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**Regulating Risk or Advancing Therapies?  
Regulation and sustainability of medicines in a cash-limited economy**

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**Abstract and Introduction**

This paper examines the issue of whether the regulation of medicinal products, which is intended to provide an effective protection against risk of injury, acts as a barrier to the availability of therapies and to innovation. It considers whether the forces of economic sustainability and demand for new products may justify a revision in individual and societal attitudes to risk.

Medicines are essential for healthcare in advanced countries, and used extensively. Most people not only rely on the safety of these products but also assume that use involves zero risk. Yet many understand little of the sophisticated regulatory mechanisms and complex decisions that are involved in regulating safety.

The regulatory systems that control the safety of medicines in developed nations are extensive, sophisticated, and based on a standardised international approach. There has been continuous development and expansion in the regulatory scheme and requirements since modern controls were introduced in the 1960s. However, the extensive tests and trials that are required to produce sufficient data are very expensive and lengthy. Furthermore, data is required for both safety and economic purposes. Systems for production and evaluation of such data are not always efficiently harmonised so as to minimise delay and cost.

It is becoming increasingly clear that the availability of future medicines, especially innovative products, is threatened by economic factors. Governments and industry are, therefore, considering the need for transformational approaches to the reduction of costs and delay in regulatory and health technology assessment systems, in order to ensure that healthcare systems, industry and innovation remain sustainable.

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Two linked developments may offer significant opportunities. First, there is an increasing trend towards strengthening of post-marketing vigilance systems for all product types, notably for medicines in the pharmacovigilance system. Secondly, the harnessing of modern information technology to post-marketing vigilance systems offers the possibility of swift and reliable monitoring of the active use of products in large populations. Taken together, these developments present the possibility of switching emphasis away from the costly pre-market testing of medicines towards complete lifetime product monitoring. Thus, medicines might be approved for use earlier than at present, dramatically cutting their research costs.

However, there are important technical and ethical challenges if such a significant change in approach were to be implemented. Such change would involve a potential but unquantifiable increase in risk for individuals who consume some medicines, but possibly not for global society. On the other hand, such change might lead to the earlier availability of more innovative medicines, and so reduce the risk of disease generally. Perhaps the leading obstacle to such a change would be public reception, driven by the media, of earlier product approval. In this respect, the outcome may be a triumph for fear over rationality.

## **I. The nature of medicines regulation in Europe**

Extensive and complex legal provisions regulate medicinal products in all advanced nations of the world. Modern regulation of medicines was introduced in response to the thalidomide tragedy of the early 1960s. Since then the controls have expanded in breadth and detail to form extensive and comprehensive codes.<sup>1</sup> Considerable international harmonisation of the detailed scientific requirements has occurred<sup>2</sup> between the legislation of the leading trading blocks of USA, Canada, the European Union,<sup>3</sup> Japan and Australasia.<sup>4</sup> Controls now cover the pre-market testing and evaluation,

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<sup>1</sup> The European regulatory system for medicinal products is the most extensive in breadth and detail of any product regulatory controls that cover other consumer products. Different systems cover product types such as cosmetics, biocides, motor vehicles, machinery, medical devices, lifts, toys, electrical equipment, and general consumer products. However, the techniques that apply for all product types utilise many of the same broad techniques (notably pre-marketing assessment, quality system controls, control on information given, post-marketing vigilance, control of manufacturing quality and of distribution) even though not all techniques are found, either at all or to the same extent, in all sectors. See C. Hodges, *European Regulation of Consumer Product Safety* (Oxford, 2005).

<sup>2</sup> Notably through the Global Harmonisation Task Force, see [www.ghhf.org](http://www.ghhf.org).

<sup>3</sup> European Union legislation governs all the relevant aspects discussed here in relation to activities within its Member States. In England, the Medicines Act 1968 was largely disapplied by the Medicines for Human Use (Marketing Authorisations Etc) Regulations 1994, SI 1994/3144, since when the EU legislation has been incorporated by reference. Although national legislation technically governs some aspects, such as national authorisations and penalties, almost all discussion between industry and regulators refers to the EU provisions.

<sup>4</sup> International pressure in the wake of various food and drug scandals has elicited an undertaking by China to raise production, testing and inspection standards: A. Ang, 'China claims progress in \$1 billion project to set up food, drug safety', Associated Press, 8 August 2007.

manufacture, distribution, information supplied, advertising, and post-marketing monitoring of medicinal products.<sup>5</sup>

The basic three principles on which regulation rests are safety, efficacy and quality.<sup>6</sup> The point at which the key decision is taken on whether an individual manufacturer has satisfied these three values comes at the end of the pre-marketing phase, when a mass of data collected from testing, toxicology and clinical trials is evaluated by experts on behalf of the proposed marketing authorisation holder and then submitted for scrutiny by the experts of the public authorities. If the public authorities are satisfied that the legal tests are satisfied, they issue a marketing authorisation for the particular product. Authorisations must also be held for manufacturing and distribution activities. Only one of every 10,000 potential compounds investigated by Western research-based companies makes it through the research and development pipeline and is approved for patient use.<sup>7</sup>

However, the evaluation of a product's safety that occurs at the pre-authorisation stage is recognised by those involved in the system as being provisional. At the pre-marketing stage of safety evaluation, a medicine will only have been tested in a limited number of humans.<sup>8</sup> At that point in time, a level of confidence in the product's safety is based on existing knowledge of the generic type of product, from laboratory and animal tests, and then from three phases of trial in human volunteers and patients. Accordingly, safety is continuously re-evaluated throughout the marketing lifetime of a medicinal product. This is done primarily by monitoring reports of adverse reactions associated with use of products through the pharmacovigilance system. The marketing authorisation holder is required to collate such information and report urgent or periodic data to the public authorities.

## **II. Economic evaluation of medicines**

In addition to safety regulation, medical technologies are increasingly subject to economic assessment. The existence of such dual systems and requirements gives rise to a need for integration, so as to avoid unnecessary costs, especially at the pre-marketing stage.

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<sup>5</sup> A more detailed explanation of the European provisions is at C. Hodges, 'Regulating Medicines and Medical Devices' in A. Grubb (ed.), *Principles of Medical Law* (Oxford, 2ed, 2004). Some specific aspects are analysed in C. Hodges, *European Regulation of Consumer Product Safety* (Oxford, 2005), notably chs 4, 8 and 11. In 2007 the US Food and Drug Administration, the European Commission and the European Medicines Agency concluded an agreement to expand their cooperative activities, including sharing safety information: joint press release June 18, 2007.

<sup>6</sup> Regulation (EEC) No. 2309/93, recital 3.

<sup>7</sup> *Pharmaceutical Industry Profile*, Pharmaceutical Research and Manufacturers of America, 2005.

<sup>8</sup> Animal tests have limited predictive precisions and are essentially as a screening stage before human use. Pre-marketing clinical trials seldom study more than 1,000 – 2,000 patients. This level of monitoring is only capable of identifying adverse reactions with an incidence of 1 in 250 patients. See A. P. Fletcher and S. Shaw, 'The Safety of medicines, in J. P. Griffin and J. O'Grady (eds.), *The Textbook of Pharmaceutical Medicine* (BMJ Books, 4ed., 2002).

