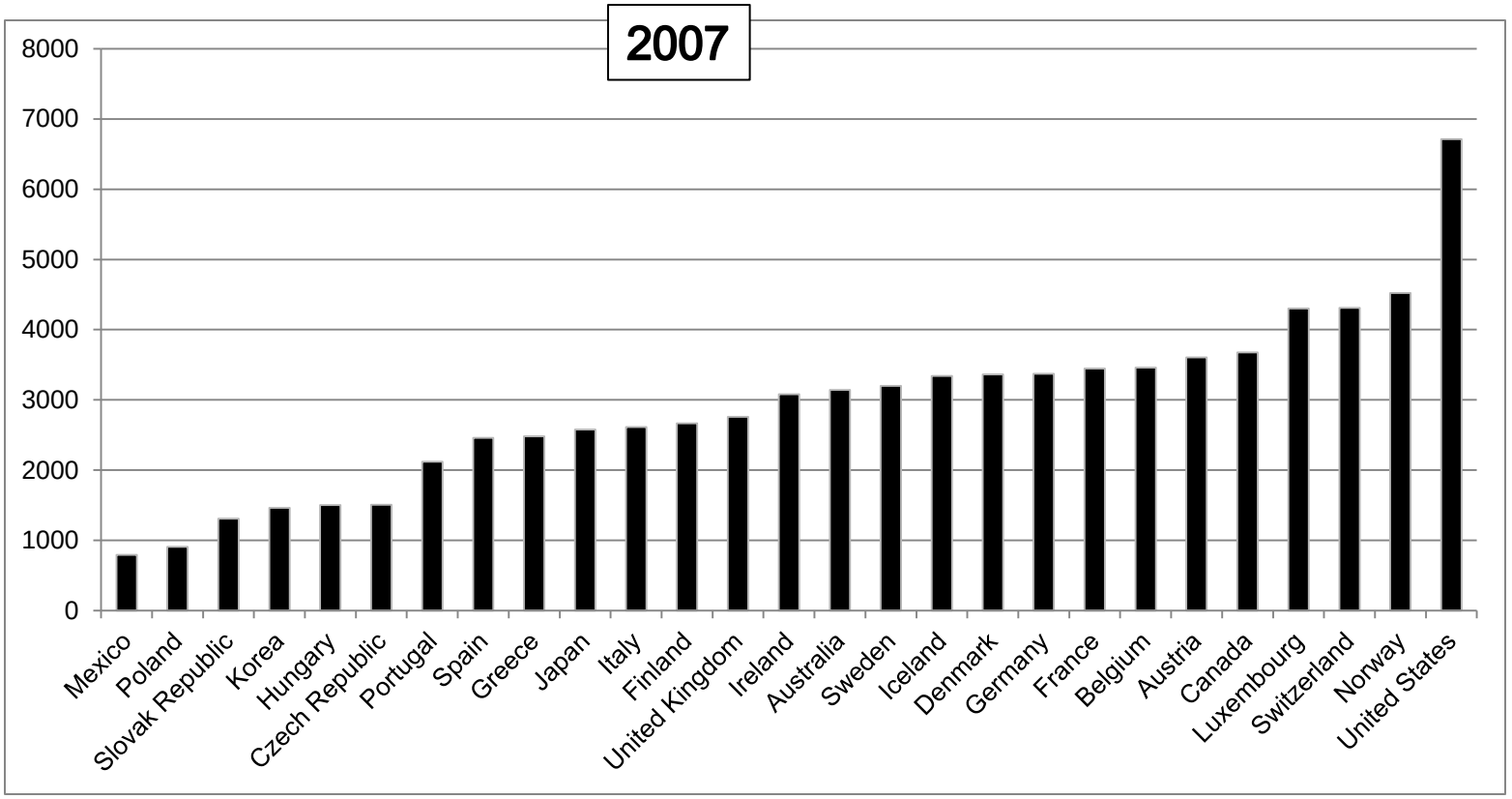
new anti-cancer drugs at launch



Bach et al 2009

Resource Constraints

Healthcare Expenditure (US$ per person)



How the law keeps us ill

Michael Hanlon – New Statesman 23 July **2001**

If anybody finds a cure for cancer, it probably won't be used. Our obsession with safety keeps effective drugs out of the surgery

