



Patients' Needs, Medicines Innovation and the Global Public's Interests

Achieving affordable universal care, enhanced public health and sustained investment in better treatments

Summary

- In 1900 world-wide average life expectancy at birth was no more than 40 years. Today it is about 70 years for men and women combined. Advances in medicine, surgery and medicines (ranging from antibiotics and anti-virals through to vaccines against diseases like pneumonia, hepatitis and HPV and drugs that reduce stroke and heart disease risks) have accounted for about half the improvements in health achieved since 1950.
- As life expectancy rises and birth rates fall people's values alter, and societies go through profound changes. Providing universal access to health care typically becomes an increased priority, while relationships between health care professionals and health service users become less directive and more questioning. The influence of patients and patient organisations on health policies and practices tends to increase. They develop enhanced roles in areas such as research and clinical trial governance and health technology assessment.
- There are important opportunities for pharmaceutical and other innovations to contribute further to improving the global public's health in areas ranging from the diagnosis, prevention and treatment of tropical infections through to the management of the common non-communicable conditions. There also are over 6,000 rare diseases that collectively affect 100 million people in the 'developed' OECD nations and up to 500 million world-wide. Many are currently difficult to diagnose and lack definitive treatments.
- By 2050 further progress towards universal health care coverage and delivery, combined with ongoing health technology innovation, could virtually eliminate disease related child and working age adult deaths. It should also support active ageing in ways that cannot be achieved by life style changes alone. Realising such gains will depend on the political will needed to provide better health care combined with continuing public and private investment in high risk research in spheres such as medicines development.
- Patients and patient organisations have important interests in both funding innovation and assuring access to effective treatments after they have been developed. Following concerns about the cost of and access to new HIV medicines in the 1990s, some commentators question the value of intellectual property rights (IPRs) such as pharmaceutical patents because they increase the prices of recent therapeutic developments. But without intellectual property rights private investment in high risk biomedical research would be very unlikely to take place. This would almost certainly have negative 'knock on' effects on public funding for fundamental research.



An issue guide for medicine users and patient representatives

- There is little realistic possibility that alternatives such as offering State or private donor backed prizes for developing therapeutic innovations could ever fully substitute for patents and regulatory data exclusivity based approaches to maintaining private investment in biopharmaceutical innovation. But initiatives like the recently proposed Health Impact Fund, Advanced Market Commitments and the examples set by organisations such as the Gates Foundation may usefully augment IPR based provisions.
- If access to new ‘essential’ medicines is to be enhanced in ways that do not undermine innovative capacity, well designed national and international purchasing arrangements backed by differential pricing strategies are likely to play key roles. There is a case for the global extension of the periods of intellectual property protection available to health technology innovators, balanced by increased minimal cost supply obligations in poor communities.
- Differential pricing between and within markets should allow innovators to enhance access to IP protected products without losing income and so reducing investment capacity. However, inappropriate movements of medicines between markets and resentments in higher price areas can make such schemes difficult to implement. International agreements about the principles and criteria on which differential pricing and allied approaches (including voluntary IPR and licence sharing) might in future enhance their viability.
- Patient organisations should seek to clarify the definitions of essential medicines and public health emergencies. This could help protect world-wide public interests and prevent the inappropriate use of powers like compulsory medicines licensing.
- There are uncertainties as to how robust intellectual property rights should be in order to sustain ongoing investments in high risk research. Individuals and organisations seeking to defend patient and public interests in maintaining the conditions needed for continuing innovation may be exposed to charges that they are defending commercial rather than health interests. Yet under-investing in research for the future would harm the interests of both patients and the global public. Lives lost and years of disability caused because innovations have been delayed can never be regained.
- Measures developed by health economists to guide short term health resource allocation decisions under-estimate the long term society-wide value derived from medicinal and allied innovations. Because of the economics of their development and supply new medicines typically become – after the expiry of IP rights – low cost resources for long periods of time. This is a powerful reason for continuing to invest in innovative research in order to improve established treatments and create fundamentally new opportunities for the relief of suffering, the elimination of diseases and the enhancement of life.

This report was researched and written by Mari Lundeby-Grepstad, David Tordrup of LSE and Tina Craig and David Taylor of UCL School of Pharmacy

The LSE research undertaken was funded by the International Alliance of Patients’ Organizations

Professor Taylor is accountable for the content of this document and for any errors it contains

Innovations can encompass entirely new inventions or involve new ways of using an existing technology in a more productive and/or more cost effective manner than was previously possible. In health care valuable innovations can relate to anything from fresh approaches to the use of professional time through to the introduction of new surgical techniques or original communication methods. Advances in social care and psychological support can also enhance health outcomes.

However, this report is primarily concerned with understanding patient interests in medicines and related forms of biomedical innovation, and the extent to which intellectual property rights such as those conferred by patents or via regulatory data protection serve to improve public health now and in the future.

Introduction

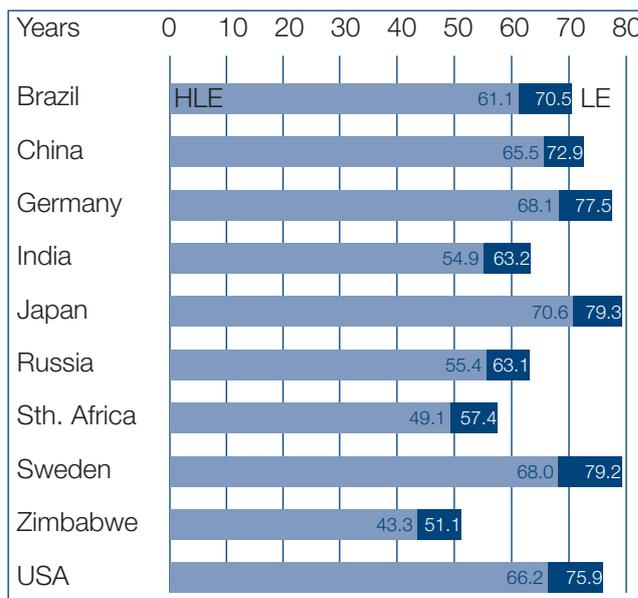
Because of scientific, industrial and agricultural innovation, the twentieth century saw major world-wide improvements in human health and life expectancy. For instance, in 1900 in Western Europe – the then richest part of the world – life expectancy at birth was not yet 50 years. But by the end of the 1940s, before the antibiotic revolution had made its full impact and despite the impacts of World War II, it had risen to 60 years. This was due in large part to declines in child and infant mortality associated with enhanced nutrition and improved living conditions.

Today average life expectancy is between 70 and 80 years in countries ranging from the US and China to Germany, Turkey, Thailand and Brazil. Since the 1980s much the additional health gain achieved in more affluent societies has occurred amongst older people. As infectious diseases have become better controlled the central health challenges facing mature economies have shifted away from reducing infant, child and young adult mortality towards preventing and treating later life conditions. However, it is important to record that as communities become richer and their members on average older the rates of mortality and severe disability caused by non-communicable conditions like vascular diseases often fall in age specific terms (WHO, 2012). Interventions which protect people from infections early in their lives and from events like heart attacks and strokes in mid-life also promote better health amongst people in their 60s, 70s and 80s.

Fundamental advances have also been made in the poorer parts of Asia and Africa. In India, for example, average life expectancy at birth was in 1950 still less than 40 years. It is now over 65 years for men and women combined. Throughout the modern world factors such as tobacco smoking, hypertension and problems associated with excessive food intake have largely replaced a lack of clean water and under-nutrition as the main causes of avoidable ill health. As Figure 1 illustrates, even in those sub-Saharan African countries that – like South Africa and Nigeria – have been severely affected by HIV and are still challenged by problems like TB, malaria and childhood diarrhoea, average life expectancy at birth is now about a decade longer than it was in Western Europe in 1900.

Such successes deserve celebration by patients and the public world-wide. Sustainable health improvement is now critically dependent on maintaining the material and social environments needed to protect physical and mental health and wellbeing. Reducing pollution levels and avoiding catastrophic climate change, while also further increasing energy and food production, are today amongst the most critical global public health tasks. But awareness of this should not draw attention away from that fact that new medicines and vaccines, along with developments in areas ranging from surgery to nursing, have been responsible for about half the global health progress achieved since the end of World War II. If therapeutic innovation continues, pharmaceutical

Figure 1: Life expectancy (LE) and healthy life expectancy (HLE), men, selected countries, 2010.



Source: Saloman et al, 2012.

products will contribute even more to health and wellbeing as the twenty first century unfolds.

Against this background this UCL School of Pharmacy report, which was originally commissioned by the International Alliance of Patients' Organizations (IAPO),¹ explores questions relating to the benefits for individuals and communities that further investment in biopharmaceutical and related forms of innovation by research based companies, Universities and other public and private institutions will generate in coming decades. It examines factors relating to public interests in the financing of ongoing innovation² and the role of intellectual property rights (IPRs – see Box 1) in facilitating the the funding of research on better treatments for conditions that as yet cannot be satisfactorily prevented, alleviated or cured. These include, for example, infections like Dengue fever and Chagas Disease (American trypanosomiasis) and NCDs such as cancers, the musculoskeletal disorders and neurological conditions like Alzheimer's disease and multiple sclerosis.

The advocates of intellectual property provisions such as patents and the temporary monopolies they award see them as an essential element in the infrastructure that underpins the global financing of medical and pharmaceutical research. By contrast, critics say that they inhibit competition and free trade and deny poorer people low cost access to medicines and other goods that they need. It was, for example, recently suggested by

1 The IAPO brief was to develop a paper to equip patient advocates with an understanding of the information, issues, challenges and opportunities appertaining to innovation.

2 Over the next few decades genetic and other biomedical research undertaken in areas such as cancer will open the way to a range of innovative technologies relevant to areas ranging from food and energy production through to pollution control. This will amplify the future public health and welfare benefits derived from pharmaceutical research.

Box 1. Types of innovation and intellectual property protection

An innovation may be an entirely new invention or a new way of using an existing technology. It can also involve improving existing technologies or combining two or more different technologies in freshly productive ways. Health technologies include drug treatments, medical devices, diagnostic tests, clinical interventions (ranging from psychotherapeutic methods to surgical operations) and preventive techniques. Innovations encompass anything from the introduction of new ways of countering ancient problems like tuberculosis or cancer to offsetting anticipated challenges, like the emergence of new types of drug resistant bacteria and viruses. They can also allow established products and services to be made or delivered in less costly ways.

The forms of intellectual property protection (IPP) or right (IPR) available range from **trademarks** such as brand names and logos (that classically serve to mark out products coming from trusted makers) through to **registered** or **unregistered designs**, **copyrights** and **patents** of various types. For example, a patent can be for a manufacturing process or for a finished product. In some countries, including the US, **trade secrets** can also be legally protected.

Copyrights and allied provisions protect the expression of ideas and concepts, whereas patents permit limited periods of exclusive exploitation of innovative ideas and concepts themselves. In highly regulated areas such as the pharmaceutical sector **regulatory data protection** (RDP – also known as regulatory data exclusivity) may play an additional role in sustaining investment. This for limited periods stops applicants who want to market ‘follow on’ versions of products

that are already being supplied by the original innovator from using the research findings submitted by the latter to obtain a new marketing authorisation. RDP does not, however, prevent anyone from providing original clinical trial data in support of a marketing application.