Insurers and governments require to be satisfied that the medicines which they pay for are good value for money. Pharmaceutical prices are regulated by most governments or insurers.<sup>9</sup> In addition, public agencies, of which the National Institute for Health and Clinical Excellence (NICE) in England is a leader, now carry out health technology assessment (HTA) of products and treatments in order to determine the most cost-effective options. HTA requirements have been introduced in some states since the mid-1990s, as purchasers seek to reduce their expenditure. HTA is a workable approach, here to stay and will develop further.<sup>10</sup> The high prices charged by innovative pharmaceutical companies in order to recoup their investments and to maintain shareholder value are obvious priority targets for HTA.<sup>11</sup> NICE aims to determine not only prices sought are fair but also whether technologies should be encouraged or discontinued.<sup>12</sup> In order to undertake comparative cost-benefit reviews of products, companies are required to produce data on clinical- and cost-effectiveness.

However, the requirement for HTA data is being recognised both as itself increasing costs, especially pre-marketing costs, and as insufficiently sequenced and integrated into the safety trial system and its requirements. A 2006 Report by Sir David Cooksey concluded:

“[HTA] arguably comes too late in the process, at least for some categories of medicines. If the NHS’s HTA programme and NICE were involved earlier in the testing of a drug, and were able to influence the questions asked, the outcome measures, and the design of studies, NICE might be more comfortable with making interim judgments on new medicines, which would allow limited earlier adoption of those thought to be cost-effective. The NHS will also need changes to its dissemination strategies for guidance about cost-effective use of medicines to ensure more rapid and certain implementation.”<sup>13</sup>

Cooksey noted criticism of

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<sup>9</sup> Different systems apply in different countries, influenced by whether primary sources of payment are private insurance or, as in UK, public taxation. In Germany, reference pricing of product families is a favoured system, whereas in UK the Pharmaceutical Price Regulation Scheme (PPRS) has historically controlled companies’ profitability rather than individual product prices. However, the PPRS has been strongly criticised (*The Pharmaceutical Price Regulation Scheme: An OFT market study*, (Office of Fair Trading, 2007)) and the government intends to review it: Press release, Department of Health, 2 August 2007.

<sup>10</sup> M. Drummond, ‘Using Economic Evaluation in Reimbursement Decisions for Health Technologies: lessons from International Experience’ in F. A. Sloan and C-R. Hsieh (eds), *Pharmaceutical Innovation: Incentives, Competition, and Cost-Benefit Analysis in International Perspective* (Cambridge, 2007).

<sup>11</sup> See industry attacks on the system in *R v Secretary of State for Health ex parte Pfizer* (1999) 2 CCLR 270 and *R (on the application of Eisai Ltd) v National Institute for health and Clinical Excellence* [2007] EWHC 1941 (Admin).

<sup>12</sup> Sir D. Cooksey, *A review of UK health research funding* (HM Treasury, December 2006), ch 7. For an analysis of whether there is societal consensus on the substantive values that should underpin distributive choices in healthcare, see K. Syrett, ‘Deconstructing Deliberation in the Appraisal of medical Technologies: NICEly Does it?’ [2006] MLR 869.

<sup>13</sup> Sir D. Cooksey, *A review of UK health research funding* (HM Treasury, December 2006), p 108.

“drug reimbursement schemes as not selectively rewarding improvements in productive efficiency. This has led to the rather startling conclusion in one review, looking at data over 13 years, that only 6% of new drugs actually represent significant clinical improvements, defined as being ‘the first drug to treat effectively a particular illness or which provides a substantial improvement over existing drug products’ upon existing ones.<sup>14, 15</sup>

### III. The Costs of Regulation

Satisfying the requirements of the medicines regulatory system is very costly and takes a long time. It is well known that requirements for pre-market toxicology and clinical trial data mean that the typical time for R&D on a new molecular entity is 12 years and that the average cost of discovering and developing a new drug is now put at over \$800 million, and rising at an annual rate of 7.4% above general price inflation.<sup>16</sup> Only companies based in a handful of countries have the capability to develop new drugs.<sup>17</sup> The cost of conducting medical research in UK is second only to USA, partly because of increased security as a result of threats from animal rights protesters.<sup>18</sup>

Manufacturers of innovative medicines typically have around 10 years<sup>19</sup> within which to recoup their very high costs on the research and development of all products that fail to reach the market, before their patent and marketing exclusivity expires on a new chemical entity, at which point generic copies enter the market typically at much lower cost,<sup>20</sup> and the former are forced to lower their prices. The rules seek to strike a balance between

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<sup>14</sup> S. G. Morgan et al, ‘Breakthrough drugs’ and growth in expenditure on prescription drugs in Canada, *BMJ*, 2005;331:815-816.

<sup>15</sup> Sir D. Cooksey, *A review of UK health research funding* (HM Treasury, December 2006), p 109.

<sup>16</sup> Boston Consulting Group, *A Revolution in R&D: How Genomics and Genetics are Transforming the Biopharmaceutical Industry*, (Boston Consulting Group, 2001); J. DiMasi, R. W. Hanson and H. G. Grabowski, ‘The price of innovation: new estimates of drug development costs’, *J Health Econ*, 22, 151-185 (2003); D. W. Light and R. N. Warburton, ‘Extraordinary Claims Require Extraordinary Evidence’ (2005) *Journal of Health Economics* 24(5): 1030-1033.

<sup>17</sup> F. A. Sloan and C-R. Hsieh, ‘Introduction’ in F. A. Sloan and C-R. Hsieh (eds), *Pharmaceutical Innovation: Incentives, Competition, and Cost-Benefit Analysis in International Perspective* (Cambridge, 2007): the authors cite U.S.A., the United Kingdom, Germany, France, Sweden, and Japan..

<sup>18</sup> *The Influence of the Pharmaceutical Industry* House of Commons Health Committee, 5 April 2005, HC 42-1.

<sup>19</sup> Normal patent life is 20 years. Since around 12 years may elapse before a new medicine reaches the market, protection from generic competitors is extended to 10 years within Europe by both supplementary patent protection and by regulatory marketing exclusivity: see C. H. Bendall and C. J. S. Hodges, ‘Legal and ethical issues relating to medicinal products’ in J. P. Griffin and J. O’Grady (eds) *The Textbook of Pharmaceutical Medicine* (Blackwell Publishing Ltd, 5<sup>th</sup> ed, 2006).

<sup>20</sup> The generic manufacturers do not incur the sizeable research and development costs of the initial manufacturer, and can copy the latter’s patent and relate their regulatory application for substantially similar products to the originator’s data for the original product.

short-term benefits from greater price competition and longer-term benefits from greater incentives for innovation.<sup>21</sup>

#### IV. Reducing Cost and Increasing Competitiveness

Both the European and British authorities are pursuing important policies to reduce regulatory burdens on business so as to improve competitiveness.<sup>22</sup> The European Commission estimates that Community regulation in general costs 2-5% of GDP.<sup>23</sup> The European Commission has said:

“Enterprise Europe requires a revolution in our culture and attitudes towards entrepreneurship.

