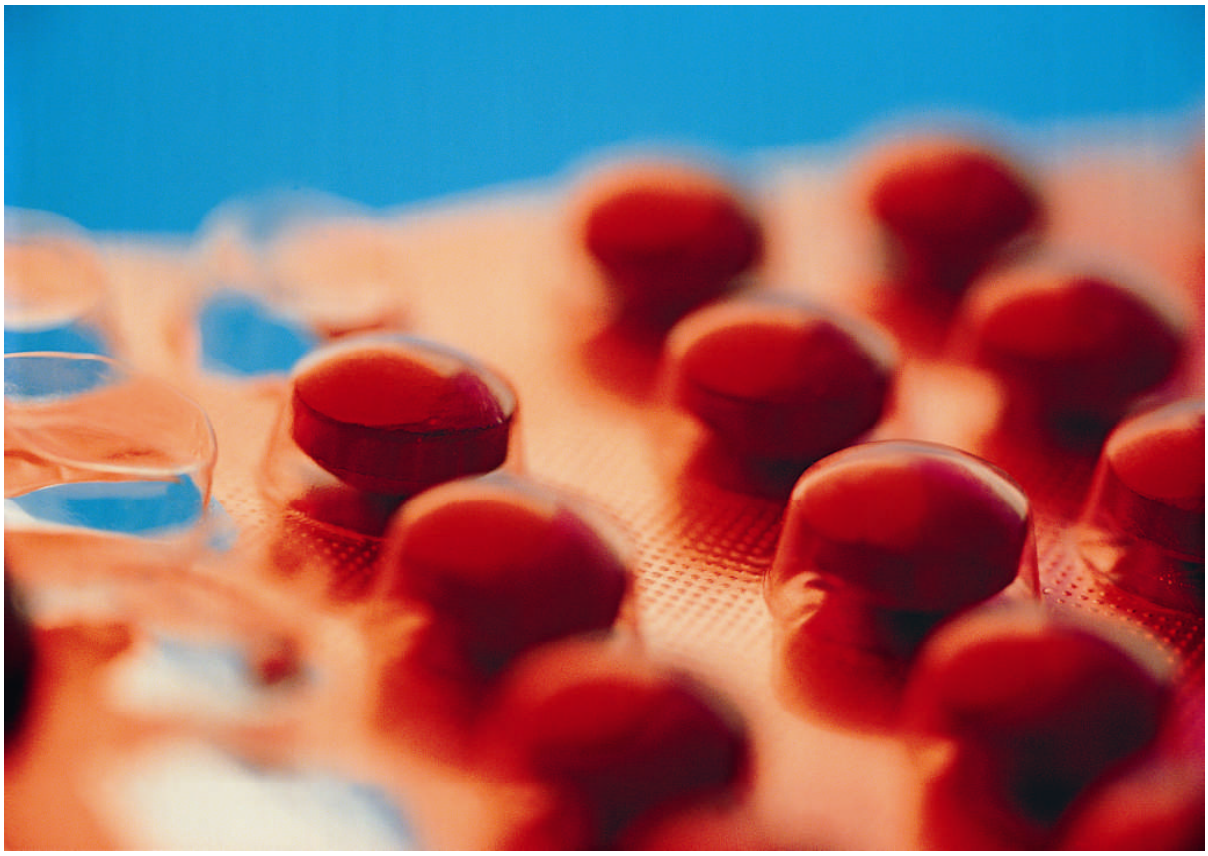
# Access to Medicines



## Report of a conference held on 1st October 2009
## All Nations Centre, Cardiff

**Organised by the Bevan Foundation**

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# INTRODUCTION

**Victoria Winckler**
*Director, Bevan Foundation*

Victoria Winckler opened the conference by welcoming delegates, and briefly outlining the work of the Bevan Foundation.

Victoria pointed out that it was timely to discuss the question of availability of medicines, some 6 months since the Welsh Assembly Government accepted the recommendations of Prof. Phil Routledge. She added that today was the first day of the new Local Health Boards in Wales, which had been covered in a piece on BBC Radio Wales earlier in the morning. The journalist had mentioned improved availability to new and high cost drugs as one of the possible benefits of the reform. Although it was unlikely that the reforms would, alone, see any change Victoria commented that it was significant that the availability of medicines was seen as one of the issues that had to be addressed – the matter was prominent in the public mind.

She thanked ABPI Cymru Wales for supporting the conference through an educational grant to the Bevan Foundation, and hoped that delegates would find the conference useful and informative.

L-R Victoria Winckler, Gwenllian Griffiths, Prof. Phil Routledge, Dr. Rick Greville

# ROUTLEDGE AND BEYOND

**Prof. Phil Routledge**
*Professor of Clinical Pharmacology, Cardiff University School of Medicine and Chair of the All Wales Medicines Strategy Group*

Prof. Routledge opened his address by saying that the biggest change in the availability of medicines occurred 61 years ago when the NHS came into being. In introducing the NHS, Aneurin Bevan had believed that treatments would be able to be generalised across the population. However this proved too optimistic with huge differences in take up of different treatments. Prof. Routledge recalled the days of the MTC when it was sometimes difficult to fund medicines, the effect of which was a great deal of publicity when individuals were unable to get the medication they needed. The high cost drug panel was subsequently established but it had limited expertise, with less thorough assessment than is undertaken now. As a result Frank Dobson MP established NICE with a dual purpose: first to reduce inappropriate variations in health and social care and second to ensure value for money.


Prof. Routledge then outlined how NICE operated, and highlighted the problems with its capacity – approximately 100 new medicines a year but it could only appraise 20 – 30. As a result of concern about progress, a group was established in Scotland to look at all new medicines, whilst in Wales a similar group was established to look at high cost medicines including ultra orphan drugs and cancer and cardio-vascular medicines.

The All Wales Medicines Strategy Group was established in 2002 under the chairmanship of Roger Walker. Its remit was to:

- Develop timely, independent, authoritative advice on new medicines.
- Advise Assembly of future developments in healthcare.
- Advise Assembly on development of a prescribing strategy for Wales.

It worked with the Wales Medicines Partnership, and successfully appraised 30 – 32 new medicines a year, meeting bimonthly. Its deliberations were

open to the public and patient groups, as well as to industry representatives – although attendance was usually limited and was typically by the pharmaceutical industry. There was no shortage of work: the group had appraised 74 medicines and 33 medicines were in the appraisal pipeline. They undertook horizon scanning to advise the Assembly Government on future developments and their report “Getting the best outcomes from Medicines for Wales” in 2008 had informed the Assembly Government’s prescribing strategy.

Prof. Routledge said that appraisal was ideally timely, robust, transparent, inclusive, responsive and independent. In terms of timelines he quoted ‘Parkinson’s other law’:

> ‘If we suppose that a drowning man calls for help, evoking the reply "In due course," a judicious pause of five minutes may constitute for all practical purposes, a negative response.”

‘Delay is the deadliest form of denial’, he added. The AWMSG aimed to complete appraisals in 6 months.

He highlighted the huge amount of paperwork associated with appraisal. Prof. Routledge quoted Aneurin Bevan’s comment on Walter Citrine, TUC General Secretary:

> ‘Poor man – he suffers from files!’

Needless to say, the AWMSG did not wish a similar affliction and tried to keep bureaucracy to a minimum and avoid duplication of work by NICE.

Prof. Routledge then explained the process followed by AWMSG, summarised in the diagram below. He pointed out that if the answer to the question ‘is the medicine on the NICE work programme in the next 12 months?’ was ‘yes’ then AWMSG did not appraise the medicine. However if the answer was ‘no’, it followed an appraisal procedure.