Intellectual property right durations vary between jurisdictions and by the type of IP involved. Trademarks, for instance, normally endure indefinitely, and an author, artist or musician can currently enjoy copyright protection throughout his or her lifetime plus (in settings such as the US and the EU) another 75 years. By contrast, design rights are normally granted for just a few years, while patent protection terms for medicines in much of the world now run for 20 years. About half of this time has typically expired before pharmaceutical products are cleared for market entry.

There is no ‘objective’ way of determining from a public interest perspective precisely how long a patent or any other IP term should last, or how much a society ought to invest in innovative research. It is important to stress that IPRs exist alongside other factors such as medicines price control schemes, health service purchasing policies and taxation systems that can also encourage or discourage research investment. In practice policy makers must pragmatically balance these variables in the pursuit of their immediate and long term health and other socio-economic goals. It is suggested here that communities often devote too little of their resources to improving the future, as opposed to consuming in the present. But this value judgement cannot be ‘proved’ or ‘disproved’ by economic or any other form of ‘scientific’ analysis.

a group of US based economists that the patent system ‘arose as a way to limit the power of [medieval] royalty to award [unlimited and arbitrary] monopolies to favoured individuals; but now its primary effect is to encourage large but stagnant incumbent firms to block innovation’ (Boldrin and Levine, 2013). At worst, it could be argued, intellectual property laws have served to protect the ability of Americans and Europeans to continue enjoying wealthier and healthier life styles than their counter parts in the ex-colonies of the world.

There is no ‘scientific’ way of judging which (if either) of these two polarised sets of views is objectively correct, in either economic or ethical terms. There are very probably elements of truth in both. The judgement offered here is that without both physical and intellectual property rights welfare promoting co-operation between people with conflicting interests is frequently if not always impossible. But any right can be abused if it is not tempered by humanitarian values and counter-balancing duties and requirements.

In the case of pharmaceuticals these range from the obligations placed on those marketing new medicines to publish information about their innovations and to

comply with safety testing requirements, through to their responsibilities to contribute via taxation to the support of health care systems. Universal health coverage (UHC) systems involving both public and private providers can, when appropriately funded, organised and regulated, share risks and costs and assure access to health services and products via efficient purchasing systems and care delivery structures.

The existence in many countries of drug price and/or profit controls limits the value of IP rights. It is argued here that patents and allied provisions such as ‘regulatory data exclusivity’ (see again Box 1) will throughout the foreseeable future continue to have an important role to play in the financing of pharmaceutical and other forms of innovation. Yet this conclusion should not obscure the need to recognise and strengthen national and international commitments to securing individuals’ rights to life and to medicines as and when they are needed for survival or for the relief of major suffering.

Cancer care is an example of an area where in future there could be medicines affordability problems comparable with those that in the past affected HIV medicines supply (IMS, 2013). At present many sophisticated anticancer

medicines are palliative rather than curative, and are difficult to use to optimum effect in the absence of advanced diagnostic and treatment facilities. There is therefore a case for arguing that in the immediate future resources should be most urgently focused on preventive programmes such as HPV vaccination and tobacco use cessation coupled with the improved alleviation of cancer related pain in less affluent populations.

But as curative treatments continue to improve it would be for many people unacceptable if poor patients were routinely denied life saving treatments commonly available in affluent communities. To avoid undesirable interventions like the use of compulsory licensing in ways that would undermine investment in continuing innovation it will be in the global public's interest to find equitable ways of ensuring universal affordable access to essential anti-cancer medicines without sacrificing innovators' intellectual property rights. Viable ways forward are likely to involve combining systematic approaches to differential pricing with the further development of national health care systems and where required international treatment purchasing support mechanisms.

Patient led care and innovation

This analysis reviews some of the key steps in medicines innovation achieved to date, and highlights patient and public needs for further therapeutic improvements. It also considers medicines as high technology products which are costly and risky to develop, but once marketed are often relatively inexpensive to copy. This underlying reality explains many of the controversies and conflicts presently linked to pharmaceutical pricing, supply and access.

This report then goes on to outline the origins of intellectual property provisions such as patents, and to explore why research based pharmaceutical producers are unusually reliant on the temporary shielding from unregulated free market forces that intellectual property rights provide. It briefly examines the reasons why patient involvement and leadership has become increasingly important in health sector decision making and addresses a series of questions relating to innovation and IP provisions of potential interest to patients and their representatives. They include the degree to which the current IPR system adequately incentivises research into orphan conditions (see, for instance, WHO, 2006; IFPMA, 2012) and whether or not the World Trade Organisation's TRIPS (Trade-Related Aspects of Intellectual Property Rights) agreement threatens, as some fear, to deprive people living in less developed countries of supplies of low cost generic medicines.

This study concludes by offering suggestions for the future. It signposts the need rationally to balance, and where possible positively combine, the benefits of low cost access to new therapeutic innovations against the long term value to humanity of investing in research and development. In the short term there is little purpose in producing new medicines if those most in need of them cannot access either them or the professional

support required to use them to good effect. Yet to maintain investment levels providing innovations must be profitable. There is also reason to argue that both individuals and nations often under-invest in the future, while on occasions (as with established antibiotics) over-consuming in the present.

All supply limiting or cost increasing policies risk being unpopular with electorates, however great their ultimate benefits. In the final analysis intellectual property laws represent a logically coherent, market led rather than centrally directed, mechanism for 'taxing' the use of recent innovations in order to defend public interests in incentivising continuing investment in areas like medicines discovery. This serves the interests of people with presently untreatable conditions, and underpins the funding of incremental and 'step change' innovation alike. In societies that lack robust welfare systems IPRs are often blamed for restricting immediate minimal cost access to newly available treatments. Yet this should not obscure their overall value to the global community.

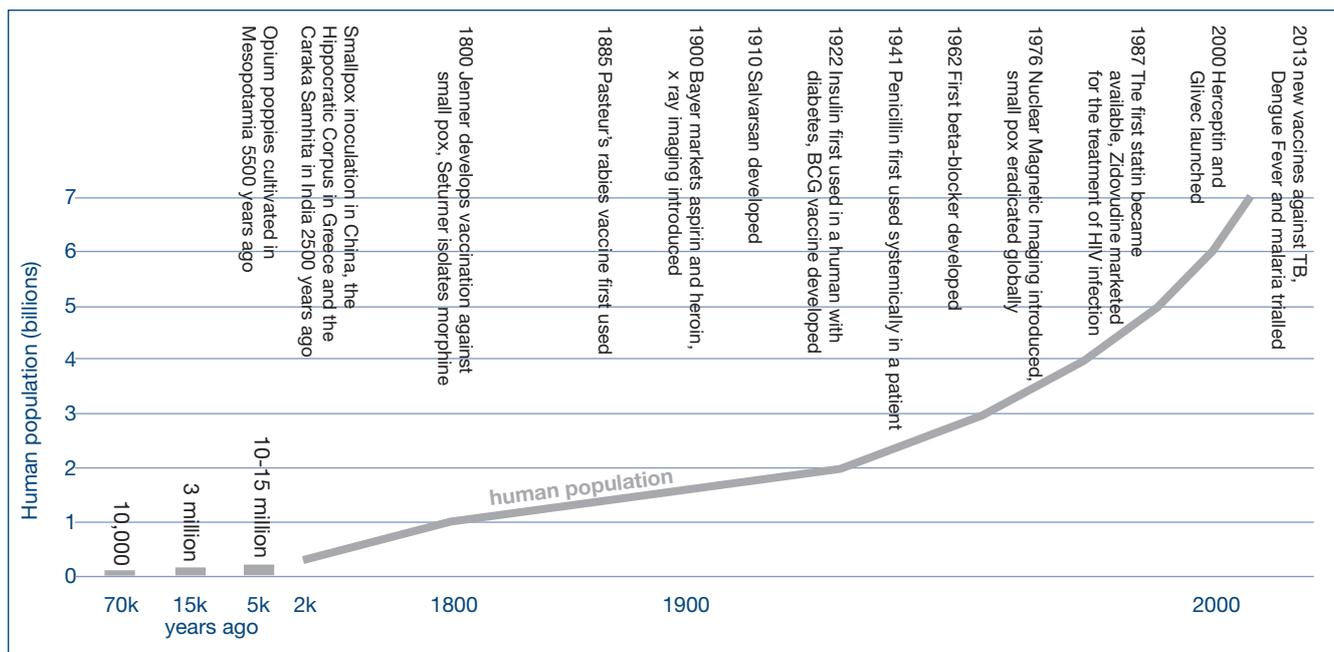
The core challenge for patients and others seeking to defend the public's best interests in both affordable medicines access and ongoing innovation is to understand the present situation in the context of local and world-wide health needs, and help societies to move forward with a balanced approach to current care delivery and ongoing medicines discovery. As already suggested, there are no absolutely 'correct' answers to many of the questions this challenge raises, just as there can be no certainty about the outcomes of high risk research projects. But patients and the wider public can expect decision makers to consider such complex issues with an open mind, and to debate ways of resolving legitimate conflicts of interest with transparency, honesty and well balanced judgement.

Why Innovate?

For all but a small fraction of the 200-250 thousand years that Homo sapiens ('wise [wo]man') has existed, people lived in small and isolated nomadic family groups. There is reason to believe that they often possessed considerable 'handed down' local knowledge of plants and minerals used as poisons and medicines. But there was no reliable way beyond word of mouth for such expertise to accumulate and be shared on a large scale. Unique understandings must often have been lost with the passing of key individuals and/or particular tribal cultures.

However, with the advent in the last 10,000 or so years of settled agricultural communities and innovations in fields such as writing and mathematics, peoples' capacities to change their lives and their environments began slowly but exponentially to increase. The establishment of larger and more inter-connected social groups opened the way to the evolution of uniquely human infections like smallpox, polio and measles. Yet it in time also led to the demographic and epidemiological transitions of the past two centuries.

Figure 2: Human population and major medical advances, from pre-history to present.



Source: the authors

With the emergence of towns and wider social systems that extended beyond family and clan structures, opportunities also arose to develop more sophisticated approaches to medicine and medicines. In parallel with the early development of monotheistic religions that served to unify and promote co-operative behaviours across most world regions, several seminal pharmacopeias and medical texts date back about 2,500 years. In the Indian context these include the Charaka Samhita and in the case of China the Huangdi Neijing, or 'Yellow Emperor's Inner Canon'. In Europe the Greek Hippocratic Corpus dates from the same time.