Europe must re-examine its attitude to risk, reward and failure. Thus, *enterprise policy must encourage policy initiatives that rewards those who take risks.*” (original emphasis).<sup>24</sup>

Innovation has been identified as a key factor in enterprise policy, and essential in order for European enterprises to be competitive.<sup>25</sup> Empirical evidence consistently indicates that technological innovation is the leading cause of economic growth in developed countries.<sup>26</sup> The European Union has a formal policy that the Community's regulatory framework must be conducive to innovation, and not involve over-regulation.<sup>27</sup> The Commission stated that the administrative and regulatory environment is too complex and this continues to be a serious obstacle to the creation of new businesses and to entrepreneurship and also affects their capacity to innovate, as

"over regulation, for example in approval procedures for new products, raises development costs and increases time to market."<sup>28</sup>

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<sup>21</sup> H. Grabowski, ‘Competition between Generic and Branded Drugs’ in F. A. Sloan and C-R. Hsieh (eds), *Pharmaceutical Innovation: Incentives, Competition, and Cost-Benefit Analysis in International Perspective* (Cambridge, 2007).

<sup>22</sup> For a general overview of this ‘Better Regulation’ policy, see C. Hodges, ‘Encouraging Enterprise and Rebalancing Risk: Implications of Economic Policy for Regulation, Enforcement and Compensation’ (EurBusLR, 2007 in press).

<sup>23</sup> Mandelkern Group on Better Regulation: Final Report, (European Commission, 13 November 2001).

<sup>24</sup> Ibid. The creation of a legal environment more conducive to risk-taking and job creation was also proposed in Opinion of the Economic and Social Committee on the ‘Communication from the Commission – Challenges for the enterprise policy in the knowledge-driven economy’ 2001/C 116/04, OJ No C 116/20, 20.4.2001.

<sup>25</sup> See Communication from the Commission to the Council and the European Parliament - Innovation in a knowledge-driven economy, COM (2000) 567.

<sup>26</sup> J-I. Kim and L. J. Lau, ‘The Sources of Economic Growth of the East Asian Newly Industrialised Countries’, (1994) *Journal of the Japanese and International Economies* 10:265-290.

<sup>27</sup> Ibid.

<sup>28</sup> Ibid. See also *White Paper on Growth, Competitiveness, Employment: the challenges and ways forward into the 21st century*, 1994; *Green Paper on Innovation*, COM (95) 688, 20.12.95; *Council Decision of 25*

Both the European Commission<sup>29</sup> and the UK government base competitiveness policy on elements<sup>30</sup> that include simplification of existing legislation and reducing administrative burdens. The Commission has prioritised the sectors of automotive, construction and waste, and intends to ‘gradually apply’ the approach to other sectors such as pharmaceuticals, mechanical engineering, information and communication technologies and energy-intensive sectors, and to services.<sup>31</sup> The only example relating to healthcare that was initially cited in the Commission’s 2006 review of progress was a simplified regulatory framework and incentives for SMEs that are developing pharmaceuticals.<sup>32</sup> This is proposed to include reduced fees, options for deferred payment of fees, simplified administrative procedures and administrative and regulatory assistance when submitting applications to the European Medicines Agency (EMA). Since then, however, reviews have been made of procedures for variations in authorizations and of the pharmacovigilance system.<sup>33</sup>

The potential for savings in healthcare costs is obviously significant, given the size of the total spent. In 2000, the UK spent £66.7 billion on healthcare, just over 7% of GDP or £1,100 for every person.<sup>34</sup> A reduction of 2-5% in those totals would clearly be significant. As part of a contribution of an 11% reduction (£132 million) towards reducing the Department of Health’s £1.2 billion budget by 25% by 2010, the Department aims to remove administrative burdens and make savings from improved processes enabling quicker time to market that should save £104.4 million for the industry.<sup>35</sup> The estimates are that electronic submission of applications will save £71m, changes to over-the-counter approvals will save £24.3m, and implementing a risk-based approach to inspection will save merely £1m a year. But no change is proposed in this programme in relation to the mass of substantive regulatory requirements, which impose considerable costs and in relation to which proposed savings are insignificant.

Given the global consensus on regulatory requirements, underpinned by international agreements, and the political sensitivities that arise from the public perception of risk in the medicines field, a national government would have enormous difficulty in introducing significant alleviations in the regulatory burden. The real question is whether any simplification programme would be able to make an impact given the political imperative of maintaining confidence in safety.

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*June 1996 on the implementation of a Community action programme to strengthen the competitiveness of European industry*, 96/413/EC, OJ No L167/55, 6.7.96.

<sup>29</sup> Commission Communication on ‘A Strategic Review of Better Regulation in the EU’ COM (2006) 689, 14.11.2006.

<sup>30</sup> It is stated in the UK Regulatory Reform Act 2001, replaced by the Legislative and Regulatory Reform Act 2006, that the burden of legislation should be proportionate to the benefit. See *Better Regulation: Draft Simplification Plan* (DTI, November 2005).

<sup>31</sup> Commission Communication *Implementing the Community Lisbon programme: A strategy for the simplification of the regulatory environment* COM(2005) 535, 25.10.2005.

<sup>32</sup> Commission Working Document ‘First progress report on the strategy for the simplification of the regulatory environment’ COM (2006) 690, 14.11.06.

<sup>33</sup> See <http://ec.europa.eu/enterprise/pharmaceuticals/index.en.htm>

<sup>34</sup> Office of Health Economics, *Compendium of Health Statistics 2001* (2001).

<sup>35</sup> *Simplification Plan* (Department of Health, December 2006).

## V. The Challenge of Sustainability

Thus, it is clear that the general costs on both the demand and supply side of the health economy are increasing. People want new and innovative products, but their cost is high and growing because of the burden of regulatory and HTA assessments. The general costs of healthcare are also increasing, and challenges will increasingly arise over spending priorities. An affordability crisis looms, which has significant implications for health systems and also for the sustainable business model of private enterprises. These issues will be considered in turn.

### A. Growth in health spending and demand

Patients want access to the latest technologies as quickly as possible.<sup>36</sup> An increase in spending on pharmaceuticals in general results in substantial increases in life expectancy.<sup>37</sup> The need for speedy access has underpinned recent moves by the Department of Health and NICE to introduce a faster initial assessment for some new treatments.<sup>38</sup> Cooksey commented that “As we have recently seen with Alzheimer’s drugs,<sup>39</sup> the ability of the NHS’s ability to control costs by carefully limiting access to treatments, especially those that are more expensive, is increasingly being challenged by patients and campaigners. A recent IPPR survey found that one-third of people questioned believe that there should be unlimited access to new drugs irrespective of cost.”<sup>40,41</sup>

Health spending globally is anticipated to grow significantly (consuming 21% of GDP in USA and 16% in other OECD countries by 2020), and to be unsustainable. The health sector’s share of the US economy grew from 13.6% in 1997 to 16% in 2004,<sup>42</sup> and is predicted to grow to above 20% of US GDP by 2015.<sup>43</sup> The UK lags behind many other states. In 2004 the UK spent less per person on medicines (£205, or 0.94% of GDP) than USA (£493), Japan (£310), France (£290) and Germany (£220).<sup>44</sup> This was despite the fact that pharmaceutical spending as a share of total health spending increased from 7.6%

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<sup>36</sup> See *Regina (Rogers) v. Swindon NHS Primary Care Trust* [2006] 1 W.L.R. 2649; J Laurance, ‘NHS Cash Crisis Deprives Thousands of Treatment for Blindness’ *The Independent* 30 January 2007.