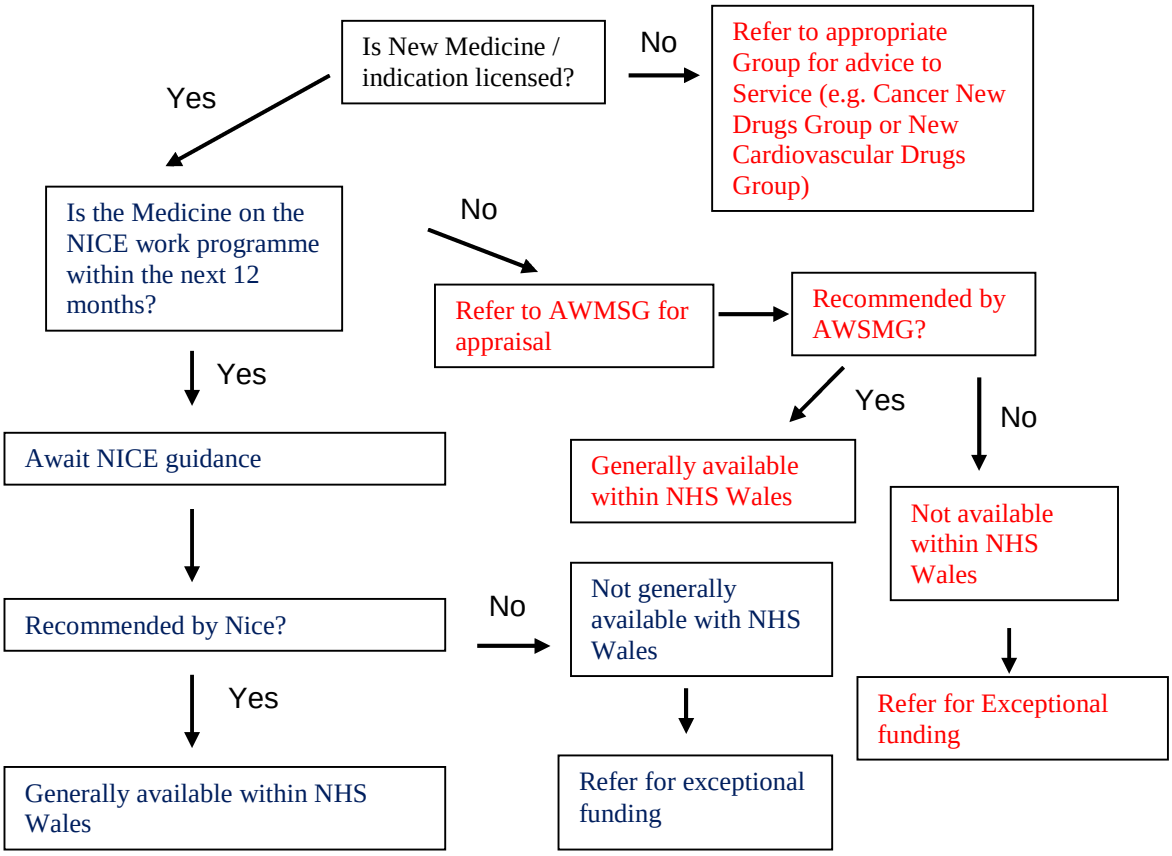
However, there were still ways in which the process could be improved. He had been commissioned to undertake a review of the availability of medicines, with his report - ‘*Towards improving access to medicines in Wales*’ - concluding that there should be:

- A central appraisal process for all medicines in Wales not in the NICE process

- A robust, consistent, transparent, inclusive and timely consideration of requests for exceptional funding of medicines, a national guideline for the structures needed and the process employed in Wales.

The process is shown in Figure 1.

**Figure 1 Decision Flow Chart**




He concluded that Aneurin Bevan and Sir Austin Bradford Hill had done a great deal for British medicines, by making them universally available through a publicly funded health care system.

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# COST AND AFFORDABILITY OF MEDICINES

**Dr Rick Greville,**
*Director, ABPI Cymru Wales*

Rick welcomed delegates and looked forward to a stimulating discussion over the rest of the day. He opened his presentation by explaining that he was going to cover three themes – comparative use and expenditure on medicines, a look at what the future might hold, and an overall forecast for Wales.

**Comparative use and expenditure on medicines**

Rick began by highlighting the significant increase in the expenditure on the NHS in Wales since 1996, compared with a relatively small increase in expenditure on medicines over the same period. This trend was also evident if spending as a proportion of GDP was considered – whilst total health care expenditure has increased from 10.6% of GDP to 12.1% between 2003 and 2007, expenditure on community prescribing has decreased from 1.41% to 1.32%.

Wales has a higher usage per head of medicines than England or Scotland reflecting the higher percentage of many chronic illnesses. The total cost of NHS prescriptions dispensed in the community per head is also higher, however the Net Ingredient Cost of such prescriptions is lower – which merits further research.


Rick went on to explore the drivers of the costs of medicines. He argued that by far the most important driver is volume - new medicines account for tiny proportion of costs. Price reductions have also helped to keep overall costs down.

Looking ahead, Rick highlighted the challenge arising from loss of exclusivity of medicines. This is defined as the loss of all legal protection not just patent. ABPI has estimated the impact of generic competition on each molecule, and found an erosion of volumes and prices relative to generic medicines. Rick pointed out that seven out of the 20 most frequently prescribed medicines will come off patent in the next five years.

The impact of loss of exclusivity is expected to be considerable. He forecast a 71% reduction in the cost of branded medicines threatened by loss of exclusivity by 2012 compared with 2007. This could reduce expenditure in the UK by £2.7 billion (and by £160 million in Wales). He reminded delegates that drug development takes time and money – around 10 to 12 years and £500 million were typical. In comparison, developing production of a generic medicine cost just £100,000.

Rick outlined work that was 'in the pharmaceutical pipeline', highlighting for example the 647 products in development to tackle cancer and the 146 for heart disease and stroke. In addition there were 321 vaccines in development, both prophylactic and therapeutic. He explained it was difficult to predict which new products would be successful and be clinically viable.

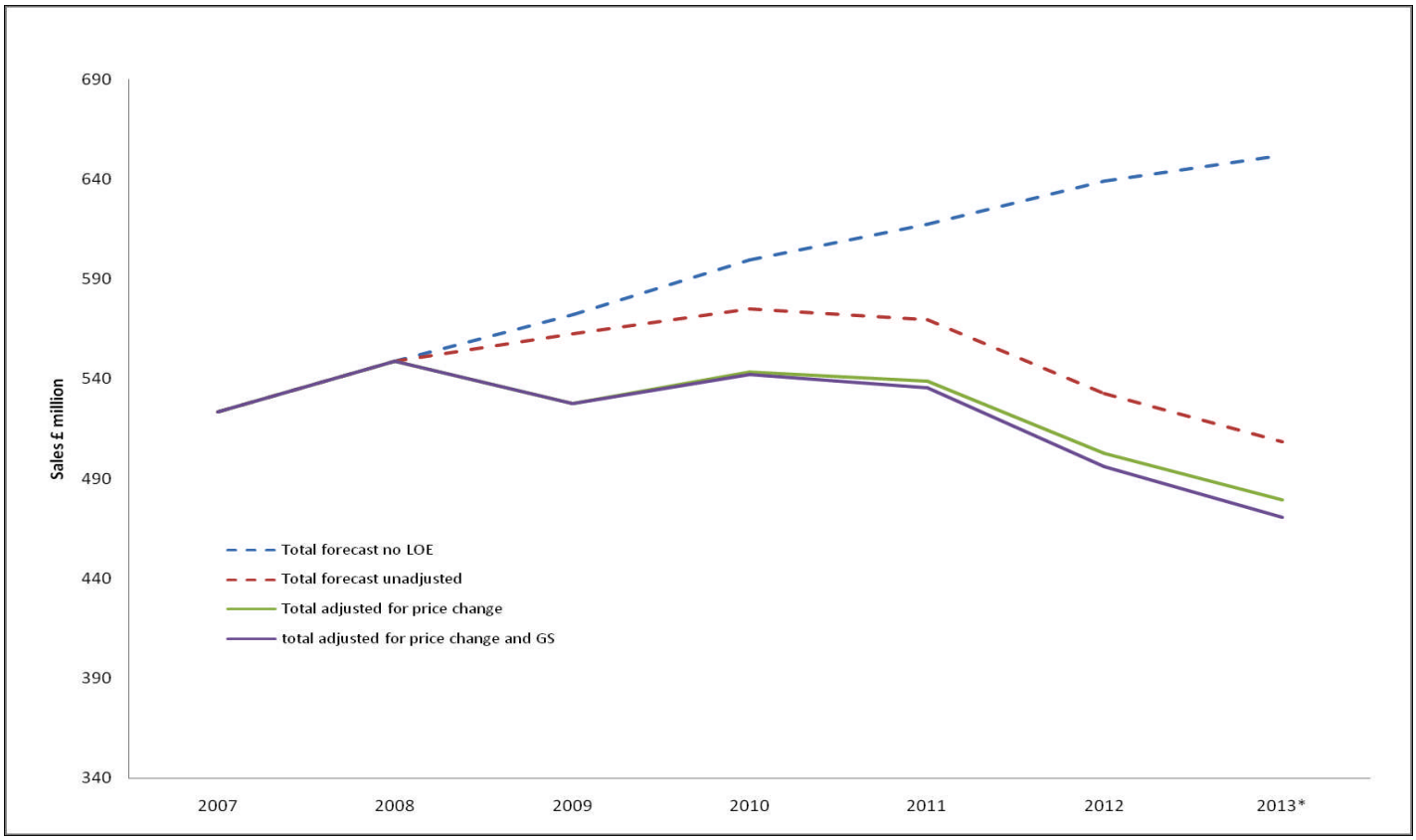
Turning to pricing, he pointed out that pricing was a UK rather than Welsh Assembly Government issue, regulated via the Pharmaceutical Price Regulation Scheme, more commonly known as the PPRS. The principles of the scheme are to:

- Deliver value for money
- Encourage innovation
- Promote access and uptake for new medicines.
- Provide stability, sustainability and predictability.

Rick stated that it was hard to change the price of medicines after launch, and recognised the need for flexibility in pricing, for example, in the light of new evidence. Patient Access Schemes (PAS) were important innovations for certain medicines, as was support for the PPRS Innovation Package. The Innovation Package included full implementation of NICE appraisal guidance, prescribing incentive schemes to promote uptake of innovative products, and published metrics on the uptake of clinically and cost effective medicines at local, national and international level. New medicines are forecasted to be a minor proportion market share of medicines in both the UK and Wales.

Rick concluded that the combination of loss of exclusivity and the Pharmaceutical Price Regulation Scheme would produce considerable savings over the next 5 years compared with the projection of past trends. This downward trend provided 'considerable financial head room', he argued, for the NHS in Wales to use the most up-to-date medicines.

## Figure 2 Trends in Medicine Prices



# A PATIENT PERSPECTIVE

**Gwenllian Griffiths**
*External Affairs Manager, MacMillan in Wales*

Gwenllian began by outlining MacMillan's activities in Wales, in which she stressed that everything they do is driven by what cancer patients say. She highlighted key statistics about cancer:

- 17,778 people diagnosed with cancer every year
- 8,515 die of cancer every year
- Cancer remains the second biggest killer in Wales
- 108,000 people living with or after cancer
- By 2012, more than 4% of the Welsh population will be living with or after cancer in Wales – 124,000 people.

These figures are a huge challenge for the NHS, charities and pharmacy.


Macmillan wants everyone to have access to effective treatment. They are campaigning for NICE to speed up their appraisals of end of life care and submit evidence to NICE as appropriate. However in Wales the key issue is exceptional funding. In 2007 nurses noted an increase in calls to the Macmillan helpline about access to treatments which had not been NICE-approved, and there were also some cases which had received a high media profile. She gave the example of a man in his 60s who had kidney cancer but whose application for exception funding for treatment took 12 weeks to be declined by his LHB. He was not told what the criteria for the LHB's decision were. He was subsequently told an appeal on his case had been held, but he was not even aware that an appeals process existed or that an appeal had been lodged.

Macmillan then undertook a survey of LHB practices in Wales and found:

- 15 different names exist for the exceptional funding process
- A third of LHBs in Wales actively promote the process to patients
- Six per cent of LHBs have an oncologist in their expert panel

- Wide variation in the factors that LHBs take into account when making decisions.

Based on these findings, MacMillan developed some recommendations:

- It was clear that the exceptional funding process needed to be strengthened.
- MacMillan also wanted the Welsh Assembly Government to develop and issue guidance outlining a framework for the process.
- The guidance should outline: the composition of the panel (i.e. an oncologist or other relevant clinician must be present when considering the cases of cancer patients), the length of time the process takes, decision-making factors, and information and support services.
- It was also vital that there was a responsibility on LHBs to inform patients about the rationale for decision making so that patients are fully informed of the reasons if access to a treatment is turned down. TRANSPARANCY IS THE KEY.

Macmillan submitted their recommendations to the Minister for Health and Social Services and to Prof. Routledge's review and were pleased with his recommendation that the Welsh Assembly Government should issue guidance on exception funding. The Routledge report recommended that this should be issued within 6 months, but the Welsh Assembly Government have now said that it is not planned to be issued until April 2010. This was a cause for concern.

Gwenllian also mentioned that MacMillan were involved in the implementation of another one of the Professor's recommendations, Recommendation 7, which is about improving the communication skills of health professionals within Oncology, in particular to help them communicate more effectively with people who are at the end of life stage. The recommendation is that:

> "The additional training needs of health professionals to help them effectively communicate with patients about difficult decisions around risks/burdens and benefits of different proposed treatments should be assessed, and an appropriate programme related to end-of-life care should be developed."

She explained that MacMillan had been approached by Baroness Finlay to contribute to work to roll out communications training around prognosis, breaking bad news and communicating the risk associated with some treatment options which some oncologists find difficult. There are clear links

between this particular piece of activity and improving the exceptional funding. If patients receive better and easier to understand information about the options available, then this should lead to better decisions being taken at the outset which could avoid unnecessary stress for cancer patients.

She concluded by stressing that inequity as a response of exceptional funding processes in Wales remains a major issue and that improving the communication skills of health professionals within Oncology must be prioritized.

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## Questions

**Q. Is there any intention to introduce NICE's citizen panels into AWMSG work?**

P Routledge: The idea has been used in work on ultra orphan drugs. AWMSG has a very small communications budget and citizens' juries and panels are expensive – they would need to be effective. The citizens' juries on the prescribing of aspirin were interesting.

**Q. The picture painted was of increasing patient access, but some think there will be less. Would you like to comment?**

R Greville: the industry does think there will be greater access – although they want it to be streamlined. There are issues about at what point in the appraisal process the patient access scheme is presented.

**Q. Should AWMSG consider patient benefits more clearly, so that the impact on the health status of the population is taken into account? This could drive the process of appraisal. Also, should the 90% of the NHS that is NOT covered by appraisal be included?**

P Routledge: AWMSG does include medicines management. Money has been saved by changing to use of generics so saving money for newer medicines. There has also been a reduction in use of non-steroidal medications e.g. which were being used inappropriately, so some morbidity issues have been taken into account.

## Reports back from discussion groups

The delegates then broke into four discussion groups, each of which was asked to consider four questions. The conclusions of their discussions follow:

***Are medicines now being appraised quickly enough? Are appraisal decisions being implemented quickly and consistently? If not, what needs to be done?***

***Group A***: No, medicines are still not being appraised quickly enough. Six months is too long when dealing with cancer and the main cardio-vascular diseases – it is longer than some patients' life expectancy.

Problems arise because price setting is usually the last thing done yet it is required for full submission. It is in the industry's interest for the review to be completed quickly but sensitivities lead to information not being submitted early.

- Industry should be able to provide banded cost estimates as companies can't give a cost at the time of submission.
- Industry needs to engage sooner with AWMSG, making their submissions at licence stage not launch.

***Group B***: Yes, the AWMSG is working quickly enough but NICE is not. The licensing and appraisal process should be done in tandem.

***Group C***: Yes, appraisal is generally quick enough once a drug is in the system. However there is a lag between licensing and appraisal that needs to be addressed.

At the moment Ministerial ratification is swift but that could change with a change of Minister.

***Group D***: Six months from licensing to decision by AWMSG is reasonable, but there are questions about getting medicines into the system, which can be lengthy:

- Are companies active enough?
- Are they aware of the system in Wales?

Also, should some, highly specialist, medicines be in the system at all? The number likely to use them is tiny – the cost of appraisal could well outweigh the cost of the drug.

***Are appraisal decisions being implemented quickly and consistently? If not, what needs to be done?***

***Group A***: There is no consistency or structure for 6-9 months after product availability, although there is more consistency for drugs that have been appraised. There were no examples of delays by LHBs where they had been approved, although this should be monitored. There was also uncertainty about whether the actual impact of a drug on budgets was as estimated by the company.