- Gene therapies, the human genome project, amazing new molecules that can zap the blood supply to cancerous tumours - it seems as if medical science is advancing in leaps and bounds. Surely it can be a matter of only a few years before cancer, Alzheimer's, Aids and the rest are consigned to the same dustbin as smallpox and the plague?
- Well, maybe not. Sadly, a paradox is emerging in medicine. **While scientific advances are taking place at an unprecedented rate, progress in the doctor's surgery is rather slower - in many instances, slower than it has been for much of the past century. And the reason often has little to do with funding or expertise, but more with our newfound obsession with "100 per cent" safety and the growing role of lawyers and litigation in modern medicine.**
- Nowadays, any new drug must be tested, and tested again. Many experts believe that the testing regimens now insisted upon by the licensing authorities have resulted in unnecessary costs and delays. **According to Professor Peter Lachmann, the president of the Academy of Medical Sciences, our legally enforced desire that all drugs are completely free of dangerous side effects has, in many instances, gone too far. "The regulatory regimen for drug approvals imposes very high costs for the few lives saved," he says.**
- Saving lives costs a lot these days. First, the drug needs to be created, and tested for efficacy. Then, after a long process of testing on animals, the procedure moves to clinical trials on human beings. Then, and only then, can a licence be applied for. In Britain, this is the responsibility of the Medicines Control Agency; in America, it is the job of the Food and Drug Administration. The administration's concern for safety knows no bounds. **Mindful of the Thalidomide disaster in the 1960s, it now insists on tests so rigorous that the introduction of a new product can take a dozen years or more, and cost tens of millions of dollars.**
- Even after the clinical trials have been completed, drug firms must usually undertake costly post-release surveillance to detect rare complications that might occur. And even after all this, problems can crop up to deny thousands of people an effective treatment for their disease because a few have come to harm. **In the late 1970s, the drug Opren was withdrawn** after it caused the deaths of a number of elderly patients. The drug was - and is - one of the most effective treatments for the agonising pain of rheumatoid arthritis. But because it was ill-advisedly licensed as a general painkiller, rather than a drug specific to this disease, it had to be taken off the market entirely, rather than being relicensed for use only by specialist physicians.
- Fuelling all this precaution is the fear of litigation. Already, patients who willingly took part in trials of drugs to combat Aids have started to sue over the side effects. **When the lawyers start to circle, disclaimer signatures are worth far, far less than the paper they are scrawled on.** In the 1970s and 1980s, thanks to the threat of litigation, the number of firms willing to produce vaccines dropped to nearly zero. Eventually, governments had to step in and underwrite the drug firms.
- Experts acknowledge that there is a problem with litigation, and admit that, when it comes to medicine, logic often takes a back seat. "We can all agree that it is better to see a few people dying than a lot of people dying, but when it is their mother who might be one of the few, people don't see it like that," one Department of Health bureaucrat told me.

Cooksey Report – Dec **2006**

18 The Review believes that, if the UK is to succeed in achieving its health and economic objectives, the government must consider ways of bringing drugs that address UK health priorities to market faster, but without compromising patient safety. It is increasingly clear that the current way of developing drugs in the private sector is unsustainable in the long-term.

The Review found
that regulations around the healthcare product development process have become ever more complex, and that Health Technology Assessment arguably happens too late in the drug development process.

Cooksey Report - 2

- The Review proposes that the government, regulators and industry create a new partnership to pilot a new drug development ‘pathway’ to create wins for all stakeholders: industry, government, the wider economy and, most importantly, patients.
- This pathway should enable:
- - more rapid discrimination between potential new therapies at earlier stages of drug development;
- - **earlier ‘conditional licensing’ of new drugs**;
- - involving NICE earlier in the process of development to accelerate assessment of
- clinical and cost-effectiveness;
- - faster uptake of cost-effective drugs;
- - clearer processes for ensuring NICE initial assessments and recommendations for further research are followed-up more systematically;
- - **the use of the NHS National Programme for IT (NPfIT) to ensure more rapid**
- **assessment of any emerging side-effects and efficacy over longer periods**;
- - streamlining of processes involved in setting up and costing clinical trials; and
- - the use of NPFIT to identify appropriate patients for clinical trials.

NO ACTION WAS TAKEN ON THESE PROPOSALS

Empower: Access to Medicine

- Lobby group founded by Les Halpin, a biotech entrepreneur and philanthropist, who suffers from Motor Neurone Disease.
- The aim of Empower is to make access to new medicines faster and more efficient
- Empower has attracted public and parliamentary support – unlike the earlier efforts
- The time may now be ripe to achieve change

The Halpin Protocol 2013

- *1. Does the Patient suffer from a life-threatening illness to which there is currently no sufficient medical treatment?*
- *2. Does the Patient give informed consent to the modification of his/her legal remedies against the Developer of the Drug and against those conducting the Clinical Trials?*
- *3. Has the Developer undertaken that;*
  a. the Clinical Trials will be conducted in a properly controlled environment and under medical supervision; and
  b. the results of the Clinical Trials will be published whatever the results.