<sup>37</sup> P-Y. Cremieux, J. Jarvinen, G. Long and P. Merrigan ‘Pharmaceutical Spending and health Outcomes’ in F. A. Sloan and C-R. Hsieh (eds), *Pharmaceutical Innovation: Incentives, Competition, and Cost-Benefit Analysis in International Perspective* (Cambridge, 2007).

<sup>38</sup> The ‘Single Technology Assessment’ (STA) process, see <http://www.nice.nhs.uk/page.aspx?o=278616>

<sup>39</sup> <http://news.bbc.co.uk/1/hi/health/6036519.stm>

<sup>40</sup> *Public ‘expect too much from NHS’*, BBC News website, 2 September 2006. See <http://news.bbc.co.uk/1/hi/health/5298824.stm>

<sup>41</sup> Sir D. Cooksey, *A review of UK health research funding* (HM Treasury, December 2006), p 109.

<sup>42</sup> <http://www.washingtonpost.com/wp-dyn/content/article/2006/01/09/AR2006010901932.html>

<sup>43</sup> See, e.g., C. Borger et al., *Health Spending Projections Through 2015: Changes On The Horizon*, Health Affairs, 25, No2 (2006).

<sup>44</sup> Sir D. Cooksey, *A review of UK health research funding* (HM Treasury, December 2006), para.

in 1948 to 13.1% in 1998-99 (Table 4).<sup>45</sup> Professor Sir Michael Rawlins, the Chairman of NICE, has recently warned that patients face much tougher rationing of treatments and restricted access to breakthrough drugs unless further funds are made available.<sup>46</sup>

A significant driving factor is the ageing demography of the population, bringing an increase in chronic diseases and conditions. Around a third of spending on UK healthcare is on people over retirement age: this group has increased from 7.4 million in 1971 to 9.2 million in 1998.<sup>47</sup> The Government Actuary's Department estimates that the population will increase by 8 million by 2020, and the number of people aged over 85 (which increased by 64% between 1980 and 1998) could increase by between 37% and 94%.<sup>48</sup> The average cost to the NHS of a person aged over 85 is approximately six times the cost for a 16-44 year old, and four times the cost for a 45-64 year old.<sup>49</sup> There are not expected to be changes in the five main disease burdens, so the burden of disease will rise.<sup>50</sup>

Wanless estimated that technology and medical advance may have contributed around 2 percentage points to the average annual rate of growth in nominal health spending in recent years, and that this would be merely a 'floor' for future spending.<sup>51</sup> There will clearly be a large number of new technologies coming onto the market. The number of drugs in late stage development worldwide in 2000 was estimated to be around 1,500, including 200 cancer drugs, 100 anti-infectives and 50 drugs for heart failure.<sup>52</sup> The most exciting areas are genetics and stem cell research, which offer the prospect of transformational developments.

A further driver is increased capacity and demand. The replacement of cholecystectomy by abdominal incision by laparoscopic cholecystectomy reduced cost by 25% but enabled gall bladder surgery to rise, increasing the overall spend on this treatment by 11%.<sup>53</sup>

The national strategy for health targets five disease areas,<sup>54</sup> which accounted for around 50% of mortality, 12% of morbidity and 10% of NHS expenditure in 2000.<sup>55</sup> Of the five

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<sup>45</sup> D. Wanless, *Securing our Future Health: Taking a Long-Term View, An Interim Report*, (HM Treasury, November 2001), para 3.26.

<sup>46</sup> P. Webster, A. Miles and H. Rumbelow, 'NHS will 'run out of funds for best drugs'' *The Times*, 13 January 2007.

<sup>47</sup> D. Wanless, *Securing our Future Health: Taking a Long-Term View, An Interim Report*, (HM Treasury, November 2001), para 3.24.

<sup>48</sup> D. Wanless, *Securing our Future Health: Taking a Long-Term View, An Interim Report*, (HM Treasury, November 2001), para 9.8.

<sup>49</sup> D. Wanless, *Securing our Future Health: Taking a Long-Term View, An Interim Report*, (HM Treasury, November 2001), para 9.10.

<sup>50</sup> D. Wanless, *Securing our Future Health: Taking a Long-Term View, An Interim Report*, (HM Treasury, November 2001), para 9.41.

<sup>51</sup> D. Wanless, *Securing our Future Health: Taking a Long-Term View, An Interim Report*, (HM Treasury, November 2001), para 10.69.

<sup>52</sup> Lehman Brothers Pharmapipelines database.

<sup>53</sup> A. Harrison, J. Dixon, B. New and K. Judge, 'Funding in the NHS: Can the NHS cope in future?' (*British Medical Journal*, 1997) 314:139.

<sup>54</sup> Department of Health, *The NHS Plan – A plan for investment, a plan for reform* (The Stationery Office, 2000), Cmd 4818-1.

areas, pharmaceutical expenditure was greatest (i.e. medicines had the most impact) in relation to coronary heart disease (9.0% of expenditure), cancer (2.9%) and diabetes (2.7%) (Table 1). Wanless estimated that if the NHS were able to deliver best practice in these areas, between 3.5% and 13% a year would be added to the cost of treating the five target diseases identified as national targets.<sup>56</sup> He also estimated the increased expenditure required to achieve the NHS targets by 2010 (table 2).

Table 1: National Service Frameworks, coverage of expenditure by sector (per cent)

Target Disease	Hospital	Primary care	Pharmaceutical	Community
Coronary heart disease (CHD)	2.4	2.4	9.0	0.9
CHD- heart failure	1.6	3.6	0.0	0.0
Cancer	6.3	3.5	2.9	0.9
Mental health	2.0	0.6	0.6	3.0
Diabetes	0.6	1.0	2.7	1.1
Renal	0.4	0.1	0.0	0.2
<b>Total</b>	<b>13.3</b>	<b>11.2</b>	<b>15.2</b>	<b>6.1</b>

Source: Department of Health, quoted in Wanless Report, above, Table 8.2

Table 2: Estimated extra cost required to achieve the UK NHS health targets by 2010

Coronary heart disease (CHD )	prescribing statins would cost £2 billion a year, and revascularisation around £500 million a year.
Cancer	£1 billion a year.
Renal failure	£400 million a year.
Diabetes	£650 million a year, which could save the health service £200 million a year in treatment costs. <sup>57</sup>

Wanless summarised the position in 2001:

“Technology and medical advance are major drivers of health expenditure and have significant potential to improve the outcomes and the efficiency of the health service. Yet there are considerable uncertainties about the future direction, pace and impact of technology in health care. ... while some technologies may reduce unit costs, overall new technology is likely to continue to put upward pressure on health care spending as it enables more people to be treated and for longer periods of time.”<sup>58</sup>

<sup>55</sup> D. Wanless, *Securing our Future Health: Taking a Long-Term View, An Interim Report*, (HM Treasury, November 2001), para 6.12 and ch 8.