This last was followed shortly after the start of the Christian era by Galen's innovative contributions to medicine in the Roman Empire. The subsequent establishment of Islamic medicine and pharmacy played an important role in, for instance, further disseminating knowledge about the role of opiates in pain control across Europe and Asia, albeit that opium poppies were being cultivated over five millennia ago by Sumerians living in part of what is now modern Iraq.³

It would be beyond the scope of this analysis to attempt to describe the history of medicines development in depth. But it is important to note that:

- **before the start of the 1800s there had been relatively little increase in the repertoire of plant based treatments (which were in Europe termed Galenicals) that had been available for the previous millennium.** Yet as Figure 2 indicates, advances such as Jenner's work on smallpox vaccination (along with innovations like in 1804 the extraction of morphine from opium by the German

pharmacist Friedrich Serturmer) and Pasteur's later contributions to the 'germ theory of disease' and the introduction of immunisation for conditions other than smallpox marked the start of a major discontinuity in medicines – and human – development. Insights into the mechanisms of infection also led, through the work of nineteenth century innovators such as the Hungarian doctor Ignaz Semmelweis⁴ and the British surgeon Joseph Lister, to the introduction of life saving antiseptic practices;

- **the introduction of the first synthetic antibacterial chemotherapeutic agent (Salvarsan, an arsenic based syphilis treatment) by Paul Ehrlich and Sahachiro Hata in 1910 and the isolation in Canada of insulin by Frederick Banting and his colleagues in the early 1920s were amongst the next important steps forward.** They were followed the 1930s by the marketing of the first commercially supplied sulphonamide antibiotic, Prontosil. This was developed as a result of the work German Nobel Prize winner Gerhard Domagk and the pharmaceutical company Bayer. The latter had before World War I led innovation. It introduced products such as Heroin (diamorphine) and Aspirin (acetylsalicylic acid – arguably the most successful product in the history of pharmaceuticals) in the 1890s, at the peak of German pharmacy's scientific influence. But it was not (partly

4 Semmelweis's insights were resented by many of his medical peers. He was eventually driven out of Vienna, where his original work on the transmission of puerperal fever had been undertaken. By the early 1860s he was probably suffering from what would today be diagnosed as a severe clinical depression. In 1865, at the time Pasteur was developing the germ theory which was to give a robust scientific basis to Semmelweis's pioneering antiseptic practices, he was admitted to an Austrian asylum. He died there shortly afterwards after a beating administered by the staff. His life and death illustrate both the benefits of innovation and the risks attached to being innovative in a conservative environment.

3 Failures to provide adequate pain control for people with conditions such as cancers still represent an important problem in many poorer parts of the world, and on occasions in richer regions as well.

Box 2. Priority needs and priority medicines

In 2004 the Netherlands Ministry of Health commissioned the WHO to produce a report entitled *Priority Medicines for Europe and the World*. At the request of the European Commission this was updated in 2013, for use as a research programme planning resource. The resulting analysis highlighted the high global burdens imposed by ischaemic heart disease/CHD and stroke, and also by depressive illness. It also emphasised the need for innovative treatments for indications such as osteoarthritis, Alzheimer's disease, hearing loss, low back pain, chronic obstructive pulmonary disease (COPD), alcoholic liver disease, malaria, tuberculosis, diarrhoeal disease, pneumonia, neonatal conditions and maternal mortality reduction in settings such as rural Nigeria and India.

Such sources also stress the collective impacts of rare diseases. Robust epidemiological data are in many places lacking. Yet in aggregate rare genetic and other conditions at any one time affect approaching half a billion people across the world as a whole. Most cannot as yet be prevented, and lack definitive treatment. Illustrative examples range from Addison's Disease and Cystic Fibrosis through to, for instance, Wegener's

Granulomatosis (which involves organ damage caused by recurrent episodes of blood vessel inflammation) and Zollinger-Ellison Syndrome. The latter is characterised by extensive gastro-intestinal ulceration.

The latest edition of *Priority Medicines for Europe and the World* also underlines the importance of tropical conditions like Buruli ulcer (a necrotising infection), leprosy, African sleeping sickness (African trypanosomiasis), Guinea Worm and Yaws. Even today these infections still severely affect around a billion people.

However, there is evidence that during the past decade substantive progress has been made towards establishing public private partnerships capable of overcoming the market and governance failures which in the past led to under-investment in research aimed at generating innovative solutions to health problems commonly affecting the world's poorest populations. Further improvements in diagnostic products, medicines and vaccines are still urgently needed. But at the same time it is true to say that the term 'neglected tropical diseases' is now well on the way to becoming redundant.

because of responses to the need to protect Allied troops) until during and after World War II that the antibiotic and wider pharmaceutical revolutions gained rapid momentum. In the following decades a tide of new small molecule based medicines for common conditions ranging from hypertension to asthma, diabetes and peptic ulcer disease reached global markets; and

- **at the end of the twentieth century innovations such as Herceptin (trastuzumab, which until resistance develops is effective in about a fifth of breast cancers) and Gleevec (imatinib mesylate, used initially in the treatment of chronic myeloid leukaemia) supplied by the Swiss companies Roche and Novartis marked the beginning of another phase of (bio)pharmaceutical development.** This is likely to involve the introduction of an increasing number of what may appear in clinical terms to be relatively modest advances for rare, low volume, indications. But the accumulation of knowledge accompanying such gains ought eventually to permit step changes in the effectiveness of a wide range of treatments.

The basic answer to the question '*why continue to innovate?*' is that if the health of people across the world is to go on improving then new technologies will be required to continue the fight against the until recently neglected tropical diseases (NTDs, of which there are around 20) and other infections, and contain the emergence of resistance in areas that are presently well controlled. They are also needed to prevent or limit the progression of non-communicable (although socially mediated) diseases (NCDs) and promote healthy/active

ageing in ways that are not currently possible. Life style changes alone will not be able to deliver goals such as increasing average healthy life expectancy at birth to over 70 years, however protective physical environments and life styles become.

As discussed further in Box 2, many common conditions cannot as yet be prevented, cured or satisfactorily ameliorated. Even in areas such as pain control and the treatment of raised blood pressure – which recent studies on the global burden of disease indicate remains the largest single cause of disability and premature death world-wide – better medicines are required to address the fundamental mechanisms of ill-health (Murray et al, 2012; Coffman, 2011).

In addition to other commonly occurring conditions like type 2 diabetes, the solid cancers and the major mental illnesses, there are some 6-7 thousand 'rare' diseases that in aggregate directly affect 100 million people in the economically developed nations alone. Much of the poorer world as yet lacks the diagnostic resources needed to reveal the true global prevalence of such disorders.

Most rare (along with many common) conditions cannot as yet be prevented, and lack definitive treatments. Further, even when communicable or non-communicable disease are in theory preventable or manageable with present medicines and vaccines, existing methods of supplying and using them often fail to achieve optimal health outcomes. Innovative clinical practices and fresh approaches to 'public health oriented pharmaceutical care' are required in fields such as the primary and secondary prevention of vascular disease (WHO, 2013; Wald, 2013). More pro-active approaches to relieving

the burdens of parasitic disease via better application of existing treatments could also generate considerable additional benefit many parts of Asia and Africa (Anderson, 2013).

There are other unexploited opportunities for, for instance, further reducing the incidence of the various forms of Hepatitis together with HPV and HIV infection rates, as well as achieving more progress against ancient scourges such as malaria and TB. These last are good examples of fields where both better use of existing treatments and new ways of immunising people at risk of such illnesses or curing those who fall victim to them are urgently needed.

Necessary conditions for innovation

It is often said that necessity is the mother of invention. It is certainly the case that patient, professional and public demand for any new technology, product or service can be a valuable pre-condition for its successful introduction. But even 'life or death' needs cannot always be met – simply wanting innovations to occur brings no guarantee of delivering them. Moreover, the full utility of new technologies on occasions only becomes apparent – in health care as well as in other areas – decades after their initial introduction.

For instance, when anti-depressant medicines were first marketed in the 1950s there was only a limited public and professional awareness depressive illness, albeit there was at that time an extensive and long standing use of drugs such as barbiturate sedatives for less well defined mental distress. (Barbiturate containing medicines were also first marketed by Bayer in the early 1900s, under trade names like Veronal and Luminal.) Such observations underline the fact that centralised interventions to support the funding of innovative research can be counterproductive if they are unduly directive. IPRs such as those conferred by patents counter this hazard, in that they can be used to reward unplanned and pre-planned innovations alike.

Over and above the availability of funding for research, the existence or otherwise of the human and cultural resources required to innovate successfully is another important factor. Inquiring and free thinking minds are often vital for the successful identification and interpretation of unexpected phenomena. However, the key point to stress is that although political expressions of medicines and other development priorities can highlight the desirability of, for instance, preventing or being able to treat conditions like Alzheimer's disease, such progress may – failing serendipitous luck – only become possible when a complaint's fundamental mechanisms are sufficiently well understood to permit effective targeting.

Research advances made since the 1970s mean that improvements in therapy are becoming increasingly available in the case of cancers. But this is not yet so with much of the neurological disease burden. Individuals and organisations seeking to protect patient interests in continuing innovation need sympathetic insight into what

is likely to be scientifically possible as a next step forward at any one time, as well as a robust understanding of the progress ultimately needed.

Medicines as economic entities

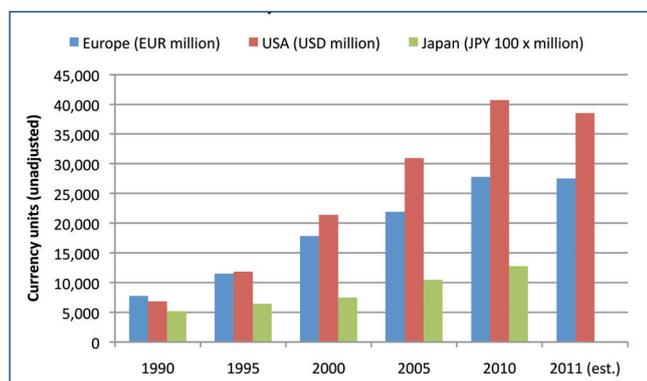
One of the reasons for misunderstandings and disagreements about issues such as the pricing of innovative medicines and the need for intellectual property rights is that although pharmaceutical products are often seen as objects of high financial, clinical and social value, the marginal cost of their production is – especially when they are being supplied in high volumes – typically low as compared with the amount of money needed to develop them. This is particularly true in the case of the 'small molecule, cell surface receptor targeted' medicines at the heart of the first great pharmaceutical revolution which took place from the start of mass penicillin use in the late 1940s through to (following pioneering academic discoveries original Japanese pharmaceutical research) the global marketing of statins for lowering lipid levels by US companies such as MSD and Pfizer in the 1990s.

An important point to emphasise in this context is that the 'value' of medicines lies not so much in the materials they contain but in the scientific challenges and material costs of their development, together with their clinical effectiveness in use.⁵ Research expenditures may reasonably be taken to include investments made in the pre-clinical development and clinical trials of not only successful products, but also innovations that fail to reach the market. Even in the case of the large molecule 'biologicals' that today account for about a half of all pharmaceutical spending in 'developed' countries, pharmaceutical products are in unit cost terms normally relatively inexpensive to supply once a marketing authorisation has been obtained and an adequate sales base established.

Hence when pharmaceutical products lose marketing exclusivity it is normally possible for generic manufacturers to offer them at a fraction (often under 10 per cent in the case of medicines with small molecule chemicals as their active pharmaceutical ingredients) of the innovators' price, albeit that when returns fall to commodity levels supply continuity can become uncertain. For observers who do not differentiate between the cost of the physical material a medicine is made up of and that of its development and end point value to its users, the existence of large differences between a generic manufacturers' price and that of the original IP protected product can seem to provide evidence of exploitation. Yet this is, barring exceptional cases, an incorrect interpretation from an informed public and patient interest viewpoint.