There should be:

- guidance on the management of **all** appropriate medicines not just AWMSG-approved medicines or new medicines;
- clear timelines for implementation;
- monitoring of compliance with AWMSG guidance;
- monitoring of patient access to and appropriate use of drugs.

***Group B***: Implementation is slow and variable. There needs to be much more work done on this issue including:

- understanding clinicians' mindset when they step outside NICE guidance;
- whether guidelines or guidance are appropriate monitoring of uptake.

***Group C***: There are issues with consistent implementation, within Wales and between Wales and England. A recent 2009 Haematology survey found that although AWMSG had approved a drug fewer LHBs were using it than English PCTs. There needs to be a dedicated resource to manage implementation.

***Group D***: There needs to be follow up to see if decisions are being implemented.

***Is there sufficient and effective communication between AWMSG and Clinicians, within Wales and between Wales and UK? If not, what more needs to be done?***

***Group A***: No, communications are not that good, despite the efforts made by AWMSG. However the vast majority of its decisions do not affect the majority of clinicians. Most clinicians would engage with specialist medicines only occasionally and so they are not familiar with the bureaucracy.

There needs to be clear communication when a decision is made, including the appropriate use of a medicine.

***Group B***: Yes, there are good communications with clinicians, although it is mostly 'passive' rather than 'active'.

***Group C***: No, there is no effective system of communications with primary or secondary care. Clinicians need to understand the appraisal process but generally don't. NICE is well known but AWMSG is not. Even if some do know about it they may not believe in it!

There need to be fuller statements about AWMSG's decisions and different systems for communication with clinicians – email is **not** appropriate and Scripswitch needs resources to keep it up to date.

***Group D***: We have some sympathy with the Welsh Medicines Partnership, but there is still a lack of knowledge and awareness.

Communications are not enough alone – they need to be linked with implementation. We could learn from England where there are 'implementation consultants; - perhaps Wales should have 1 or 2.

***Are patients aware of how to access medicines? Is there still local variation in access? How can the processes of ensuring patient access be improved?***

***Group A***; Access is very variable because it depends on patients' knowledge, which is likely to differ between socio-economic groups. More should be done to improve information for patients, including information in primary as well as secondary care.

It is also not clear who is the patient's advocate in the event of seeking exception funding.

Consistency is also important – there should be a consistent pathway across Wales.

***Group B***: Patients are not aware of the exceptions process. Too often the rationale for the original decision not to approve the drug is not clear. Patients going through the exceptions process are often very ill and are not necessarily able to fight it.

There is still considerable local variation – which can mean that some cancer network patients being treated in the same hospital receive a medicine whilst others have been denied it.

***Group C***: Awareness is variable but for older people and people in rural areas the answer must be no.

***Group D***: The evidence given by MacMillan is fair and reflects the position with other conditions. How is a patient to know about and understand the process? How are they supposed to know if something has been appraised by NICE or by AWMSG?

Patient groups are very useful where the number of patients could be relatively large. But where patient numbers are small individuals should be able to give their views directly. Clinicians have a role to advise and support patients.

The process and decisions are contributing to a lack of trust – it has been broken down by the 'hotchpotch' process and by the perception that decisions appear to be made on the grounds of cost.

# PHARMACEUTICAL COMPANIES, GOVERNMENT AND SOCIETY

**Sir Michael Rawlins**
*Chair, National Institute for Health & Clinical Excellence*

Sir Michael Rawlins opened the afternoon session and gave an excellent address.

The pharmaceutical industry, as we know it today, originated in the late 19th and early 20th centuries. Until that time physicians prescribed "recipes" that apothecaries compounded and prepared and sold to patients. Official, and semi-official, "pharmacopoeias" describing the recommended constitutes of commonly used recipes had existed since the 16th century. But there were no pharma-ceutical companies to produce them - apothecaries dominated the scene.

Nor were there any legal controls on the preparation or sale of medicines. Apothecaries were free to sell their products with little restraint. There were attempts at the end of the 19th century to limit the ability of pharmacists, the successors to the apothecaries, to supply members of the public with "dangerous drugs" such as morphine. But the pharmacists were able to fight off these proposals: it was only in 1917 that a legal category of "prescription medicines" came into existence.

The modern pharmaceutical industry arose from three sources. Some evolved from chemical companies, like Hoffman La Roche and Novartis in Switzerland, the German company Bayer and AstraZeneca is an offshoot, in part, of that famous British chemical company ICI. Others began life as specialty food and medicines companies - Glaxo began as a manufacturer of infant feeds in New Zealand, and Henry Wellcome and Charles Pfizer were both pharmacists who started companies making medicines. But it was the patent medicines businesses that began the first serious engagement between the emerging pharmaceutical industry, government and society.

The patent medicines business appeared in the latter half of the 19th century in both the US and the UK. A typical example is Rexall – a "blood purifier". It

was claimed to be an “excellent blood cleanser” and “especially recommended for clearing the skin and the complexion”.

By 1900 the patent medicines business was flourishing. It was predominantly mail order, with products widely advertised in newspapers and for whom it brought a very significant income. We know much of the volume of sales because the government levied a special tax of 1½ pence a bottle or box on each transaction. Treasury records show that the income generated in 1907-8 amounted to £334,000. The estimated total sales for that period were therefore over 40 million boxes, packets and bottles.

If you have criticisms of the claims of some modern pharmaceutical companies they are as nothing compared to the totally unregulated claims of the manufacturers of patent medicines. Take Beecham’s pills for example. The advertisements included claims that it “cured” a wide range of disparate conditions including:

- spasms at the stomach
- sick headaches
- restlessness
- insomnia
- lowness of spirits
- scurvy and scorbutic infections
- maladies of indiscretion
- menstrual derangements

The patent medicines business was also rife in the US where like the UK there were no legal restraints. In part it was fuelled by their own domestic brands – many based on the perceived therapeutic properties of rattle snake oil. Clark Stanley’s “snake oil liniment” was especially popular and when rubbed into the body claimed to relieve the pain of Muscular Rheumatism, Lame Back, Contracted Muscles, Sprains, Bruises, Corns, Chilblains, Frostbites, and the bites of most insects.

But the UK’s patent medicines had also reached the US and Beecham’s pills as well as many other products from this side of the Atlantic were widely bought and used. As in the UK it was mainly a mail order business. Things came to a head though in 1909 when the British Medical Association published “Secret Remedies” – and three years later – “More Secret Remedies”.

“Secret Remedies” was an expose of the patent medicines business. It examined the therapeutic claims – the ingredients – and the costs of the raw

materials – of many of the products on the market. It noted that Beecham's Pills for all its claims contained only aloes, powdered ginger, and a small quantity of powdered soap. The total cost of the ingredients needed to make the 56 pills in a box was estimated to be about half a farthing.

Sales of "Secret Remedies" were initially slow. With one exception (the Daily News) no newspaper for fairly obvious reasons was prepared to accept advertisements for it. Nevertheless, sales from newsagents and bookshops increased and within 6 months of publication 600,000 copies had been sold. The expose in Secret Remedies led to public outrage. And after the publication of "More Secret Remedies" in 1912 Parliament felt it had to act. A "Select Committee on Patent Medicines" was established by the House of Commons. The Committee sat over 3 sessions of parliament, held 33 public meetings and examined 42 witnesses, including Sir Joseph Beecham, whose company manufactured Beecham's Pills.

They gave Sir Joseph a hard time. When asked about the composition of his pills, he claimed that the analyst had failed to identify a secret ingredient whose nature he was not prepared to disclose as it represented a "trade secret". The Committee were not impressed. They gave him an especially hard time over the claim the Beecham's Pills cured "Menstrual Derangements". This, Committee members suggested, was a covert claim for an abortifacient action. Sir Joseph hotly disputed this but again the Committee appeared to be unimpressed. The cross-examination by the Select Committee did not appear however to do Sir Joseph any lasting damage. He was made a baronet 2 years later!