<sup>56</sup> D. Wanless, *Securing our Future Health: Taking a Long-Term View, An Interim Report*, (HM Treasury, November 2001), ch 8.

<sup>57</sup> D. Wanless, *Securing our Future Health: Taking a Long-Term View. Final Report* (H M Treasury, 2002), p 25.

<sup>58</sup> D. Wanless, *Securing our future health: Taking a long-term view, An interim report* (HM Treasury, 2001), p 159; [http://www.hm-treasury.gov.uk/consultations\\_and\\_legislation/wanless/consult\\_wanless\\_interimrep.cfm](http://www.hm-treasury.gov.uk/consultations_and_legislation/wanless/consult_wanless_interimrep.cfm).

## **B. Implications for industry and the sustainable flow of innovative products**

The commercial realities for the research-based pharmaceutical industry are significant. Drug development is becoming ever more expensive. The 1970s and 1980s were the era of blockbuster drugs. Companies increasingly attempted to spread the investment risk within their pipelines by developing alternative versions of pre-existing drug compounds, aimed at delivering incremental improvements on the current treatments ('me too' drugs).<sup>59</sup> Currently, however, impending losses of patent protection on 'blockbuster' drugs by many of the large companies, which are not being replaced by new products, have affected investors' confidence, leading to significant falls in share prices.<sup>60</sup>

It has been commented that the increasing cost of drug development is likely to promote the situation where companies invest only in the development of those new drugs that are expected to yield peak annual sales greater than \$500 million.<sup>61</sup> This has prompted arrangements to develop 'orphan' products for important but rarer diseases, by helping them through the regulatory system more quickly, on the basis of early provisional approval, and more intense post-marketing vigilance.

It is now argued that the drug industry is in desperate need of a new business model, as the cost of development continues to rise and the baby-boom generation ages.<sup>62</sup> Large pharmaceutical companies used to be engines of innovation but are susceptible to falls in share prices, competition from generics and bureaucracy. Biotech firms used to be nimble but the bursting of the bubble has left them starved of cash and largely unprofitable.

Cooksey identified the following trend:

“the pharmaceutical industry could face a future financial crunch. ... It has been claimed that the number of new drugs being produced has fallen,<sup>63</sup> although the latest statistics from the FDA do not show a clear trend.<sup>64</sup> It could be argued that the mid-1990s ... was a period of exceptional productivity, and that the current level of new drug development is simply a return to an earlier, more sustainable trend. But equally, drug company expenditure on R&D has risen by almost 80% between 1995 and 2004,<sup>65</sup> perhaps driven by the higher cost of developing biologics as opposed to more 'traditional' chemical-based medicines....

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<sup>59</sup> Sir D. Cooksey, *A review of UK health research funding* (HM Treasury, December 2006), p 42.

<sup>60</sup> *Confronting the Future: Getting High Performance Back into the Biopharmaceutical Industry* (Accenture, 2006). 'Billion dollar pills' (*The Economist*, 27 January 2007).

<sup>61</sup> M. D. Rawlins, 'Cutting the cost of drug development?' *Nature*, Vol 3, 360, (April 2004).

<sup>62</sup> G. Pisano, *Science Business* (Harvard Business School Press, November 2006).

<sup>63</sup> 'Challenge and opportunity on the critical path to new medical products: view from the US Food & Drug Administration', FDA, March 2004, p 2.

<sup>64</sup> <http://www.fda.gov/cder/tadm/>

<sup>65</sup> CMR International 2005 Pharmaceutical R&D Factbook.

There has been an increased focus in the last decade on finding new ‘blockbusters’, but this model is not sustainable. Only around 35% of new drugs are genuinely new molecular entities.”<sup>66</sup> Some form of new approach is likely to be facilitated by a ‘seismic shift in medical science’. Cooksey notes “the potential for a step-change in our approaches to diagnosing and treating illness and disease. In particular, there is an increasing complexity of types of treatments available, ranging from conventional chemical compounds to biopharmaceuticals, molecular medicines, exploitation of gene therapy and cell replacement therapy using stem cell. These discoveries are a driver for increasing drug specificity, leading to smaller and more select target patient groups, with implications for drug development business models and costs.”<sup>67</sup> This approach would also, hopefully, have implications for safety, since it should be possible to ensure, with proper diagnostics and monitoring, that particular drugs are given only to those patients who will benefit from them, and are less likely to suffer serious adverse reactions.

Such changes would, however, have major financial implications. Smaller patient populations mean that the development costs of new medicines will need to be spread over a smaller group of patients, increasing the average cost of those new medicines. In turn, this should be a driver for efforts to reduce the costs of new medicines, to ensure equitable access to cost-effective new treatments. This means not only investing in R&D to reduce the cost of drug development, but also producing better diagnostics so that new medicines are only given to patients who will benefit from them (efficiency gains) and also looking again at the regulatory process, to see for example whether new technologies can help reduce the length of time it takes to get a new medicine to market.<sup>68</sup>

Cooksey notes:

“.. it does appear that new drugs are likely to become more expensive, given the likelihood that an increasing proportion of new drugs will be ‘personalised’ medicine,<sup>69</sup> and will therefore require a higher return per patient treated in order to cover their development costs. ... A recent, well-publicised example is Herceptin, which is targeted at about 20% of patients who have a particular form of breast cancer.

... The cost of Herceptin has been estimated at £20,000 per patient per year. This comes on top of recent trends in NHS drugs expenditure, which rose by around 50% between 2000 and 2005. ... This presents real financial challenges.”<sup>70</sup>

Economic consultants say that “preventive care and disease management programmes have untapped potential to enhance health status and reduce costs, but require support and integration across industry for their benefits to be realised.”<sup>71</sup> In other words, without

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<sup>66</sup> Sir D. Cooksey, *A review of UK health research funding* (HM Treasury, December 2006), p 108.

<sup>67</sup> Sir D. Cooksey, *A review of UK health research funding* (HM Treasury, December 2006), p 9.

<sup>68</sup> Sir D. Cooksey, *A review of UK health research funding* (HM Treasury, December 2006), p 42.

<sup>69</sup> See the Royal Society’s report, *Personalised medicines: hopes and realities*, <http://www.royalsoc.ac.uk/document.asprid=3780>

<sup>70</sup> Sir D. Cooksey, *A review of UK health research funding* (HM Treasury, December 2006), p 109.

<sup>71</sup> *HealthCost 2020: Creating a Sustainable Future* (Pricewaterhouse Coopers’ Health Research Institute, 2005). The authors call for, amongst other things, use of regulation to encourage and strengthen

investment there will be no innovation. But where are the funds to come from if both payers and producers will increasingly be strapped for cash?

## VI. Options for sustainability

What options might be available in order to deliver fast access to safe, effective and cost-efficient medicines at an affordable total price, whilst maintaining a vibrant and innovative pharmaceutical sector?

A logical solution to the crisis of revenue to fund research and innovation by companies would be to extend patent life or marketing exclusivity. Such a solution is, however, unlikely to recommend itself to payers, especially as they try to spread limited budgets across an increasing range of purchasing priorities.