⁵ Substances such as gold and diamonds have been valued throughout history because of their scarcity as well as the variety of decorative and practical uses to which they can be put. But modern medicines can normally be produced relatively cheaply in large volumes. The value of such innovations relates much more to their intellectual substance than their material scarcity, a fact which traditionally minded observers can find difficult to fully accept.

Figure 3: Pharmaceutical R&D Expenditure in Europe, USA and Japan



Source: EFPIA, 2012 (data not inflation adjusted)

Related points include:

- modern medicines are high technology products, but unlike items such as aircraft engines they do not have multiple parts.** This adds further to innovators' needs for patents and/or alternatives such as regulatory data protection. The relative simplicity of pharmaceuticals often makes them easy to copy. At the same time their manufacturers are not, because of the need for regulatory approvals, easily able to modify medicines once they are on the market. In many other sectors innovative manufacturers are able to 'keep ahead of the competition' through serial re-designs;
- the effective removal of brand name and trade mark protection for innovative medicines in most OECD markets has since the 1980s further increased reliance on patents or regulatory process linked exclusivity for the revenues needed to support ongoing R&D.** In advanced pharmaceutical markets medicine producers can no longer employ brand name protection to secure 'extra-normal' earnings.⁶ This is desirable in as much as markets that are mainly reliant on brand names to differentiate between medicines with the same active ingredients can become distorted. But it once again leaves investors in pharmaceutical research and development in a vulnerable position. Taken together with other factors such phenomena help to explain why pharmaceutical research outlays may now be stabilising or falling in Europe and the US – see Figure 3; and
- the introduction of more low volume 'orphan' treatments and the expanding role of complex biological molecules in modern therapeutics has fundamentally changed the world pharmaceutical market.** Medicines for rare disorders

⁶ The term 'the generics paradox' applies to the fact that in the past innovative manufacturers were able to retain earnings by raising (or at least not dropping) the prices of their products after patent/IP expiry by virtue of the inelastic behaviour of brand-loyal prescribers (Kanavos et al, 2008). In today's conditions such strategies are not normally viable in markets such as the US and most EU member States, albeit that in less developed markets brand loyalty remains an important factor.

have by definition smaller markets than those of the 'blockbusters' of the 20th century. But this does not reduce their development costs to a commensurate degree. It may, for instance, sometimes be more expensive to run clinical trials for 'orphan' conditions than it is for more prevalent ones (Davies et al, 2012). At the same time the growing number of biological as opposed to 'chemical' medicines has altered the economics and techniques of pharmaceutical manufacturing. When it cannot be assumed that it is safe to substitute one biological product with another 'biosimilar' agent this might – for a period, at least – reduce the reliance of pharmaceutical sector innovators on IPRs. However, patient interests could be negatively impacted if this were in future to result in an undue reliance on secret production 'know how' as opposed to published science.

Given these and other considerations it might be that in coming decades (during which biopharmaceutical research and development could prove still more difficult and time consuming to conduct, and health care resources may become more limited) policy makers seeking affordable and more effective medicines will consider extending the periods of exclusive supply available to innovators. In return for permitting the latter longer periods of time to accrue returns from their investments, legislators could require extended research based industry commitments in areas such as tiered global pricing and the supply of essential treatments free or at minimal/marginal cost in very poor communities.

Such reforms might be able to serve patient interests better than existing arrangements. However, before questions relating to such options are considered in more detail this analysis briefly considers the nature and purposes of intellectual property protection.

Intellectual Property Law and Access to Treatment

The terms 'intellectual property' and 'intellectual property rights' have been in use for about a century. Yet they were not widely employed until relatively recently. Their growing utilisation underlines the fact that in the modern world patents are not the only way of providing potential innovators with an incentive to risk investing substantial resources in research and development projects that may well fail, however competent the people running them.⁷

Concepts relating to the rightful ownership of objects that individuals have made (or animals they have bred, or lands that they 'discovered') go back far in human history. The modern English term 'branding' can, for instance,

⁷ Research and development projects aimed at finding lower cost ways of making given medicines and other products are also of value to society, as well as to individuals seeking commercial advantage. Production and supply 'frugality' can and should contribute to enhancing affordability and access over the life cycle of a technology. But the failure risks involved in investing in this sort of innovation are very much lower than those associated with developing new therapies. Hence the 'price' of the capital required is lower.

be linked to the old Norse word for burning, 'brandr'. There is evidence that people inscribed animals' hides with marks denoting ownership during the early Iron Age. Subsequently artisans working in the ancient world also put personal marks on the items they fabricated. In the Roman Empire, for instance, both builders and sword smiths used early forms of trade mark.

The granting by Royal courts – and in Greek history some City States – of monopolies to permit income (and tax) generation also has a long history, as has the use of 'trade secrets' to prevent what inventors have seen as undesirable competition from copyists. In feudal China, for example, revealing the secrets of silk production or smuggling silkworms beyond the nation's borders was subject to the death penalty. For around two millennia this prevented the production of silk outside the country, and ensured high prices. Similarly, diamond polishing techniques were kept secret in India. In ancient India the Shreni – a form of early guild – in part served to protect what may today be termed manufacturing secrets.

The more immediate origins of modern intellectual property law relating to on the one hand products with practical applications such as new drugs or, say, diagnostic imaging machines and on the other artistic designs and creations like works of music date back some 500 years, to Venice in southern Europe and Britain to the north. In 1623, for instance, James 1 of England revoked all previously granted patents by introducing a new Statute of Monopolies.

Until then, Royal grants had often served to restrict competition and reward individuals who were supporters of the monarchy, rather than innovators *per se*. But as a result of modernising pressures associated with the gradual strengthening of merchant and trading interests located outside the Royal Court, the revised legislation provided for the issuing of *'letters patent and grants of privilege for the term of fourteen years or under,.... of the sole working or making of any manner of new manufactures.... to the true and first inventor'*.

Copyright provisions (that have now been extended far beyond the periods of protection provided for by patents) were first introduced at the start of the 18th century. As industrialisation and mass production gained momentum, laws to protect designs were also introduced. In the US, where individuals' rights to intellectual property were enshrined in the 1787 Constitution,⁸ a pioneering Patent Office was established in 1836. As the quotation from Abraham Lincoln's 1860 lecture *'Discoveries, Inventions and Improvements'* on the rear cover of this report illustrates, intellectual property ownership has throughout the United States' history (and from long before its economy was able to compete with those of the major European powers) been regarded as central to the support of innovation and democratically underpinned economic progress.

8 Philosophically, such thinking can be linked to the work of seventeenth theorists such as John Locke, as well as to the analyses offered by more recent American entitlement theorists such as Robert Nozick.

One important aspect of patents and allied provisions is that they demand publication. Hence although they award temporary monopolies they also promote change in a way that secrecy based approaches do not. In 1883 the Paris Convention for the Protection of Intellectual Property represented the first international attempt to co-ordinate the protection of innovator's and the global public's interests. The conclusions agreed at that time were in part revised via a meeting held in Stockholm in 1967. However, substantive progress towards harmonised world-wide arrangements has been slow. This has been because of deep seated conflicts of perceived and actual interest, coupled with an apparent lack of political appetite for leading fundamental reform.

Many commentators describe intellectual property provisions in terms of their capacity to enable successful innovators to recover the 'sunk costs' of past activities. There is some validity in this perspective. But from a public interest viewpoint the primary purpose of grants such as patents is not to provide rewards for innovations that are already available. It is rather to address concerns relating to the willingness of investors to go on putting large amounts of money into innovating for the future.

The first 'neo-medicinal' patent was granted for Epsom salts in England in 1698.⁹ But the term 'patent medicines' has until quite recently had 'snake oil' connotations that stemmed from the development of pharmacy in the United States. Despite the fact that a school of pharmacy was established in Philadelphia in as early as 1813, American 'drug sellers' were throughout the nineteenth century normally unqualified and not infrequently charlatans. In this context 'patent' or 'secret' medicines were often corrupted derivatives of traditional treatments that were branded but did not in fact enjoy patents. These 'cure alls' were in many instances both clinically ineffective and hazardous, not least because of common additives such as cocaine and/or morphine.

WHO estimates suggest that at the end of the twentieth century approaching half the world's population was still primarily dependent on traditional medicines for the day-to-day treatment of common complaints (Zhang, 1999). Despite changing public demands and attempts to improve access to allopathic (modern science based) medicines this is still likely to be broadly the case today, despite the fact that virtually all the pharmaceuticals classified as essential by the WHO are already available as generic, or at least as off-patent but branded, products.

The word 'essential' carries with it connotations of both effectiveness and suitability for low cost mass use. Medicines which can marginally improve or to a limited degree extend (but do not save) lives only when supplied as a part of a highly sophisticated health care programme should not, it can be argued, be classified as essential, especially when the service infrastructure needed to support their being taken beneficially does not exist.

9 A form of magnesium sulphate. Epsom salts have various external and internal medicinal applications. The compound is highly soluble and an early use was as 'bath salt'. Epsomite was initially extracted from a source close to the Surry town of Epsom.

Box 3. The shared determinants of private and public spending on innovation

In an ideal world the public funding of innovative research would arguably focus on areas where the incentives intended to motivate private investment are least likely to prove adequate. This should minimise the risk of harmful market failures. This has been the case in that, for instance, public money is more likely to be devoted to 'fundamental' scientific investigations, while private agencies are more oriented towards the commercialisation of new therapeutic concepts once the possibility of a viable application has been demonstrated. But in terms of research topics both public and private investors have in the past often concentrated their attention on issues of primary importance to countries at the forefront of human development, rather than the priority needs of poorer and less advanced communities.

It was perhaps assumed that the latter could use existing technologies to overcome the problems other nations had left behind them. But this is not necessarily the case. In contexts such as the development of new treatments for tropical conditions, new approaches to funding and risk sharing are now correcting such imbalances. Relevant drivers have ranged from the examples set by institutions such as the Gates Foundation and the Carter Center through to the globalisation of the world economy and the changing situation and priorities of the research based pharmaceutical industry.

However, were the support structures that encourage private spending on high risk medicines and allied innovative research initially intended to meet needs in OECD and other relatively affluent markets to in future prove inadequate to sustain investment levels, it would be unwise to assume that public expenditures will automatically replace reduced private capital and allied financial flows. Governments, like businesses, seek competitive advantage. In the context of innovation they can create and sustain the educational and other infrastructures and the social and regulatory environments required for success, using funds raised from domestic taxes. Further 'downstream', companies generate international sales through their commercial activities. This can in turn further sustain public sector revenues.

The danger for patients and the other beneficiaries of pharmaceutical innovation is that if the prospect of private profit from the supply of new medicines declines, so too in time will public investment in the discovery processes that open the way to their development. There is also a possibility that, despite the importance of public sector values, a decline in commercial ethos driven innovation will weaken the efficiency of the overall system. The key point to emphasise is that publicly and privately funded agencies have vital and mutually complementary roles to play in pharmaceutical and other science based innovative processes (Mazzucato, 2013).

Inadequacies in essential medicines supply and the lack of basic professional help needed to facilitate their effective use, coupled with problems of poverty and the social complications associated with changing patterns of health belief, make some modern day communities as vulnerable to medicines related harm as people were in nineteenth century America. The challenges they face range from having little or no access to effective treatments through to being exposed to the risks of falsified (counterfeit) and/or sub-standard products.