Abolition of Phase 3 Trials

- Advantages
- Would cut both time to market and cost by around half
- Would encourage drug development for less common diseases and by more companies
- Post-marketing surveillance would monitor both efficacy and side effects (NHS very good for this purpose)
- Trials to improve use of drug would continue, as now, after licensing
- Disadvantages
- Some drugs would fail after licensing (some already do)
- Some unforeseen side effects may occur (sometimes already happens)

Or more simply-

- Where phase 2 trials show favourable risk/ benefit, remedies should be made available to those who agree to waive litigation rights (in a form that is lawyer proof) and who participate fully in follow up surveillance and agree to the (suitably anonymised) data being put on a public data base.
- The myth that any remedy is ever entirely risk free should finally be abandoned
- *Early release would also allow the real cost per "Quality Adjusted Life Year"(QALY) saved by phase 3 trials to be measured. If such figures (which may well prove to be negative) exist now they are not easily accessible.*

How could abolition of Phase 3 Trials be brought about?

- It would need itself to be trialled!
- Potential patients would be given a brochure containing results up to end of Phase 2 and explaining risks and uncertainties
- They would then need to sign a legally binding indemnity against any ill effects.
- This appears to conflict with the strict liability provisions of the Consumer Protection Act 1987 and of the European Directive on Product Liability.
- There may also be a problem that such early release could be regarded as promoting the use of an unlicensed medicine
- These are problems for the lawyers and the lawmakers to sort out
- Until they do so it may be possible to look at an insurance based system to provide indemnity

Consumer Protection Act 1987

(Explained by David Howarth)

- The test in the 1987 Act is that "*the safety of the product is not such as persons generally are entitled to expect*".

- The court must take into account any "*warnings with respect to, doing or refraining from doing anything with or in relation to the product".*

- That means that, although it is not possible to exclude liability by notice or contract (e.g. *"you agree that you can't sue us if this goes wrong"),* it is possible to affect the level of safety persons generally are entitled to expect by giving suitably clear warnings about the risks.

A v National Blood Authority

- *Case brought by recipients of blood transfusions who were infected with Hep C at a time when no test for this virus existed*

Judgement

- People are not entitled to expect absolute safety in all circumstances (***helpful***)
- There can still be liability even where the level of safety they do expect is in fact physically impossible. (***very unhelpful***)
- Risk-benefit calculations don't count and it doesn't matter that nothing could have been done to make the product safer. (***totally mad***)

Risk Benefit

- **Central to virtually all medical decision making**

- Also important because it allows consideration of public as well as individual benefit.
  (vaccination is a good example).

- Risk-benefit analysis is standard practice in judging reasonableness of the defendant's conduct in the tort of negligence, and that includes benefits to others. The case law has contained the idea for more than 60 years, and was (somewhat pointlessly) repeated in a statute in 2006.

- One of the central problems of strict liability is that it fails to take account of positive externalities.

With thanks to David Howarth

Is an Insurance based system feasible?

- In the US the Federal Government indemnifies companies who make vaccines for children.
- In New Zealand, Sweden and Denmark there are no fault insurance schemes for medical malpractice ("Administrative Compensation for Medical Injuries: Lessons from Three Foreign Systems" Michelle M. Mello, Allen Kachalia, and David M. Studdert, Commonwealth Fund, 2011)
- Could a privately and/or Government funded insurance scheme be used for Early Access to Drugs

Fear of Litigation

- Regulation (cl)aims to achieve favourable risk-benefit and cost-benefit ratios
- In practice, this is a pious fiction
- The real concern is **fear of litigation**
- The public (those who comment on blogs etc anyway) enthusiastically support suing drug companies.
- They fail to appreciate that it is they – the consumers - who really pay the compensation in higher drug prices.
- Such litigation is also unfair as it seeks to compensate only where fault can be shown
- “No fault” compensation for harm or a fully comprehensive NHS could be better alternatives

The Litigation Culture

- Where companies or people cause harm by negligence, fraud, deceit or other malfeasance they should expect to be held to account
- However, where patients suffer harm from rare side effects; or where the harm is only statistically related to the drug use and where direct causality can not be established, the growing practice of litigation against drug companies has no obvious justification and has done great harm to healthcare

What is to be done?

- Require proof of direct causality before compensation is due
- Abolish no win no fee arrangements
- Ensure that indemnities are legally binding
- Abolish *strict liability* and replace with *tort of negligence* in respect of medicines so that risk benefit can become central to decision making in regulation
- Abolish legal distinction between harm caused by commission and by omission.
- *Ensure that NHS and other health systems are adequately financed to provide necessary care for all – including those who have suffered drug side effects*

There is only one argument for doing something; the rest are arguments for doing nothing

From “Microcosmographica Academica”
by FM Cornford (1874-1943)

No Fault Insurance in Sweden, Denmark and New Zealand