The first amongst the realistic options is that the pharmaceutical industry has actively to cut costs and adopt a new business model.<sup>72</sup> Research is being carried out in cheaper parts of the world, notably China and India, although there are concerns about lower standards and hence the reliability of data generated.<sup>73</sup> New approaches towards reimbursement are being evaluated, such as that sponsors might pay annual rewards based on the therapeutic effectiveness of innovative drugs.<sup>74</sup>

Expenditure on marketing is one important area that will come under scrutiny. The largest U.S. companies spent over one third of their annual sales on average on “marketing and administration” during 1999-2000.<sup>75</sup> However, the evidence on direct-to-consumer advertising (currently banned in Europe) points towards the impact being primarily on overall sales of the therapeutic class of medicines rather than on individual brand market shares.<sup>76</sup>

The second option is to ensure that regulatory and HTA systems are fast, efficient and integrated. Cooksey has recommended a ‘Critical Path’ programme that would reduce the time taken in product development and HTA. The objective would be to enable more rapid discrimination between potential new therapies, at earlier stages of drug development, thereby reducing the failure rate at each stage of the drug development

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competition; better use of technology and interoperable electronic networks; making error reporting voluntary and anonymous, and incentivising clinicians for outcomes, not activity, through pay-for-performance; instilling a climate of innovation; and harnessing global convergence.

<sup>72</sup> In 2007 workforce cuts of 10,000 were announced by Pfizer, and of 4,820 by Johnson & Johnson: Associated Press, 1 August 2007. The largest biotechnology company announced a cut in workforce of up to 14% or 2,600 positions: Associated Press, August 15, 2007.

<sup>73</sup> M. Scott, ‘Ever-increasing pressure on ‘big pharma’ business model’, *Financial Times*, August 6, 2007.

<sup>74</sup> A. Hollis ‘Drugs for Neglected Diseases: New Incentives for Innovation’ in F. A. Sloan and C-R. Hsieh (eds), *Pharmaceutical Innovation: Incentives, Competition, and Cost-Benefit Analysis in International Perspective* (Cambridge, 2007).

<sup>75</sup> *Prescription Drug Trends: A Chartbook Update* (Kaiser Family Foundation, 2001).

<sup>76</sup> E. R. Berndt, ‘The United States’ Experience with Direct-to-Consumer Advertising of prescription Drugs: What Have We learned?’ in F. A. Sloan and C-R. Hsieh (eds), *Pharmaceutical Innovation: Incentives, Competition, and Cost-Benefit Analysis in International Perspective* (Cambridge, 2007). This reports that although direct-to-consumer advertising of prescription medicines had grown rapidly, it was nevertheless only 15% of total marketing expenditure in 2000-2003.

process, hence reducing cost and allowing attention to be focused on those therapies most likely to be successful. The HTA assessment body<sup>77</sup> would also be involved at this earlier stage to enable faster assessment of clinical and cost-effectiveness, on the basis that ongoing post-marketing assessment could continue with the assistance of real-world data.

Every step in the drug development pathway is likely to be scrutinized. Prof Sir Michael Rawlins has proposed all steps should be tested against two criteria: is there a clear evidence-base to support the continuing inclusion of the measure in the requirements; and does each regulatory requirement offer value for money?<sup>78</sup> The outcome might be a different path for different product types. The Academy of Medical Sciences has recently noted possibilities for alternative safety testing that may stem from advances in transcriptomics, proteomics, metabolomics, biomarkers, imaging, mathematical modelling, and genomics, but also the need for full collaboration and sharing of data by companies.<sup>79</sup>

Thirdly, more radical approaches could be taken to decision-making on risk issues. Regulatory decisions could be made the responsibility of manufacturers, as opposed to public agencies. Seen from the perspective of all product regulatory systems, the medicines system is in fact anomalous in requiring all essential decisions to be taken by public authorities. Authorisation of marketing is the ultimate responsibility of manufacturers for medical devices, machinery, motor vehicles, cosmetics, general consumer products, even though some auditing or approvals are required from public bodies for products that have higher risks. Such an approach is in line with governmental policy on a risk-based approach towards regulation and enforcement. It would also not be inconsistent with future increased emphasis on post-marketing systems as a major mechanism in monitoring safety. It is interesting that the risk-based approach towards regulation of medical devices leads to very much shorter timescales for product development, and hence much lower costs and constantly evolving innovation of new products.

A fourth possible approach to reducing cost and time in product development would be to shift the balance of regulatory controls from *ex ante* to *ex post* mechanisms. The development of *ex post* controls for all consumer product types has in fact been a feature of developments over the past 15 years, such as for general consumer products<sup>80</sup> and now for all products within the EU's 'New Approach' system.<sup>81</sup> For medicines, the

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<sup>77</sup> HTA in the UK is carried out by the National Institute for Clinical Excellence (NICE).

<sup>78</sup> M. D. Rawlins, 'Cutting the Cost of Drug Development?' *Nature* 3 (April 2004), 360.

<sup>79</sup> *Safer Medicines: A report from the Academy of Medical Sciences FORUM* (Academy of Medical Sciences, 2005).

<sup>80</sup> Directive 2001/95 on general product safety evidenced a conscious shift towards strengthening post-marketing surveillance and recall systems.

<sup>81</sup> CERTIF 2005-16 Rev. 2: Note to the Senior Officials Group on Standardisation and Conformity Assessment Policy: Elements for a horizontal legislative approach to technical harmonisation, 23.02.2006. draft Instrument on the EU New Approach, N560-1 EN, 6 September 2006. The Commission has recently mooted that the cosmetics legislation should be amended to include elements of the 'New Approach' system, in particular through "shifting the focus from detailed regulation of individual substances to tighter checks on products on the market, based on the manufacturer's responsibility plus improved technical documentation which would allow better control of the safety of the products on the market": Public

pharmacovigilance system has expanded from the 1990s, followed more recently by ‘medical device vigilance’. Vigilance systems are also being expanded holistically, by requiring all stakeholders to act collaboratively in reporting and assessing adverse events, and taking appropriate action, on an ongoing basis.

A crucial change from the safety perspective would be earlier ‘conditional licensing’ of new drugs.<sup>82</sup> Cooksey proposes that conditional licensing should apply at an earlier stage in the drug development pathway.<sup>83</sup> Earlier licensing would be undertaken on the basis that developments in information technology (ICT) would enable systematic pilot studies and review of drugs in real patient populations, rather than in controlled trial settings. Industry argues that the authorities’ demands for more safety data from clinical trials delayed patient access to medicines and produced no significant new information that would answer safety questions.<sup>84</sup>

Two major assumptions underlie the Cooksey approach. First, the ICT systems would in fact work and produce reliable contemporary data when required. The track record for large government-run ICT computer systems is not encouraging in this respect.<sup>85</sup> Secondly, the necessary change in the regulatory legislation could only be made if EU and possibly global partners were persuaded to do so. There would need to be a significant shift in EU and global legislation, through enhancing reliance on post-marketing pharmacovigilance, underpinned by scientific and public acceptance of the justification for earlier marketing approval, and that the system will not entail a lowering in the controls or standard of safety.