Some observers (in line with the comments made by Indira Ghandi at the start of the 1980s, quoted on the rear cover of this report) attribute such phenomena to the effects of intellectual property laws. But this position is very questionable. The former Prime Minister's remarks may have fairly represented the situation in which India found itself in the 1950s and early 1960s, after the departure of the British (who during their period in power had failed adequately to support Indian industrial development and local medicines supply) and the shock of the 1962 Sino-Indian conflict. Yet the fact that widespread problems relating to inadequate medicines provision have persisted after India became the world's most successful generic medicines exporter indicates that their causes – like those of inadequate health care provision more widely – are more complex than is sometimes assumed.

There is a danger that if the undesirable impacts of pharmaceutical sector IPRs are exaggerated and their

benefits under-stated, the end result will be a significant undermining of medicines research funding in both the private and public sectors (Box 3). At the same time challenges surrounding the treatment of HIV have demonstrated that on occasions a lack of affordable access to innovative as opposed to mature medicines can on occasions seriously endanger public health in poor communities that lack universal health coverage systems. As already noted, similar concerns are starting to emerge in other fields, most notably cancer care.

The significance of policy questions linked to the above is explored below with regard to the World Trade Organisation's TRIPS (Trade Related Aspects of Intellectual Property Rights) agreement, and the relevance to global patient and public interests of the flexibilities declared (in 2001) in Doha. But before this a further brief discussion of issues relating to the treatment of HIV is offered. The past weaknesses of not only pharmaceutical industry but also some governments' approaches to this area has in recent decades done much to increase patient and wider public concerns about the negative public health impacts of IPRs. The development of effective anti-HIV drugs was a triumph for research based companies and their University and other public sector partners. However, the reputational damage to the innovative pharmaceutical industry associated with HIV patients not being able to afford life saving treatment has been comparable to that inflicted by the Thalidomide tragedy of the early 1960s.

Anti-retroviral (ARV) medicines affordability

The origins of Human Immune Virus (HIV) infection lie in sub-Saharan Africa, and transfers of microbes found in apes to people via hunting. Such events almost certainly occurred many times during the course of history. But with the opening up of the African interior in the twentieth century the chance of infections spreading into the wider human population progressively increased. The first clearly identified cases of what came to be known as AIDS occurred in the United States in the early 1980s. It was at that time often seen as a disease of relatively advantaged gay men. For example, the French philosopher Michel Foucault – an occasional visitor to American West Coast sauna houses – died of it in 1984.

Initially little could be done for people with HIV, other than providing compassionate nursing care. But following the introduction of AZT (which was originally investigated as a possible anti-cancer therapy) in 1987 and the development of its use in combination with other drugs in 1992, academic and pharmaceutical industry researchers developed incrementally more effective ARV treatments. Today few individuals who have access to modern pharmaceutical care and are able to take their medicines as recommended are likely to die prematurely as a result of HIV infection.

There is also evidence that the use of HAART (highly active anti-retroviral treatment) regimens reduces HIV transmission risks. It might be that in as yet rare instances the timely use of ARV medicines has delivered effective cures. Even if the development of a vaccine remains elusive, drug based therapies employed alongside other public health interventions may – given continuing innovation sufficient to offset the challenges of acquired viral drug resistance – ultimately be capable of eliminating HIV from the world-wide human population.

The available data suggest that in substantial areas of sub-Saharan Africa up to 50 per cent of the people who could benefit from ARV therapy are now in receipt of it (see, for instance, UNAIDS 2012). In settings such as India this figure could in fact be closer (allowing for undiagnosed infections) to 25 per cent, and there are also likely to be reservoirs of poorly treated infection in countries such as China, the Russian Federation and some other parts of the former Soviet Union. Yet the overall global response to this historically new threat to human health can now be seen as successful. At no other time in history could the HIV pandemic have been so effectively and equitably contained. The rapid development of new treatments was made possible by the conditions for innovation already being in place (Box 4).

Nevertheless, the cost of patented HIV treatments has been a matter of frequent concern. At first US based activists feared that because HIV was regarded as a 'gay' disease its treatment would be neglected by both governments and pharmaceutical companies. This proved unfounded. Yet as in settings from the US White House to the towns and villages of southern India and Africa it became better understood that the disease had already spread within many less affluent communities, questions about the price of patent protected anti-HIV medicines became increasingly pressing.

By the middle to late 1990s the cost of patented HIV treatments was a central focus of attention. At \$10,000 or more per capita per annum it was acceptable in richer nations with universal health care systems. Yet even in America uninsured people, especially minority group members, were worried that they would not get access to effective care. For most individuals and families in the developing world life saving anti-retroviral treatment was clearly unaffordable.

As a result companies that had played major roles in creating the technology needed to combat AIDS became seen as the instigators of barriers to its humanitarian

Box 4. Innovative surroundings

Innovative environments are characterised by combinations of scarce resources being available, including critical masses of educated, skilled, creative and motivated people through to suitable physical environments for them to live and work in. Systems for funding research via mechanisms such as grants from public bodies along with opportunities to provide private services profitability are also important, as are open cultures which encourage new thinking and original knowledge applications. Innovative potential is closely associated with overall human development and the establishment of settings in which ideas and information can be exchanged safely, with a confident sense that individual and corporate contributions to knowledge will be fairly recognised.

Non-innovative environments may in the health care context be characterised by poor leadership that fails to prioritise treatment and service improvements, coupled with weak IT and other service infrastructures,

low public expectations and limited personal development opportunities. Poverty is a major driver of such negative variables. But above and beyond this, differences between national approaches in contexts such as regulation and IP and allied legal provisions can have significant impacts. For example, the increasing monetary and time cost of establishing clinical trials in Europe appears in recent years to have reduced the number of investigations being undertaken in the EU, if not their cost.

The existence or otherwise of major research oriented Universities is another potentially important influence on national abilities to conduct the scientific inquiries needed to underpin innovation. Patient organisations with an interest in the development of better medical and pharmaceutical treatments should arguably be aware of such factors, and able when necessary to defend public interests in the balanced support of efficient innovation.

application, largely because – it was alleged – of their uncaring use of the IPRs available to them. They were charged with being narrowly concerned with keeping the price base for their products universally high in order to maximise their ‘rich world’ incomes, even though they could have saved large numbers of lives by supplying at production cost levels in regions like sub-Saharan Africa and South Asia.

There was some truth in such allegations, albeit that the situation was more complex than is often assumed. In many very poor countries patents were not even filed, because of the lack of infrastructure needed to establish medicines production (Attaran and Gillespie-White, 2001). Supported by organisations such as Medicines Sans Frontiers (MSF), Oxfam and Health Action International (HA), countries like Brazil and South Africa moved to defend the health of their populations by granting compulsory licences for ARV medicines and/or against the threat of such interventions negotiating lower prices with their originators.

At the same time activists such as James Love of Knowledge Ecology International co-operated with Dr Yusuf Hamied of the Indian pharmaceutical company Cipla to develop a \$1 a day combination therapy. This ‘offer’ made world-wide headlines and arguably catalysed several forms of progress. Its impact has been linked with the subsequent development of the Global Fund for HIV, TB and Malaria and adoption of the Doha declaration on TRIPS and public health at the end of 2001.

Putting public health first

From a public and patient interest perspective, a key point to make in relation to the establishment of the still improving essential drug supply system for the global management of HIV is that research based pharmaceutical companies and many governments were (despite warnings) in the 1990s slow to understand the gravity of the HIV pandemic. Many public officials and industry executives seemed initially blind to the health consequences of failing to provide universally affordable treatment, and the impacts this would have on patient and public opinion. In retrospect there seems little excuse for such inadequacies. However, models of development in which ‘new’ diseases typically only became problematic as populations grew richer and aged may have created mindsets in which it was difficult to see that meeting the challenge of HIV would demand making the world’s newest medicines rapidly available in the world’s poorest and least sophisticated societies.

In the leadership vacuum that for a time ensued, pharmaceutical companies on occasions became scapegoats for the inability of the world community to take effective action. But regardless of the faults of others, the governance and direction of the research based pharmaceutical industry itself failed to meet the standards that many 21st century consumers had come to expect (Wolff, 2012). Companies’ did not always appear to have the pursuit of better global public health, via both medicines innovation and facilitating good access to essential care, as a high priority goal. Saying

in an unqualified manner that the primary responsibility of any health care related organisation is to its shareholders is in today’s environment widely regarded as unacceptable.

Patient Interests in Better Medicines and Better Health

The existence of patents and similar forms of exclusivity for innovators sometimes appears to be regarded as the root cause of people being unable to obtain essential medicines in timely and affordable ways. (See, for example, MSF, 2012.) But the view taken here is that IPRs (as opposed to factors such as poverty and a lack of the political and managerial will needed to improve health care systems) are not the fundamental cause of such supply problems. Without IPRs the development of effective anti-retroviral therapies and many other innovations would almost certainly have been slower than has in fact been the case, and there is no logical reason to believe that IP provisions such as patents are incompatible with the systems needed to assure good global access to essential treatments.

Given that new mechanisms for drug and allied product purchasing and supply are now evolving to protect the interests of the world community in better access to treatment (as is so, for instance, in the case of the GAVI Alliance with vaccines) it is important not to lose sight of parallel global public interests in investing in innovation. It is against this background that a series of questions that patients and their representatives may wish to ask are explored below. However, before this it is relevant to consider why it matters more than ever before what patients and their representatives think about medicine research and supply.

Self care in health care

Throughout history individuals have sought to care for their own health and that of their families. Yet as populations pass through demographic and epidemiological transition people living in them become increasingly informed and intellectually more able (Flynn, 2009). Such trends enhance peoples’ abilities to pursue their goals and change their relationships with authority figures such as health care professionals. As individuals in post transitional societies come to feel themselves, their children and others in and beyond their immediate communities to be entitled to long and healthy lives they become more questioning, and access to good quality health care tends to become more of a collective priority (Taylor and Bury, 2007).

At the same time health service users also become increasingly likely to reject paternalistic relationships in favour of more equal partnerships (Charles et al, 1997). Hence the demands placed on not only clinicians but also researchers, patients and patient organisations change. For example, concepts such as obtaining informed consent to medical interventions gain greater currency

(Stacey et al, 2008). Demands for the full publication of clinical trial findings similarly increase.

In addition to enhancing therapeutic dialogue at the personal level, strengthened patient participation in health and social care decision making can add systemic value. This is achieved via enabling individuals and groups to bear witness as to how power is exercised in therapeutic relationships and to promote awareness of good and bad practices. Such reforms reduce the dangers associated with institutionalised professional and other provider side interests dominating practice, research and/or policy cultures. In much the same way that unlocking closed hospital wards can reveal abuses, opening both service and research planning to challenge and debate focuses attention more clearly on the pursuit of consumer interests.