But in its final report the Committee was scathing in its criticisms of the Patent Medicines business. It stated:

> *"For all practical purposes – British law is powerless to prevent any person – from procuring any drug – or making any mixture – whether potent or without any therapeutic activity ….and selling it under any name – for any price he can persuade a credulous public to pay."*

The Committee made many recommendations including legislation to control the advertising and sales of medicines, the establishment of a registration system, a requirement for full disclosure of the ingredients and enforcement powers. The Committee was – in effect – proposing the creation of a drug regulatory authority.

Unfortunately though, the Report was published on 4th August 1914 – the day Britain declared war on Germany. It was forgotten and for the next 50 years no real controls were placed on the activities of the manufacturers of medicines.

A turning point came with an epidemic of phocomelia in the late 1950s and early 1960s. It was caused by the use of what was then a new hypnotic – thalidomide – taken during pregnancy. Probably over 10,000 babies were born world-wide with this terrible deformity. The failure of successive governments to enact legislation controlling the pharmaceutical industry was responsible for allowing thalidomide to be marketed. And as my good friend Ron Mann has poignantly written "The thalidomide victims were the last casualties of the First World War".

The thalidomide tragedy prompted the introduction of the first real controls in the form of the 1968 Medicines Act, on the production and supply of both new and established pharmaceutical products in the UK. And along lines not too dissimilar to the ones suggested by the Select Committee on Patent Medicines 50 years earlier.

Since 1995, the regulation of medicines has become increasingly an EU function but the same principles apply now as they were when the Medicines Act was placed on the statute book in 1968. New products can only be introduced onto the market – and established products can only remain on the market – provided they show and continue to show evidence of:

- good quality
- efficacy – for the indications which the manufacturer seeks to "claim".
- and safety in relation to efficacy – the so-called "risk-to-benefit ratio"

Drug regulatory authorities may not by law take any account of the cost of a product and nor does a manufacturer have to demonstrate superior efficacy compared to similar products already on the market.

These licensing arrangements have – up to a point – served society well. Of the 583 new active substances products licensed in the UK between 1972 and 1994, only 23 have been withdrawn for clinical (as opposed to commercial) reasons – 22 for safety and one for lack of efficacy.

Society is protected from ineffective medicines. And although, occasionally, drugs are allowed onto the market which are subsequently found to be unsafe this is unusual.

The modern pharmaceutical industry has over the past 50 years developed products of unquestionable benefit to society. They include:

- vaccines to prevent a wide variety of infections ranging from 'flu to hepatitis B
- drugs to prevent cardiovascular disease – antihypertensive and cholesterol-lowering agents
- a range of anti-microbial products to treat fungal, bacterial and viral infections
- drugs to treat mental illness, cancer
- safe and effective anaesthetic agents
- immuno-suppressants allowing successful renal, hepatic, cardiac and lung transplantation

There is no question but that the pharmaceutical industry has benefited billions of people over the last 50 years. There have also in Britain been indirect benefits. The UK pharmaceutical industry is a major contributor to the UK economy. It employs directly over 70,000 people and indirectly a further 250,000. And it brings in a positive trade balance of over £4 billion a year.

But both the pharmaceutical industry and healthcare systems globally are facing a new set of problems. I'm now – and for the rest of this lecture – going to focus on the economic problems facing both the pharmaceutical industry – governments – and society – in relation to healthcare. It isn't pretty. And it applies just as much to the US – the EU – and Japan – as it does to Britain. It's global.

The industry currently faces 5 main problems.

1. By 2012 on average 21% of the current sales of the major pharmaceutical companies are at risk of generic erosion as many "block busters" lose their patent protection. This "patent cliff" – as it's known in the business – varies from company to company – but appears to be particularly serious for Pfizer, Johnson and Johnson, and SanofiAventis.

2. Although the industry's spend on research and development has risen very substantially over the past 10 years, fewer new drugs are appearing on the market. This is due in part to the fact that, curiously, drug hunting has apparently become much more difficult. I say "curiously" because you might imagine that with our escalating

knowledge of the biology of disease many more druggable targets would be available for therapeutic exploitation.

3. Regulatory authorities are placing greater and greater demands on pharmaceutical companies before allowing their products to go on the market and to remain on the market. I will be saying more about this in a moment.

4. Healthcare systems across the globe are increasingly under pressure to cut their rising health budgets and are putting cost containment measures in place, including pharmaceuticals. Again I will be returning to this later in my lecture.

5. Shareholders in the pharmaceutical industry have over the past 25 years done well from their investment. They are putting pressure on companies to maintain this. But the problems facing the industry that I've already referred to are making this more difficult. And when I speak of "investor" – I don't just mean the Warren Buffets of the investment world. Those of you who have – or expect – your pensions to be paid by the Universities Superannuation Scheme (USS) may care to know that you have about £1 billion invested in the pharmaceutical industry.

The discovery and development of a new drug is a complex and costly enterprise. There have to my knowledge been three relatively recent estimates of the total cost of bringing a new pharmaceutical product to the market. They are shown below – all converted to 2000 prices.

| Source | Estimate US$ millions |
|---|---|
| Boston Consulting Group (2001) | 880 |
| Di Masi et al (2003) | 802 |
| Adams and Branter (2006) | 868 |

All three reached broadly similar conclusions. Although there is some controversy about the way these results were arrived at they are indicative of the sums involved. They are massive. And they are rising at a rate of around 10% per annum. Since all 3 of these estimates are based on prices in 2000, the current cost must be well over a billion dollars.

About half of this is spent during the clinical development programme. Over the past few years the regulatory requirements for clinical trials have become increasingly stringent, for those carried out in the private and the public sectors. And with the stringency comes added costs.

Much of these costs arise from the requirements of what is called "Good Clinical Practice" – or GCP. GCP requirements were developed by an organisation called the International Conference on Harmonisation. GCP has been adopted by the national drug regulatory authorities of the EU, the US and Japan. And it has now been incorporated into the EU's Clinical Trials Directive.

The numbers of different documents required to be submitted "before", "during" and "after the completion of" a clinical trial is huge. Some of these documents run to several hundred pages.

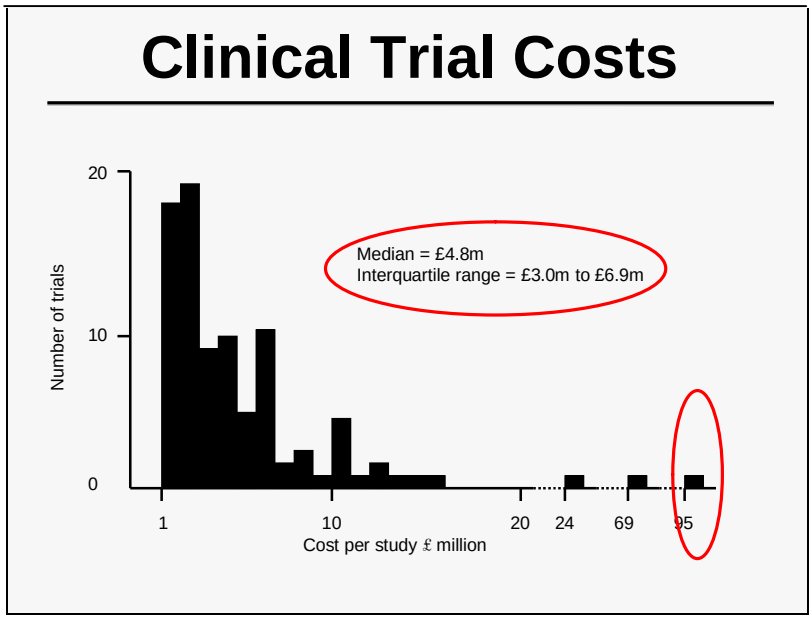
GCP and the EU's Clinical Trial Directive were written with the best of intentions:

- the desire to protect patients from unscrupulous investigators and sponsors;
- to ensure the collection and timely reporting of adverse event data during trials;
- to audit individual case report forms – thus avoiding the consequences of untruthful behaviour by investigators.

But they also have several inherent problems. They were published in 1996 – and have never been revised. They are "evidence free", that is to say there is no evidential basis for any of the requirements. By no stretch of the imagination can GCP be regarded as "evidence based". They were compiled by an anonymous group of authors. They are now applied, thanks to the EU's Clinical Trials Directive, to commercially funded research as well as trials initiated by clinical academic institutions.