However, the option of shifting the emphasis from *ex ante* to *ex post* in safety regulation would require considerable change in public attitude to risk in relation to medicines and their regulation.

## VII. Safety of medicines: the mismatch between criteria and perception

Scientific reality is that no medicinal product is ‘safe’. Medicines are in this respect unusual amongst widely-used consumer products, since their use will always give rise to a level and a range of adverse reactions in the user population.

It is recognised that the evaluation of whether a medicine is sufficiently safe to be publicly available involves the exercise of judgment, based on an evaluation of risks and benefits:

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Consultation Paper on the Simplification of Cosmetics Directive 76/768/EEC, [http://ec.europa.eu/enterprise/cosmetics/doc/simpl\\_consult\\_doc\\_en.pdf](http://ec.europa.eu/enterprise/cosmetics/doc/simpl_consult_doc_en.pdf). This introduced the prospect of ‘cosmetovigilance’!

<sup>82</sup> Also recommended in *Safer Medicines: A report from the Academy of Medical Sciences FORUM* (Academy of Medical Sciences, 2005).

<sup>83</sup> e.g. at the end of Phase II testing, rather than at Phase III as currently.

<sup>84</sup> A Jack, ‘Pharma bosses call for faster approval of new medicines’, *Financial Times*, July 4, 2007.

<sup>85</sup> ‘NHS computer system ‘will not work’ PublicServantDaily, February 13, 2007.

“... there is no absolute standard of safety. Very few drugs are entirely free from the risk of inducing adverse side effects in some patients. The question must always be whether the degree of risk is sufficiently low to be acceptable, and this cannot be addressed without an appreciation of the benefits to be gained from taking a risk of that degree.”<sup>86</sup>

This safety evaluation is undertaken by medical and scientific experts. The level of expertise deployed within Europe is very high: employees of the European Medicines Agency and of leading Member State agencies are highly qualified, very experienced and impartial, and the committees involved comprise leading private sector physicians, surgeons, toxicologists and other specialists.

However, perception and political considerations of maintaining confidence in the system can also influence decisions. Safety decisions are ultimately taken by the European Commission under the EU system and by Ministers in UK (and other Member States), on the advice of the expert agencies and committees, so political considerations may influence decisions.<sup>87</sup> There is little public understanding that the safety of medicines involves complex and sophisticated risk-benefit decisions. It is argued that there has not been enough public education and discussion on the meaning of safety, on the processes that are used to regulate it, and on the costs and benefits involved.<sup>88</sup> Accordingly, there is inevitable lack of public involvement in the evaluative processes and an inherent democratic deficit in the acceptance of the expert decisions that are taken. Such fundamental misconception and lack of transparency give rise to a crisis of confidence in the regulatory system whenever reports of potentially serious adverse reactions occur.<sup>89</sup>

Medicines safety is a prime example of the observation that risk and safety have become politicised terms.<sup>90</sup> The political response to bad news is often to introduce more legislation that increases regulation. Many examples can be cited in the healthcare and product fields, starting with Thalidomide leading directly to the introduction of medicines regulation in the 1960s. The BSE crisis of the 1980s led to over 10 years of legislative

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<sup>86</sup> *Organon Laboratories Limited v. Department of Health and Social Security* [1990] 2 CMLR 49 CA, at 78 per Mustill LJ.

<sup>87</sup> Legally, licensing criteria may be based on ‘safety’ but since this is a subjective criterion, there is room for considerable discretion, and matters of maintaining public safety may be legitimate. Although rare, a politically motivated decision was the initial refusal of Kenneth Clark MP when Secretary of State for Health to approve the injectable contraceptive Depo-Provera in 1983. A recent example is that regulators are reported as taking an increasingly tough stance to approving new products in response to a series of safety scares: M. Barriaux, ‘Drug companies scarred by US watchdog’s tougher stance’, *The Guardian*, August 13, 2007.

<sup>88</sup> The US medical profession has recently called for greater communication by the FDA to the public on how the drug approval process works and what FDA review entails, *The Future of Drug Safety: Promoting and Protecting the Health of the Public* (Institute of Medicine of the National Academies, Washington, September 2006).

<sup>89</sup> Notable recent examples include the ‘pill scare’ of 1995 on early reports of the incomplete results of clinical trials on oral contraceptive products, which led to an increase in abortions, and subsequently unaccepted allegations of the lack of safety of MMR vaccines, in which the subsequent fall in child vaccinations led to an increase in measles.

<sup>90</sup> R. Baldwin, C. Scott and C. Hood, *A Reader on Regulation* (Oxford, 1998), 35.

activity in reform of EU food law.<sup>91</sup> The Bristol and Alder Hey organs scandals led to new regulatory frameworks.<sup>92</sup> Shipman is producing a new regulatory framework for all professionals in healthcare.<sup>93</sup> In relation to the product regulatory requirements, a recent comment was: “It is widely argued that Government regulatory standards had become increasingly stringent, reflecting greater public concern about safety issues.”<sup>94</sup> The principal EU medicines regulator has called for *slower* drug release times for new medicines and improved independent monitoring.<sup>95</sup> This comes at a price.

A recent example arose in a clinical trial. In reporting the injury of six healthy volunteers in the clinical trial of TGN1412 in 2006, the media ran shocking pictures of six (formerly) healthy volunteers, one of whom was referred to as looking like an ‘Elephant Man’. Although the Report of the Duff committee Report was at pains to note that the adverse reactions suffered were unprecedented, and that the aim was to optimise the safety of first-in-man trials “without stifling innovation or raising unnecessary barriers to the development of useful new medicines”, its main recommendations that first trials in man of some substances should be done in a single subject will inevitably prolong the product development timescale.<sup>96</sup> The Duff recommendations are entirely logical from the safety perspective, but it may be reflected that the additional costs of including more human subjects in clinical trials so as to detect one extra ADR, depending on its incidence, were calculated,<sup>97</sup> on 1984 data, to be at least \$4 million if the ADR had an incidence of 1:100,000, and the point was made that such extra cost spent on drug X reduced the budget for drug Y.<sup>98</sup>

Scientifically, the clinical trial of TGN1412 was an experiment involving risk, undertaken on humans who gave informed consent. As the US Institute of Medicine has said, post-marketing withdrawal of a drug does not necessarily represent a failure:<sup>99</sup> it shows that the system is working. The real questions are: can we design a better system, should the system have worked more quickly, and have we put in place adequate care and compensation for any injured research subject?<sup>100</sup>

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<sup>91</sup> Commission of the European Communities, *White Paper on Food Safety* COM (1999) 719 final, 12 January 2000.

<sup>92</sup> Human Tissue Act 2004: see *Explanatory Notes to Human Tissue Act* (HM Stationery office, 2004).

<sup>93</sup> *Shipman Inquiry: Safeguarding patients – lessons from the past, proposals for the future*, The Stationery office, 2004. R Smith, ‘A remedy for the soul of medicine’ (*guardian*, 25 October 2006).

<sup>94</sup> Sir D. Cooksey, *A review of UK health research funding* (HM Treasury, December 2006) p 42.