Beyond this, patient participation in areas such as research governance can contribute to the understanding of both 'objective' and 'subjective' facts (Kaye et al, 2012; FDA, 2013). For instance, the work of organisations such as the EURORDIS (Rare Diseases Europe) and other similar bodies has helped to enhance scientific understanding of disorders that due to their rarity are often poorly described in the available clinical literature (Mavris and Le Cam, 2012). Likewise in the US NORD (the National Organisation of Rare Disorders) was in large part responsible for generating the political understanding and will that led to the original 1983 Orphan Drug Act (Box 5). In the UK patient involvement in the work of NICE (now the National Institute for Health and Care Excellence) has also helped to inform approaches to valuing medicines.

Patient led understanding of the impacts of rare conditions on individuals and minorities can counter-balance crude 'greatest good for the greatest number' thinking about social justice. Even the communication of subjective experiences of particular forms of illness, disability and exclusion can contribute usefully to developing appropriate treatment and care approaches.

This is not to deny the dangers of policy being led by idiosyncratic judgements as opposed to systematically gathered and statistically validated evidence, or that there can be hazards associated with involving patients in areas such as Health Technology Assessment (Hailey and Nordwall, 2006; Bijker et al, 2009; Drummond et al, 2013). Yet provided problems such as isolated patient representatives being 'used' by sectional (professional, commercial or State) interests to legitimate inappropriate activities or decisions are guarded against, there is good reason to think that enhanced patient involvement in health care and pharmaceutical governance can make decision making more responsive to needs (see Elberse et al, 2012, and Figure 4). It is against this background that the innovation linked questions below are considered, with a view to supporting further patient led debate in relevant policy arenas.

Figure 4. Patient Involvement in Health Care and Research Governance and Policy Decisions



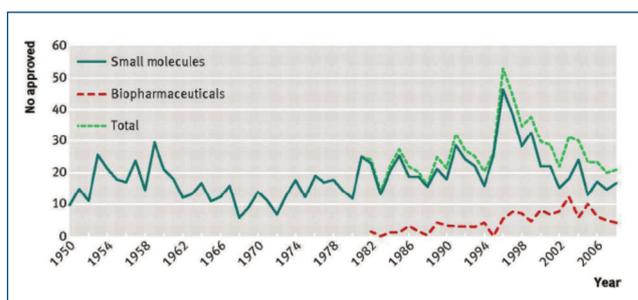
Source: The Authors

Are the costs of pharmaceutical research being exaggerated?

One question of recurrent interest is 'how much does an innovative medicine on average cost to develop?' The figures most commonly quoted are in the order of \$1,000 to \$2,000 million per successful innovation – see, for example, DiMasi and Grabowski (2007a) and OHE (2012). Such estimates are broadly consistent with data indicating that total private sector research spending on pharmaceutical research in the US, EU and Japan is presently in the order of \$70 billion a year, and that globally about 25 new molecular entities are launched as human medicines annually.

But some commentators have claimed that the 'true' cost of pharmaceutical research is much less. For example, Light and Lexchin (2012) suggested that it is in fact about \$100 million per product. Their figure is relatively low because it does not include the expenses

Figure 5. New medicines approved by the FDA, 1950-2010



Source: Light and Lexchin, 2012

Box 5. Incentives for meeting special needs

Conventional approaches to maximising welfare typically seek to provide 'the greatest good for the greatest number'. They emphasise the importance of 'cost effectiveness' in fields such as health care provision. But other concepts of social justice focus more on providing for the needs of the least advantaged in society. Hence the 'orphan drug' legislation pioneered in America in the 1980s – and subsequently introduced in places such as Australia, Japan and the EU – seeks to confer special advantages on innovators who develop treatments for relatively small groups of patients. These range from providing support aimed at accelerating and/or minimising the costs of drug licensing through to the use of regulatory data protection (RDP) to provide medicines that have been developed for orphan indications with a period of freedom from minimal cost competition.

Provided purchasers (and bodies such as price setting agencies) do not attempt to negate the impact of such legislation by, for instance, encouraging the 'off label' (unlicensed) use of cheaper alternatives when these are available, such policies balance short term market forces with a considered long term understanding of meeting human need.

Awareness of the fact that many pharmaceuticals developed for use in adults have been employed on an 'ad hoc' basis in the treatment of children led to similar legislation in the field of paediatric medicine. In the United States, which also led global reform in this area, two forms of targeted legislation promote investment in paediatric drug development. They are the Best Pharmaceuticals for Children Act (the BPCA) and the Paediatric Research Equity Act (PREA). The BPCA was passed in 2002. It built on reforms first implemented in the 1990s, and allows innovators to qualify for an additional six months of marketing exclusivity for innovative drugs (added to the end of the patent life) if studies related to their role in child treatment are voluntarily completed and submitted to FDA. The PREA, by contrast, requires such studies.

The equivalent legislation in Europe, which was introduced in 2007, also adds six months to the effective patent life of medicines that are appropriately tested and presented for use in children. There are additional RDP provisions for off-patent medicines developed for use in children. Once again, for the latter arrangements to incentivise ongoing investment it is vital that prescribers do not bow to pressures use lower cost presentations 'off label'.

Such regulatory innovations have helped to improve the working of the overall pharmaceutical market. But other problems remain, or are emerging. For example, in relation to challenges such as developing more effective treatments for cancers and other complex NCDs there is a strengthening case for adaptive medicines licensing. This involves moving away from a simplistic 'on/off' approach to deciding whether an innovative (bio) pharmaceutical product is 'safe' or 'unsafe', towards a carefully phased introduction process. But for this to work in the public's best interests it will probably require an equivalently stepped approach to IPP, with each new step attracting a fresh period of targeted market exclusivity.

Another possible example of market failure is that of antibiotic development. Innovation in this field has been discouraged by the fact that well intentioned prescribing policies often minimise the early use of new medicines. This allows them to be held in reserve for use when resistance to established anti-bacterial product means that they are no longer effective. Despite the widely recognised need for new antibiotics (WHO, 2013) this has paradoxically meant that commercial research funders (and indirectly public agencies) have had little reason to invest in this area. This is because new products are unlikely to achieve significant sales until after IPR exhaustion. Such problems highlight the continuing need to tailor incentives for therapeutic innovation to fit specific public health requirements.

incurred as a result of failed research projects and makes no allowance for the costs of 'risk capital'. The latter term refers to the premium needed to encourage investors to put money into projects with a high chance of failure.

These authors have also pointed to data indicating that, notwithstanding rising research outlays stemming in large part from extended clinical trial requirements, the number of fundamentally new medicines entering markets like that of the US has stayed broadly constant since the 1950s (Figure 5). This they believe refutes claims that the pharmaceutical sector is facing an innovation crisis and might require enhanced IPRs such as longer periods of regulatory data exclusivity to remain viable.

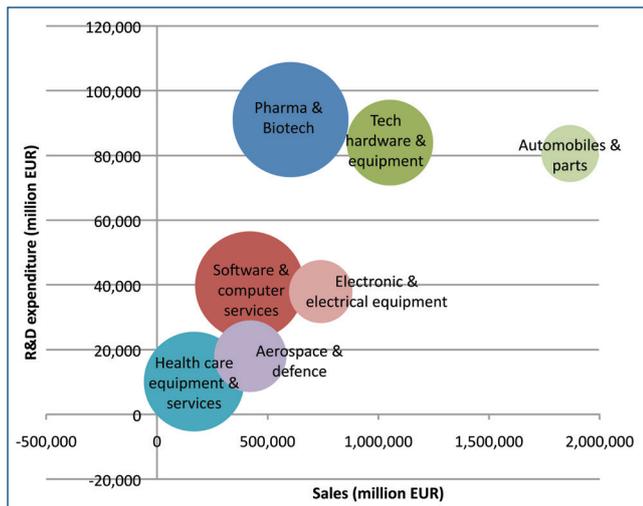
From a patient and public interest perspective such observations are important. They suggest that too much is being charged for innovative medicines, and/or that

industry – and also public and voluntary sector¹⁰ – funded research could be managed more efficiently. (Voluntary sector organisations and public bodies like Universities often possess IP rights that pharmaceutical companies exploit on their behalf. Hence a share of the earnings from pharmaceutical innovations is returned to them.)

Both research and regulatory processes could probably be made more efficient. Yet the conclusion drawn here is that estimates that the development costs of innovative medicines are now well over US \$1,000 million are not

¹⁰ In some areas public and charitably funded investments exceed those of industry. For instance, Kanavos et al (2010) calculated that in the period leading up to 2010 in Europe, the US and Japan, research based pharmaceutical industry expenditure in the oncology field was, at a little over \$3 billion per annum, only about a third of that made by public bodies such as the US National Institutes for Health (NIH). Voluntary sector spending was about \$900 million in that year.

Figure 6. R&D spending and sales, selected industries



Source: The 2012 EU Industrial R&D Investment Scoreboard

exaggerated. This is in part because it is reasonable to factor in variables such as expenditures made on research and development projects that fail to lead to marketable therapies. Given the reality that new pharmaceuticals are increasingly focused on meeting the needs of relatively small patient populations, the evidence available also indicates that companies are facing genuine difficulties in sustaining research investment levels.

Is the pharmaceutical industry more profitable than other industries?

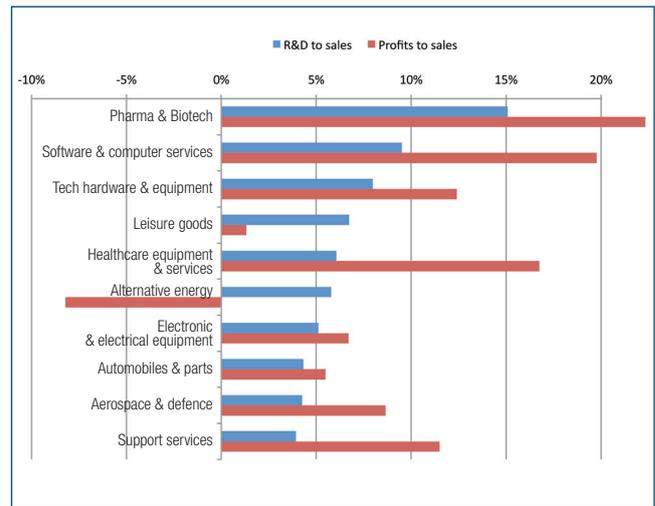
Similar points apply in the context of the pharmaceutical industry's profitability and the decreasing number (and declining market capitalisation – see Kaitin, 2010) of major research based pharmaceutical companies. Figures 6 and 7 are derived from the European Commission's 2012 EU Industrial R&D Investment Scoreboard. They confirm that there is across all types of industry a relationship between the share of total income devoted to research and development and profitability. The more the relative amount invested in innovation the higher the level of return.

The private pharmaceutical and biotechnology sector has in the last half century or so been more profitable than many other areas of enterprise. But companies operating in this sphere invest an unusually high proportion of their income on R&D. Taking this into account, their returns are not out of line with those of other successful industries. The interpretation offered here is that the reason why the profit to sales ratio seen in the research based pharmaceutical industry has for much of the last half century been above the average figure for industry as a whole has primarily been due to factors such as cost of risk capital effects, rather than non-productive market distortions.

From a public health viewpoint, would it matter if pharmaceutical patents were abolished?