And the law of unintended consequences has stepped in. The graph below shows the costs of over 90 randomised controlled trials that were completed in 2005 and 2006 by 3 pharmaceutical companies who have been generous

enough to share their data with me. I cannot claim that these costs are therefore necessarily representative but they are indicative of the sums involved.




Trial costs are clearly skewed, with a median of nearly £5 million per trial but in one case reaching almost £100 million. There is also unsurprisingly a tendency for phase 3 studies to cost more than phase 2 studies. And it seems to be getting worse. One manufacturer kindly provided me with data about both the costs of trials completed in 2005-2006 as well as those due to be completed over the next 3 years.

| | **Completed Trials (2005 – 2006)** | **Current Trials** |
|---|---|---|
| **Median** | £3,858,000 | £7,067,000 |
| **Interquartile Range** | £2,223,000 to £8,222,000 | £3,906,000 to £13,300,000 |
| **Range** | £728,000 to £13,549,000 | £594,000 to £180,701,000 |

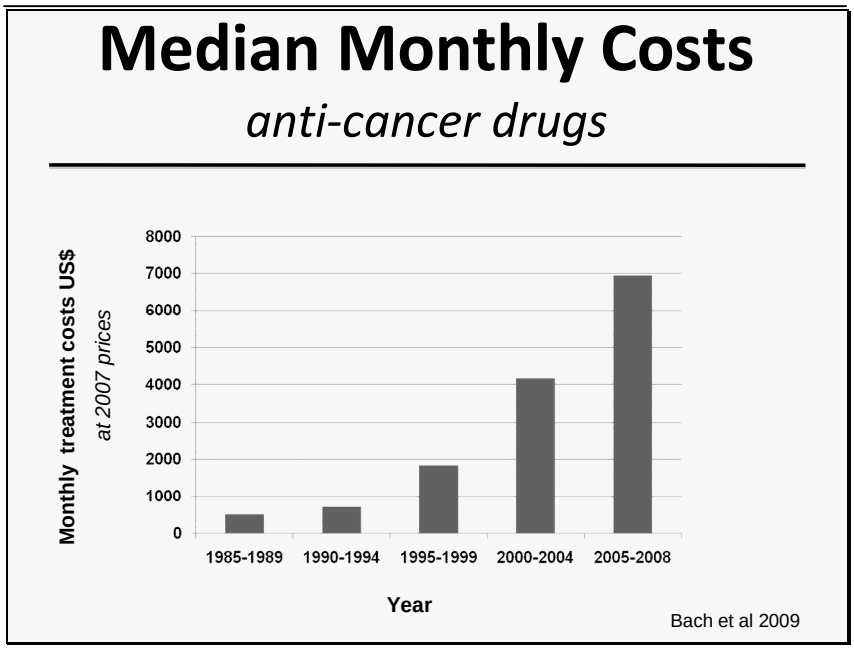
To make a fair comparison, the left hand column shows the trial costs for this particular company for studies completed in 2005 and 2006. The right hand column shows the costs for trials currently in progress. Cost estimates have almost doubled – and the range extends in one instance – to £180 million for a single trial.

This is completely unsustainable. Unless steps are taken to reduce substantially the costs of clinical trials two consequences will surely follow. First, the costs of drug development will become so great that the price of new innovative products will be unaffordable to every healthcare system in the world. Secondly, since these burdens apply equally to clinical trials sponsored by publicly funded bodies like universities, these studies too are under very serious threat.

An international group of academic scientists has recently proposed relatively simple measures that would reduce trial costs by between 40% and 60% without adversely affecting their quality. For example, electronic data capture and a reduction in the length of case management forms.

The pharmaceutical industry – globally – is not blameless in all this. The industry forms part of the International Conference on Harmonisation – but agreed to sign up to GCP in 1996. Presumably they believed they could recoup the additional costs by charging higher prices. I'm afraid this is no longer possible.

The combination of the patent cliff, weak pipelines, excessive regulatory requirements and investor demands means that the asking price for new drugs is rising sharply. Here for example are the median monthly costs at launch of all the anti-cancer drugs introduced over the past 25 years, expressed at 2007 prices. The real price at launch has increased almost seven-fold. This is unsustainable, especially as healthcare systems have their own equally serious financial problems.




The problems that society faces in providing people with adequate healthcare are broadly fivefold.

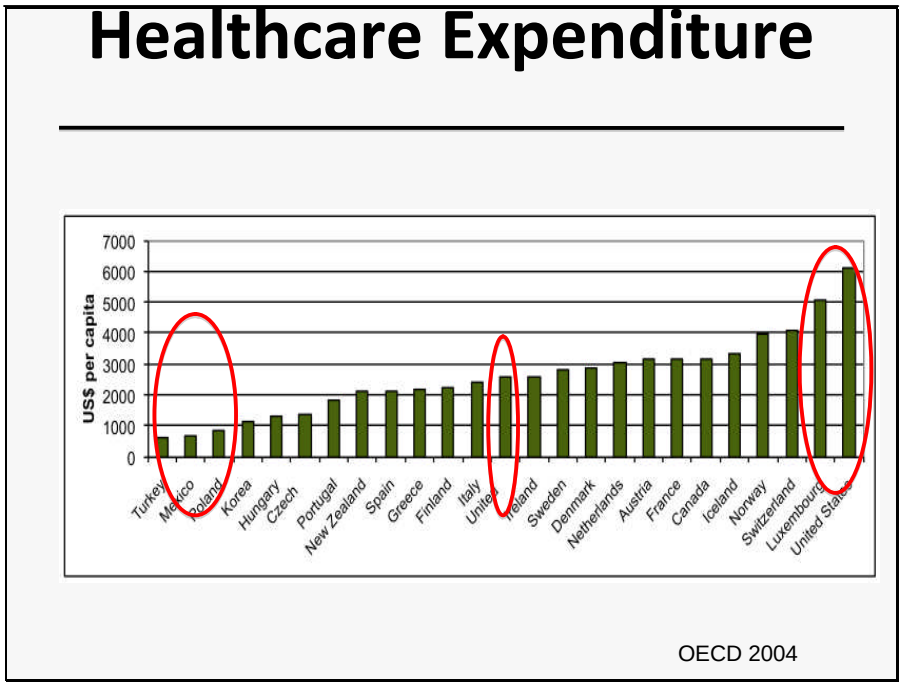
1. All developed countries face a “demographic time-bomb”. People are living longer after retirement and making ever greater demands on their healthcare systems.

2. Advances in health technologies - not just pharmaceuticals but increasingly devices and diagnostics – offer opportunities for diagnosis and treatment that were unimaginable a decade ago. But they will not be cheap.

3. The public’s expectations of healthcare systems have increased very substantially over the past 2 decades. Younger people are much less tolerant of inadequate care than their parents or grandparents.

4. In every healthcare system there are inappropriate variations in clinical practice. This comes not from a desire to provide patients with suboptimal care but because the pace of medical advance is so great that it is impossible to keep up. It has been estimated that to keep up-to-date I should be reading 18 to 20 peer-reviewed articles every day, including weekends and public holidays. It’s impossible.

5. All healthcare systems face resource constraints and this problem is emphasised in the graph here.




This shows the money expressed as international US dollars that developed countries spend per capita on healthcare. It ranges from just over $500 per person per year in Turkey to over $6,000 per person per year in the US. And these data combine private and public expenditure on healthcare.

This variation is largely explained by differences in wealth. Richer counties such as Luxembourg and the US are able to spend much more on healthcare than poorer ones like Turkey and Mexico. We in the UK are somewhere in the middle, as befits our economic standing.

A country's expenditure on healthcare is therefore governed by what it can afford – bearing in mind that countries have other priorities – law and order, education, transport infrastructure, pensions and so on. All countries have finite resources for healthcare. Moreover it is obvious that what is cost effective in the US and Luxembourg, can't necessarily be cost effective in say Turkey, Mexico or Poland.

Healthcare systems have broadly been trying to take four approaches to address these problems.

1. **Service re-engineering**. This includes re-configuring services to achieve economies of scale such as closing some hospitals, re-organising services so that efficiencies can be made without impairing the quality of care; giving greater responsibility to health professionals other than doctors in patient care - allowing nurses and pharmacists to

prescribe drugs for example. All this sounds easy but it isn't. There are powerful, entrenched forces that will try to subvert all these measures.