<sup>95</sup> Reuters, 28 January 2005 quoting Thomas Lonngren, Executive Director of the European Medicines Agency.

<sup>96</sup> G. Duff et al, *Expert Scientific Group on Phase One Clinical Trials: Final Report* (The Stationery Office, 30 November 2006). The recommendations were incorporated into the ABPI Guidelines on Phase I clinical trials: ABPI Press release, August 16, 2007.

<sup>97</sup> See summary of the data in J. Silcock and C. Pritchard, *To Heal and Harm: An economic view of drug safety* (Office of Health Economics, 2003).

<sup>98</sup> G. Pedroni, ‘Drugs and adverse reactions: an economic view of a medical problem’, *Social science and Medicine* 18:1 73-182.

<sup>99</sup> *The Future of Drug Safety: Promoting and Protecting the Health of the Public* (Institute of Medicine of the National Academies, Washington, September 2006).

<sup>100</sup> It appears that the level of insurance held by the sponsor of the TNG1412 trial may be insufficient to cover the potential compensations: personal communication.

There is a strong argument that the general public perception is that all licensed medicines are absolutely safe.<sup>101</sup> Recent research commissioned by the UK regulator<sup>102</sup> found that the general public has a confidence in the safety of medicines and medical devices that seems to stem from overall confidence in doctors, and in their ability to weigh up the risks and benefits.<sup>103</sup> The participants found ‘risk’ difficult to conceptualise, their general feeling being that if you can buy the product, you can assume it is safe.<sup>104</sup> In this survey, around half of British adults in fact said they do know about the risks and side effects of medicines, whilst 4 in 10 said this about medical devices. Two-thirds of respondents said they had confidence in the way that both medicines and medical devices are regulated.<sup>105</sup> Public perception may be beginning to be affected by exposure to the expensive marketing of the government’s public health strategy of targeting certain diseases, notably a reduction in obesity and smoking, which inherently involve confronting individuals with a greater sense of personal responsibility for their actions and their consequences.<sup>106</sup> However, it is suggested that, as the TGN 1412, Vioxx and numerous other examples show, public perception does not accommodate the (real) risk that *serious* adverse reactions are in fact possible and unavoidable.

*Public* concern about the safety of medicines and the reliability of the regulatory system should be contrasted with *individual* decisions by patients when faced with therapeutic choices, hopefully on an informed basis. In the latter situation, the Academy of Medical Sciences has underlined that

“.. it must never be forgotten that it is the balance between efficacy and safety that is most important. Patients will accept quite severe drug toxicity for potential benefit in deadly diseases such as cancer and HIV; conversely drugs intended for less serious conditions such as the treatment of obesity or mild allergy must be very safe and well tolerated.”<sup>107</sup>

The key here is probably that if patients are seriously ill, they will accept even serious risks that are warned about before treatment. However, serious adverse occurrences that occur after treatment for minor conditions give rise to concern, certainly if they are not

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<sup>101</sup> In a MORI poll in 2002 61% of the public questioned expected science to guarantee that a medicine is safe National Audit Office: *Safety, Quality, Efficacy: Regulating Medicines in the UK* (London, 2003), para. 3.30.

<sup>102</sup> The Medicines and Healthcare products Regulatory Agency (MHRA).

<sup>103</sup> *Risks and Benefits of Medicines and Medical Devices – Perceptions, Communication & Regulation*, Ipsos MORI, November 2006.

<sup>104</sup> *Ibid.*

<sup>105</sup> *Ibid.*

<sup>106</sup> White Paper *Choosing health: making healthier choices easier*, CM6374, 19 November 2004.

<sup>107</sup> *Safer Medicines: A report from the Academy of Medical Sciences FORUM* (Academy of Medical Sciences, 2005), para 3.1. The US Institute of Medicine regards safety (defined as avoiding injuries to patients from the care that is intended to help them) as the first of six dimensions of quality: Committee on Quality of Health Care, Institute of Medicine, *Crossing the quality chasm: a new health system for the 21<sup>st</sup> century* (National Academy Press, Washington, 2001). This approach was adopted in D Wanless, *Securing our Future Health: Taking a Long-Term View, An Interim Report*, (HM Treasury, November 2001), para 13.36. [http://www.hm-treasury.gov.uk/consultations\\_and\\_legislation/wanless/consult\\_wanless\\_interimrep.cfm](http://www.hm-treasury.gov.uk/consultations_and_legislation/wanless/consult_wanless_interimrep.cfm).

warned about but maybe even if a warning is communicated. There is inevitably much emphasis in both medical treatment and in product regulation on communication of accurate information. In addition, issues of proportionality between action and consequence seem to apply.

### **VIII. Conclusions**

The conclusions of the above analysis are as follows. Whilst regulatory systems for medicines are extensive, they are costly and take a long time. This delays the flow of new products and restricts innovation because of the high cost barrier. Pre-marketing evaluation is of predictive value only, and only capable of identifying a high incidence of adverse reactions. A continuous dynamic reassessment of safety is required, which requires a sophisticated and expensive pharmacovigilance system. As costs rise, the need for payers to ensure value for money grows, but the requirement to produce data for HTA imposes further cost and is insufficiently integrated into the safety regulatory system. Attempts are being made to improve integration of requirements, so as to minimise overall costs.

Various factors are increasing the demand for innovative medicines and also their research and development costs. The economic consequences raise serious issues over sustainability, affordability and availability of health systems and therapeutic products. Some drastic measures may need to be taken, such as shifting the balance of regulatory controls from historical reliance on extensive pre-marketing requirements towards continuous post-marketing vigilance, and hence to permitting earlier licensing decisions that would lead to a significant reduction in costs. Such a solution is logical given the limited safety data that is produced under the present pre-marketing evaluation system.

However, some citizens will continue to be injured by medicines that are manufactured, prescribed and taken in good faith: a level of unpredictable adverse reactions is unavoidable. Zero risk is unattainable for therapeutic medicines. There is a fault line between expert and public understanding of the safety that can be expected of medicines and of the regulatory system. The public expects zero risk, but industry, regulators and politicians know that this is unachievable. If earlier licensing decisions are taken, this would provide a greater and swifter flow of new products to treat disease, but may also produce an increase in injuries. The vigilance system should identify problems swiftly, and hence limit overall exposure. But it is questionable whether public confidence could be maintained in such a system, given current misconceptions of the realities of the real incidence of adverse events, and of what constitutes acceptable risk. On the other hand, will public reaction change when patients are told ‘we could develop a drug that would cure you but you cannot have it because people are generally not willing to accept that some of them may get hurt and so the drug is too expensive to develop’?

These conflicts involve opposition between powerful forces. There is a conflict of policy goals between innovation (for health and economic growth) and the need to limit costs so

as to spread constrained resources on an equitable basis (rationing).<sup>108</sup> How can the challenge be managed? Is public perception capable of being influenced by economic realities? Or will the influence of the popular media continue to mean that fear of dramatic adverse events will outweigh rational considerations of reality?

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<sup>108</sup> F. A. Sloan and C-R. Hsieh (eds), *Pharmaceutical Innovation: Incentives, Competition, and Cost-Benefit Analysis in International Perspective* (Cambridge, 2007).