In 2006 a Commission established by the WHO produced a report entitled 'Public health, innovation and intellectual property rights'. This pointed out – in

Figure 7. Ratios of R&D costs and profits to sales, selected industries



Source: The 2012 EU Industrial R&D Investment Scoreboard

line with the quotation from Bill Gates on the back of this publication – that when a disease like, for instance, a parasitic condition only affects poor people in poor countries, then patents and other IPRs may well fail to stimulate relevant innovations. This neglect occurs because even if new products are developed there may not in such circumstances be enough money available for them to be purchased. In such 'market failure' conditions it makes little difference whether or not innovators enjoy temporary periods of supply exclusivity. In the past many treatments for tropical conditions only became available because nations such as the US and the UK wanted to protect the health of soldiers stationed abroad.

At the extreme, evidence of market failure could be taken to imply that IPRs are of little positive or perhaps negative value in global public health terms, and should be replaced by better targeted incentives for investing in innovation (see below). Yet this would almost certainly be a naive interpretation. An alternative view is that although there may be a global need for new forms of direct public or alternative 'extra-market' funding of research and/or medicines purchasing in some contexts, commercially funded pharmaceutical innovation facilitated by the existence of IPRs makes valuable contributions to the wellbeing of people everywhere in the world. This implies that provisions such as pharmaceutical patents should not be abolished, but may need to be augmented.

In relation to this it is of note that the members of poor populations normally suffer from all the conditions that are prevalent in affluent communities, plus an additional 'special' disease burden (WHO, 2012). In age standardised terms non-communicable diseases such as, for instance, hypertension related heart, cerebrovascular and kidney disorders are in fact more common in less developed countries than in the OECD nations. Hence most if not all innovations initially provided in rich world markets have a global potential to prevent or relieve ill-health. Also, advances initially made in one area of biopharmaceutical research are likely to have subsequent applications in many others. To artificially

Box 6. Ramsey pricing in a global economy

The term 'Ramsey pricing' refers to the work of Frank Ramsey, an English mathematician and philosopher who died in 1930 at the age of 26 from a rare autoimmune liver condition which at that time could not be managed effectively. His seminal work in the field of economics demonstrated that an exclusive supplier of any product seeking to assure both optimal financial returns and maximum welfare levels should charge more affluent consumers higher prices than those paid by poorer customers.

In the global pharmaceutical market of the early 21st century there is a strong case in favour of differential pricing for innovative medicines between and within countries. This could enable essential and other products that enjoy IPRs to be made available at affordable prices to everyone able to benefit them, without undermining world-wide public interests in maintaining ongoing research investment. There are already many examples of related strategies (such as charging different prices for different presentations of given medicines) working in practice. Yet a number of challenges will need to be overcome for classically defined differential medicines pricing to be satisfactorily and comprehensively introduced at the international level. They involve:

- overcoming the objections some 'rich market' citizens may have to paying more for treatments than people living in less advantaged regions;

- preventing 'leakages' of lower priced product back into higher price areas; and
- balancing the interests that producers who are therapeutically non-innovative and national governments in low GDP areas have in manufacturing and supplying low cost versions of new medicines themselves with other appropriate concerns relating to sustaining global investments in high risk research.

None of the problems that exist are insuperable. For example, inward investment guarantees could in some cases help to relieve State level concerns about the possible balance of trade implications of differential pricing arrangements. But more fundamentally the lack in many poorer countries of adequate health care funding systems that share financial risks in an equitable way means that many poor people cannot access or use medicines to best effect even when they are supplied at very low prices. In such circumstances stratified medicine pricing strategies employed by innovative pharmaceutical producers will need to be complemented by either strengthened national pharmaceutical care systems, or by international purchasing and distribution arrangements that in effect make essential treatments 'free goods' in the world's least advantaged communities.

classify any fundamental scientific innovation as being relevant to only one part of the global community is frequently unhelpful and ill-informed.

Dimasi and Grabowski (2007b) reviewed a range of criticisms made of the role of IPRs in medicines innovation and concluded that there is little or no evidence that abolishing or weakening them would do anything but harm to overall public health interests. From a logical perspective there can be little question that the incentives they provide are needed to support sustained private investment in high risk R&D. For example, Thomas Pogge,¹¹ a leading advocate of reform in the area of global justice and worldwide poverty reduction, remarked relatively recently that *'very little innovative pharmaceutical research would take place in a free-market system'* (Pogge, 2005).

DiMasi and Grabowski also noted that measures such as 'orphan drug' legislation in the US and Europe, which provide for periods of regulatory data protection, have strengthened the position of innovators operating in areas where there is a risk of market failure. Sonderholm (2010) also analysed a variety of suggested alternatives to IPRs for incentivising investment in pharmaceutical/biomedical innovation and decided that on careful examination none were actually advocating the abolition

of intellectual property rights. They were rather in this author's view suggesting modifications to current intellectual property law, coupled with the introduction of complementary mechanisms for financing innovation.

Having said this, the extent to which generic (or branded off-patent) medicine manufacturers or other health sector stakeholders located in emergent economies such as India (which along with major health care delivery weaknesses is struggling with both balance of trade and government spending deficits) would agree with the view that IP rights are essential and desirable is likely to be limited. Many such manufacturers might welcome forms of IP 'sharing' for new medicines which, as can be the case with Compulsory Licences, offer them profit taking opportunities without requiring significant research contributions. But this should not be taken as supporting IPRs that are capable of fostering ongoing therapeutic innovation.

Seen from the perspective of politicians and planners based in countries with very limited financial resources, IP 'sharing' and the granting of CLs is likely to appear attractive. Yet patient groups and others seeking to defend the interests of not only the poorest in the global community but also people with currently untreatable conditions might be better advised to focus on seeking the free or 'marginal cost' supply of essential new medicines in communities that are unable to pay more, while recognising that global welfare will be further enhanced if innovators retain an ability to generate substantive returns elsewhere in the global market place – see Box 6.

¹¹ Professor Pogge was educated first in Germany and later studied for his PhD in Harvard where his supervisor was John Rawls, who was arguably the most important moral philosopher since Jeremy Bentham. Thomas Pogge is presently Professor of Philosophy and International Affairs at Yale.

Did the TRIPS agreement stop poor communities getting access to low cost essential medicines?

The TRIPS agreement is a topic of continuing controversy, albeit that its terms are in some instances now being superseded by those of separately negotiated bilateral trade agreements. The origins of TRIPS, which in the context of patents on pharmaceuticals is not due to come into full effect in the least developed nations until 2016, date back to the 1980s and a General Agreement on Tariffs and Trade (GATT – the forerunner of the WTO) meeting held in Uruguay. It was during the so-called ‘Uruguay round’ that it was agreed that all member nations should move towards granting patents with the same terms of protection as those existing in ‘the developed world’.

This led on to in 1994 the WTO Agreement on Trade-Related Aspects of Intellectual Property Rights. India, for example, signed the TRIPS agreement when it elected to join the WTO in 1995. This was with a view to it coming into full effect in 2005, the year in which a new Patent Act was introduced in that country. The global pharmaceutical industry and the governments of countries like the US and the UK supported the TRIPS approach (Abbott, 2009). It extended *‘the western concept of intellectual property (IP) to developing countries. Members of the WTO... have had to adopt a patent system... that would allow product and process patents for pharmaceuticals and vaccines’* (Milstien and Kaddar, 2006).

Many observers saw this as a desirable raising of IP protection standards to a global ‘best practice’ level. The proponents of the TRIPS agreement believed that it would open the way to increased investment in emergent economies and more trading between poorer and richer countries, while at the same time protecting global patient interests in continuing innovation. There is research evidence that the introduction of strengthened IP protection correlates positively with inward capital investment levels (Pugatch et al, 2012). But for the critics of TRIPS it threatened an inappropriately early introduction of advanced standard IPRs into economies that do not as yet have the research and allied capacities to compete with more developed nations.

Some have termed such developments *‘kicking away the ladder’* (Chang, 2002). The prominent American welfare economist Jeffrey Sachs has commented that: *‘We were proposing, in a sense, that the rest of the world be made safe for American ideas, as they adopted intellectual property rights that gave patent protection to our very innovative economy.’*

There are obvious welfare hazards that could arise from moves that reinforce the power and position of richer nations as against their poorer partners. Nevertheless, increased international trading since the start of 1990s appears to have been associated with a closing of average national living standards across the globe. There have also been more rapid increases in life expectancy in less affluent communities as compared to mature industrial economies, even though cutting infant and

child mortality is a different task from that of promoting healthy ageing and improving age specific survival and freedom from disability in later life.

However, TRIPS was agreed before concerns about access to effective HIV treatments had fully materialised. In the face of the at that time growing concerns that access to new HIV treatments would be further limited, a Ministerial Conference held in Doha in 2001 *‘reaffirmed the principle that TRIPS does not and should not prevent countries from taking measures to safeguard public health’* (Milstien and Kaddar, 2006). A waiver was agreed to the effect that *‘the scheme ultimately negotiated.... envisioned a process of back-to-back compulsory licences that would enable any country needing medicines at lower prices than those charged by local patentees to seek assistance from others able and willing to produce the drugs for export purposes, without interference from the patentee in either country’* (Reichman, 2009).

This view of the resultant Doha declaration suggests that countries that judge that their populations are at risk because an innovative medicine is too costly¹² can issue a Compulsory License (CL) for its local manufacture, and also export the CL version of the medicine in question to other nations in a similar position. Yet commentators concerned with the financial sustainability of pharmaceutical innovation argue that there is a danger of *‘public health emergencies’* being defined so broadly as to justify CLs being granted against any medicine of any type, regardless of whether or not this would in practice mean better outcomes for less advantaged consumers. Coupled with factors such the low level of royalties typically granted to innovators and fears – justified or not – that low cost copies of patented medicines might be supplied in affluent markets or used to treat ‘medical tourists’, this has raised concerns that the world-wide intellectual property system is in danger of being seriously undermined by the inappropriate use of CL granting powers.

There is a risk of overstating such hazards, given that two thirds of the global pharmaceutical market by value still lies within the North America, the EU and Japan. There is also a risk of exaggerating their importance, given the continuing reality that 1-2 billion of the world’s people still lack consistently adequate access to essential medicines. But in seeking to reconcile conflicting public and patient interests in optimising present access to medicines while sustaining investment in future therapeutic improvements the view suggested here is that it would be desirable if the WTO, where possible in consultation with patient representatives and agencies such as the WHO, could establish a generally accepted supra-national mechanism for defining ‘public health emergencies’ and determining when IPP treatments for non-communicable disorders such as, for instance, cancers should be made universally accessible.

¹² Remembering that well over 90 per cent of all medicines on the WHO’s essential drug list are off patent, and that in the poorest parts of the world a significant proportion of new medicines have to date been neither registered nor covered by actively enforced IPRs. This leaves the field open for non-original suppliers to offer alternative products as and when they are available.

What is patent 'ever-greening' and is it a significant problem?

In common usage, patent ever-greening is a term often used to describe the process of making minor changes to a medicine so that a new version can be patented and sold at a premium price, as compared to off-patent versions of the original treatment. It may on occasions be assumed that this, along with the intentional marketing of so-called 'me too' medicines, is common practice in the modern research based pharmaceutical sector. Yet this is not in fact the case. Key points to be made about this issue include:

- **The lead times for the development of new pharmaceutical products often exceed a decade from the time of patenting to that of marketing.** It is not today possible in adequately regulated markets to make quick and/or ill considered changes to existing pharmaceutical products simply to reposition them in order generate more income. Further, in very poorly regulated markets there would – even if it were possible to act in such a way – normally be little economic reason for a research based company to behave in such a manner.