2. **Disinvestment**. It is often claimed that much of clinical practice lacks an evidence base is ineffective and should be abandoned. This is a gross oversimplification. There aren't really any ineffective drugs in the BNF. And despite the absence of evidence – in areas like physiotherapy and speech therapy – it would take a brave person to abandon these disciplines in the NHS. There are – for sure – measures that could be taken but they're not going to produce too much in the way of savings.

3. **Public health**. There are very considerable savings to be made, as was shown a few years ago by Derek Wanless, in engaging society over public health measures like smoking cessation, reducing alcohol intake, unprotected sex, over-eating, substance misuse and so on. But there are two problems: we have invested too little in research to find out how to do these things most effectively and when we do know what to do, we too often find it too difficult to do the right thing. Making smoking in public places illegal took 40 years to put in place.

4. **Value-for-money**. There are too many demands on all healthcare systems to be able to provide for everyone's wants. We all in our various ways have to "ration" care.

How best to share finite resources, in society generally, is known to political and moral philosophers as the problem of "distributive justice". Three broad approaches are recognised in healthcare: utilitarianism, egalitarianism and libertarianism.

***Utilitarianism*** tries to maximise the health of the population as a whole or provide *"the greatest good for the greatest number".* Although superficially attractive, it has problems. It does nothing for example to reduce health inequalities between socio-economic groups.

***Egalitarianism*** demands that forms of healthcare that prevent, limit or compensate for normal functioning should have a priority. It seeks to provide care to everyone in need. Despite its attractions, it is unaffordable for any healthcare system in the world.

***Libertarianism*** espouses a free-market solution to the allocation of healthcare resources and considers that decisions are best left to the market place. This places the responsibility for obtaining healthcare on

individuals and their families. It leads, as we see in the US, to gross inequities that we in Europe find distasteful. I won't be discussing this approach further.

Resolutions to the problem of distributive justice have been discussed by philosophers since the time of Plato, and I'm afraid I don't have a solution either. Norman Daniels, one of America's most distinguished bioethicists, and James Sabin, a psychiatrist, have pioneered the concept of procedural justice. Together, they have developed a process which they have called "accountability for reasonableness" in an attempt to allocate healthcare resources in the face of funding restraints.

Accountability for reasonableness has four components.

- **Publicity** – decision-makers should make clear the fact that they are making decisions and the processes they will use. They should explain the conclusions they have reached and why.
- **Relevance** – the grounds for decisions are ones that fair-minded people agree are relevant.
- **Revision** and appeals – means that there are opportunities for challenging decisions.
- **Regulation** - refers to ensuring that there are mechanisms in place for all these three other conditions to be fulfilled.

The principles underpin NICE's approach to decision-making whether it be technology appraisals, clinical guidelines or public health guidance. Indeed, NICE's own four cardinal principles, robust processes, inclusiveness, transparency and independence, closely match the criteria of 'accountability for reasonableness'.

This approach to balancing utilitarianism against egalitarianism, in the context of NICE's work, is ultimately a judgement. I am not ashamed that NICE and its advisory bodies exercise judgement. As William Blake put it:
*God forbid that truth should be confined to mathematical demonstration.*

Anti-cancer drugs are an example of judgement in action. We have a threshold range of £20-30,000 per quality-adjusted life year below which we normally expect our advisory bodies to accept interventions as being cost effective but above which we expect our advisory bodies to exercise caution. But we allow our advisory bodies latitude, and if they consider that special circumstances apply and if they consider on grounds of equity that the threshold should be exceeded, then we expect them to exercise their judgement.

In the case of the products above the £30,000 threshold, NICE's Appraisal Committee regarded them as representing appropriate value-for-money in the particular circumstances. For example the Committee said "yes" to temozolomide in the treatment of advanced gliomas and to sunitinib for advanced renal carcinomas, both increasing life expectancy for patients at the end of life. On the other hand they said "no" to products costing £60,000 a year or more. To accept them as "value-for-money" would deprive other people with other diseases cost effective care. They would incur an unreasonable opportunity cost.

These are tough decisions to have to make, but someone has to make them if the NHS is to serve the best interests of all those who rely on the service for their care.

Conclusion:

**One:** The industry has unquestionably provided great benefits to society and even its fiercest critics would not attempt to deny this.

**Two:** I'm afraid though that some of its new products are unaffordable.

**Three:** The responsibility for this rests with us all. On the one hand, the industry and its investors – a group that includes most of us in this room tonight – have been too avaricious. On the other hand, the behaviour of governments and their drug regulatory authorities has become too cautious, too risk averse.

**Four:** We must all somehow help the industry as it goes through this period. But industry must also do its part: no more failures to publish the results of clinical trials, even if they are negative, and even if they are not the subject of an application for marketing authorisation. And industry needs to make real efforts to develop products we can afford.

**Five:** To achieve this we will all have to make compromises: industry, government and society.

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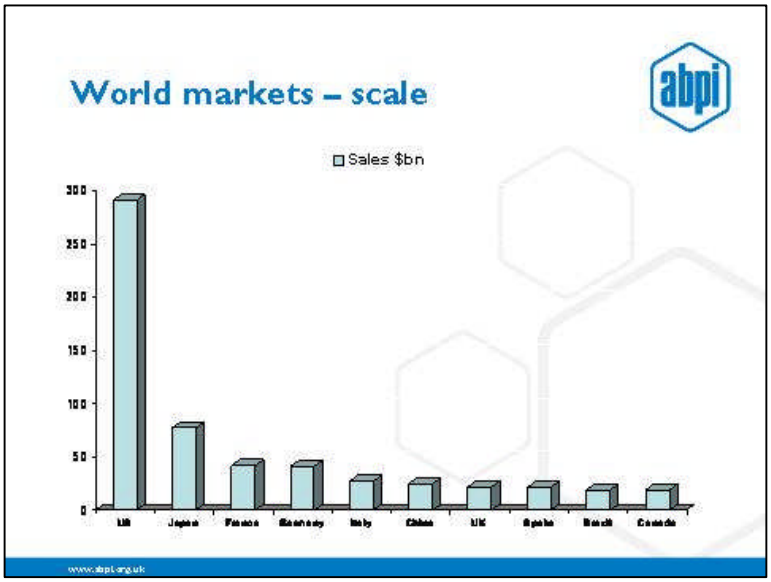
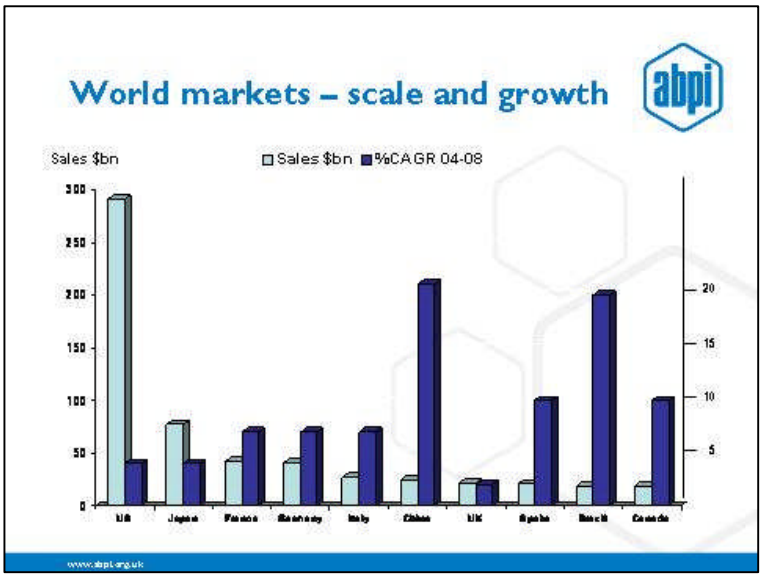
# Response

**Chris Brinsmead**
President, ABPI

Thank you to Sir Michael for that illuminating review of the evolving relationship between industry, government and society. I am going to respond by looking at how that relationship is likely to develop in the future. In doing so, I'll look at global trends, but with a particular eye to the position of the UK.

If we look first at the global pharmaceutical market, we see that the US still dominates the scene with sales of nearly $300 billion a year in 2008. Japan is the second largest market with $77bn while other countries all have markets of less than $50bn. The most significant point here is that China entered the top ten for the first time last year, coming in just ahead of the UK. In terms of growth rates over the past four years, China and Brazil stand out at around 20%. Other markets all grew at 10% or less. And the UK had the slowest growth in the top ten, at just 2%. In the last four years, the UK's share of the global market has fallen behind those of both China and Italy. In terms of the potential for *future* growth, as indicated by population size, China is clearly in a league of its own with its population of over a billion.





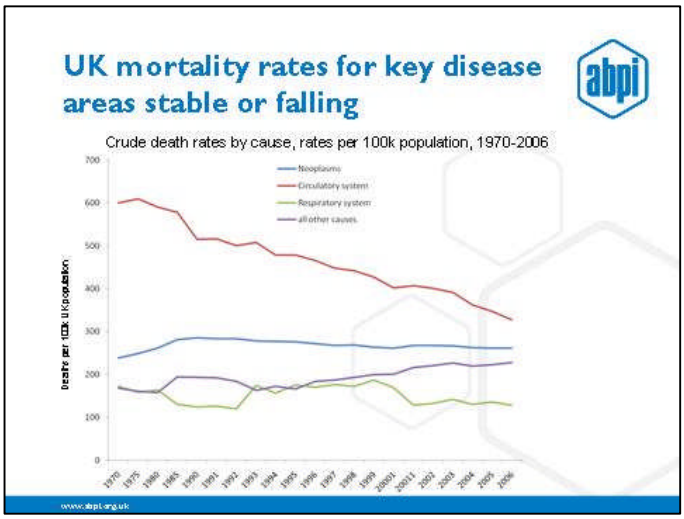

Demographic trends are also going to affect demand for medicines. Over the last half century the world's population has doubled - from around 3 billion to over 6.5 billion, and by 2050 it's expected to reach 9 billion.

And the population is not only growing but ageing. Average life expectancy worldwide has risen from around 45 to around 65 in the last 50 years[1]. In the UK, there are now more pensioners than under-16s.[2] In Wales, even though incidence of chronic illness remains relatively high, people are now living around 3 years longer than in the early 1990s.[3]

This means that there will be growth in demand for medicines that treat the diseases that are prevalent among older people, including CVD, cancer, diabetes, mental disorders and arthritis.

One of the reasons for the ageing population is that mortality rates from such diseases have been stable or falling. The most dramatic decline in the UK has been in the death rate from cardiovascular disease. An ambitious target was set in 1999 to reduce deaths from CVD for people under 75 by 40% in 10 years. In fact the target was achieved five years early[4].

[1] http://www.un.org/esa/population/publications/sixbillion/sixbilpart1.pdf
[2] http://www.statistics.gov.uk/cci/nugget.asp?ID=949
[3] http://wales.gov.uk/docs/statistics/2008/081202sb692008en.pdf?lang=en
[4] http://nds.coi.gov.uk/Content/Detail.asp?ReleaseID=353202&NewsAreaID=2




Medicines have played a significant part in this process. It's been estimated that the number of lives saved by statins in the UK has increased from 3,000 a year in 2000 to around 10,000 now.[5] The fastest growing class of medicines is cancer treatments, where many novel approaches are being tried. And medicines that address the central nervous system form the largest single category.

The industry has delivered these benefits at a very reasonable cost. While total NHS expenditure has been rising, the proportion accounted for by medicines has been falling for some years and now stands at around 10%. The overall medicines bill has risen but that's because more medicines are being taken, around 55 million prescription items a year in Wales[6]. Unit costs have mainly been stable or falling. Comparatively, the UK is a relatively low spender on medicines spending less per person on prescription and hospital medicines than many major European markets and significantly less than the USA and Japan.

So the industry is making headway against the world's killer diseases. But of course there are still major unmet needs in areas such as cancer, stroke and Alzheimer's. And it is becoming more difficult to bring new medicines to market. The number of new molecular entities being launched each year has been in the 20s during this decade, whereas in the 1990s it was typically in the 40s. This is partly due to the increasing costs of clinical trials. Our current estimate is that it takes around $1 billion and 12 years to bring a medicine from the concept to the patient. [7]

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5 http://www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_083060

6 http://www.abpi.org.uk/wales/wales_nhs.asp

7 John Patterson BioCity lecture 10.10.07

If we look at how that global environment affects particular countries, it's noticeable that the UK lags many of its peers in providing patients with access to new treatments. Regulatory hurdles have been getting higher, often for good reasons. But we also believe that regulation should be proportionate and not overly bureaucratic. A recent review of UK Bioscience under Sir David Cooksey said: "The theory behind Health Technology Appraisal is good, but the effect has been to delay the introduction of new therapies and shorten patent protected marketing periods. When you add to this the uncertainty of receiving a positive recommendation from NICE, the result is that fewer drugs are coming to the market and benefiting patients."[8]

So the industry today operates in a mixed environment. The economic downturn is affecting growth, threatening biotech companies and putting pressure on health budgets. The number of new medicines approved is falling, at the same time as many patents are expiring. But at the same time, the industry faces rising development costs and a higher bar being set by regulators.

On the positive side, there are many new opportunities for innovation. Emerging markets are offering opportunities for growth. Medicines are helping to improve the health of the population. There is also recognition from the government down that innovation is never more critical to an economy than during an economic downturn.

Industry has been responding in various ways. Consolidation has been one reaction, with several big mergers announced this year already – Pfizer buying Wyeth, Roche buying Genetech, Merck buying Schering – and this week Abbott buying Solvay's pharmaceutical business. Other companies – AstraZeneca among them - have put more emphasis on collaboration to access new innovation. All major companies have been striving for efficiency. And it's also a case of 'the survival of the focused', with companies concentrating on their specialist areas.

As the representative body of the UK industry, the ABPI has four priorities for progress in respect of medicines – access, value, innovation and trust. And we are seeing good progress in each area. In terms of access to medicines, for example, the government has committed itself to end the postcode lottery and has announced plans for a new 'innovation pass' to make selected new medicines available before full cost-effectiveness data is available. It is designed to support highly innovative medicines that address unmet needs among relatively small patient groups. The PPRS review last year also ended in a settlement that for the first time went beyond purely financial factors and

[8] The Review and Refresh of Bioscience 2015

included measures to increase access and uptake.

The value of medicines is also being looked at closely. Part of the PPRS settlement was an agreement on flexible pricing which will create greater rewards for medicines that are demonstrated to provide real value to patients. This year has also seen the report by Sir Ian Kennedy on this topic. He agreed with the industry that a wider view needs to be taken of the gains that are achieved by medicines, including, for example, the ability to be treated at home instead of a hospital. And he recommended that more research be carried out into whether social benefits should be taken into account, such as the ability to return to work and avoid the costs of care.

We could look at this in a very different way. We have tended to focus on the costs of particular drugs rather than the fact that medicines are used for different purposes. There's a huge difference between a pain-killer, a drug that extends the life of someone who is very ill, and a medicine used to manage a condition and enable someone to live a normal life. Perhaps medicines should be seen as parts of the different pathways of care, with a budget that is categorised according to those pathways. This would promote a more co-operative approach in which we analyse the costs of healthcare holistically, rather than stripping out medicines as a separate line item. Medicines should be seen as an investment in health, not simply a cost of sickness.

If medicines are valued properly then that will enable us to channel more funds back into the vital business of innovation, in which we lead the UK. Our industry invests over five times more in R&D than any other sector. The UK Government has shown increasing commitment to the sector, for example by setting up the Office for Life Sciences. This year the OLS published a blueprint containing the 'innovation pass' and other measures such as mechanisms to drive up uptake of medicines and clinical trials in the NHS.

Such developments show that trust is growing between government, industry, regulators, NHS and patients. It's not only happening in Whitehall but all round the country where pharmaceutical companies are increasingly becoming involved in joint working projects with local healthcare providers. And as an industry we're now taking steps to ensure that we increase our transparency and behave with complete integrity in our relationships.

Access to medicines enables people to live longer and better lives. Value for medicines enables the industry to make a fair return. And that return enables us to invest in more innovation to meet unmet need. It's a cycle and each of the elements depends on working with others. And that is why trust is vital.

Events like this play a part in building trust so I’m grateful to have had this opportunity to set out some views.

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