The extent to which in today's environment pharmaceutical company discovery programmes overlap should not be exaggerated (Agarwal et al, 2013). But in the past the main reason for several variants of a given class of medicine becoming available within a limited period of time is that competing research based companies often started projects at around the point an innovative opportunity is first scientifically identified. Despite failures, this in fruitful areas often meant that several viable versions of a fundamental advance emerged ten or more years later. This may have appeared wasteful. But for patients such duplication can offer an insurance against lead compound failures and consequent technology access delays. It may also foster incremental advances that benefit sub-groups of treatment users.

- **Producing a new medicine does not make the original product unavailable.** Patent expiries mean that older medicines can and should be made available as low cost generic products. Those most likely to lose out in instances where marginally improved medicines are launched at around the time that IP protection for an original production is exhausted would not be those patients receiving the newer product, or those enjoying low cost generic versions of the established treatment. It would rather be manufacturers of relatively costly branded versions of the original medicine whose customers constitute the group most likely to move on the next generation therapy, when they are have choice.

Measures ostensibly taken to protect against 'ever-greening' as defined in this manner may be used to narrow the definition of patentability or to limit innovation based competition. This, if it occurs, is arguably against patient and public interests and is likely to driven more

by industrial policy linked pressures than by genuine health priorities.

However, there are additional, less widely understood, meanings of the term 'ever greening'. They relate to innovations enjoying more than one patent or other form of IP protection. This may, for instance, involve initially filing a relatively broad patent during the course a long term research project, followed by a more precise one as and when a viable therapeutic agent has been specifically identified. This was in essence the situation involved when the Indian Supreme Court in 2013 confirmed earlier decisions not to grant a patent for the pioneering chronic myeloid leukaemia treatment imatinib mesylate (see Box 7). Because in other parts of the world (but not in India) an earlier patent had described a range of imatinib salts of potential therapeutic value Gleevec was judged not to be patentable in India, notwithstanding the fact that it was one of the most significant pharmaceutical innovations in medical history.

This case was unusual, in part because relevant events spanned a time period that started before India's TRIPS commitments came into force. It is not suggested that the Indian Courts at any level made incorrect judgements, given Indian law. But from global patient and public interest viewpoint it raises a number of significant issues, not only about supplying 'new generation' anti-cancer and allied advanced treatments to poor and vulnerable populations but also about how companies involved in long term research projects should seek to protect public and shareholder interests.

If what might be termed 'intermediate IPP' arrangements cannot be used to safeguard accumulating interests during the course of long term investment programmes, it might be concluded that secrecy is the only alternative way forward. However, the unwanted costs of this in terms of restrictions on publications and other impediments to healthy scientific communication could prove unacceptable to those seeking to optimise innovation rates.

What should and should not be patentable?

The idea that private companies might patent naturally occurring human genes or other complex molecules such as proteins or peptides that can be used therapeutically or for research purposes has disturbed many observers. In the EU, debate about this area dates back to events such as the adoption in the late 1990s of Directive 98/44 on the protection of biotechnological inventions. But the most widely discussed issue relating to this aspect of IP law has been Myriad Genetics' ownership of patents on isolated forms of two genes, *BRCA1* and *BRCA2*. These are strongly linked to breast cancer and to varying degrees ovarian, prostate and some other forms of cancer.

In addition to concerns about the use of these patents in the context of exclusively supplied and high cost risk testing it is was feared that the company could legally prevent others from conducting research relating to *BRCA1* and 2 unless they were prepared to pay royalties. This led to a lawsuit by the American Civil Liberties Union and the Public Patent Foundation. It

Box 7. Meeting the needs of people with Chronic Myeloid Leukaemia (CML)

Chronic myeloid (or myelogenous) leukaemia is a form of ‘white cell blood cancer’ that is normally – but not always – associated with the ‘Philadelphia chromosome’. The latter was discovered just over 50 years ago in laboratories in the US city of Philadelphia. It occurs as the result of an abnormal translocation (misplacement) of genetic material during cell division, which inappropriately ‘switches on’ a further cell replication signal. Understanding the mechanisms involved in this process was an important step in the build up of knowledge about the causes and nature of cancers that has accompanied what on occasions is misleadingly seen as the fragmented development of anti-cancer drugs since the 1950s.

The introduction of imatinib mesylate (Gleevec or Glivec – see main text) as a treatment for CML four decades after the identification of the Philadelphia chromosome was a milestone in the history of medicines. Used consistently in the manner intended by its originators, this medicine can extend the lives of many people with CML for a decade or more. However, a significant number of patients miss or miss-time their medication doses (in part because of a desire to control side effects, the occurrence of which may be thought to be evidence of treatment being ‘too powerful’) and are consequently exposed to a greatly increased risk of drug resistance. Alternative medicines are now available which are starting to ‘block off’ resistance pathways. But they do not as yet offer definitive solutions to this problem.

One way of further helping to meet CML and other patients’ needs is therefore to establish ‘adherence support’ programmes as an integral part of later stage drug research development. It is also vitally important to facilitate the early and accurate diagnosis of conditions like cancers, alongside timely access to correctly prescribed treatments. In countries like the US and

UK the incidence of CML is a little over 10 per million population and the mean age of diagnosed onset is approaching 65 years. In India the best available research suggests a similar picture (Dikshit et al, 2011). Yet some sources claim that there is a mean age of CML onset of only 40 years, and an overall incidence rate of around 40 per million in India’s relatively young population.

Discrepancies like these underline the fact that there are often uncertainties about the level of unmet need for innovative medicines in developing communities. In India executives working in Novartis, the research based pharmaceutical company responsible for Glivec’s original development, believe that its free supply scheme (which is currently serving over 15,000 people – Shahani, 2013) is meeting the requirements of the great majority of Indians with a confirmed diagnosis of CML who are unable to access treatment via other routes. They emphasise the need to increase accurate and early diagnosis rates. Yet other observers appear to believe that there are large numbers of people who are not being well cared for, primarily because of inadequate medicines supply. This they suggest is despite the Novartis scheme and the long standing availability of low cost versions of imatinib mesylate on the Indian market.

Without population wide-access to adequate diagnostic services and checks as to whether or not suggested treatments are in fact needed, assessing the extent to which patients are being under (or over) medicated is highly problematic. Achieving better access to effective medicines is important. Yet patient organisations and other agencies concerned with meeting health care needs should be aware that simply supplying medicines does not guarantee their appropriate use in complex contexts like CML therapy.

claimed that Myriad’s patents were invalid in that they could hinder biomedical research and impair patients’ access to diagnostic testing, and so to potentially life-saving medical interventions (Chuang & Lau, 2010).

Early in 2013 an Australian Federal Court judgement favoured Myriad Genetics’s case. However in June 2013 the US Supreme Court ruled against Myriad’s patents on the isolated natural genes, whilst confirming the patentability of artificially synthesised ‘cDNA’ and other ‘man made’ biological substances. Although this does not remove all concerns surrounding intellectual property rights for products such as monoclonal antibodies produced by recombinant DNA techniques, it provides significant assurance that IPRs cannot be used to inhibit fundamental research. An increasing number of new therapies are biopharmaceuticals. It is therefore important from a consumer perspective important to insure that legal mechanisms operate appropriately, and allow for legitimate income generation by innovators without blocking ongoing discovery processes or imposing undue costs on patients or service funders.

Kent (2006) has underlined the fact that the *BRCA1* and 2 debate has in a number of important respects been a special case, and that even before the Supreme Court ruling research has not in the main been impeded by patent holders seeking to prosecute investigators for (non-commercial) infringements of IP rights. He, along with many other commentators concerned with enhancing patient welfare, concluded that – despite a potential for abuse – when properly used IP rights are a necessary component of innovative health care environments.¹³

When knowledge can be applied via novel interventions to achieve defined practical ends there is good reason

¹³ It could be argued that Cuba offers an exception to this rule, in that in the context of medicines and vaccines it has achieved a relatively robust innovative record in the absence of conventionally defined IP rights. However, in market economies IP rights serve to limit temporarily the impacts of unfettered competition. In communist Cuba, which has historically enjoyed a medically well informed leadership and a command approach to economic development, such protection has not to date been required. This is because its command based economy has largely operated outside the more competitively based global system.

to conclude that it is in the public's interest that the resultant technologies should be granted IPRs. But undefined restrictions on the use of natural phenomena by scientists in attempts to understand the world around them and develop new products with useful applications should not be accepted. (See also, for instance, the Nuffield Council on Bioethics, 2002.) For the purposes of this analysis a key finding to highlight is that although IPRs may on occasions have been put to counter-productive uses, this does not mean that they are inherently undesirable. What ultimately matters is the end being pursued and, as in other areas, a robust policy underpinning for legal provisions: *'a patent is not a goal in itself, rather it is a right created.... as a means to achieve a larger social goal'* (Trotter, 2012).

Are new forms of intellectual property protection needed?

As already noted, the measures contained in the US Orphan Drugs Act passed at the start of the 1980s and the subsequent provisions introduced in Europe and elsewhere have served to reinforce traditional IPRs with additional regulatory data based forms of protection. Similar approaches have been adopted in the context of paediatric (child) medicine development. There are differences between the strategies employed in the US, the EU and Japan. But typically the arrangements introduced have permitted medicines developed for orphan indications 10 years of 'data exclusivity', independently of any other entitlements.

This means that regulators cannot approve new marketing applications for innovative 'orphan' products during the regulatory data exclusivity period granted to encourage innovation on the basis of pre-existing safety

and efficacy information. Similarly, in both the US and the EU conducting paediatric trials on a medicine formulated to be fit for purpose can extend the period of exclusivity available on all protected presentations of the relevant active ingredient(s) for a period of six months. From a patient and public interest perspective concerns and issues of special note in this context include:

- the introduction of such measures reflects an acceptance within the world's stronger economies that forms of exclusivity over and above those associated with conventional patenting are necessary for the maintenance of pharmaceutical innovation; and
- incentives like those outlined above are of no value to innovators and ultimately to meeting patients' long term requirements if purchasers fail to buy appropriately licensed products once they are available, on the grounds – for example – that they are more expensive than alternative versions that can be used 'off licence'. This underlines the need for coherent policies and practices which respect the full range of public interests involved in pharmaceutical sector regulation, and do not just focus on cost minimisation.

Similar points apply to the protection of patients' interests in developing new clinical uses for mature (established, off-patent) medicines. Innovative pharmaceuticals often have more than one potential therapeutic application, but at the time of initial marketing have normally only been developed for what was at the time regarded as the clinically most important (and/or most financially viable) use. One barrier to developing two or more initial indications early in a drug's life cycle is that if markedly different doses are required to generate given measure of health gain pricing complications may well ensue (Box 8).

Box 8. Different prices for different uses of the same medicine?

There is evidence that charging different amounts for the same medicine in richer and poorer communities can, although sometimes controversial, be in the global public's interest. In some circumstances charging differing sums for a given medicine when it is used in different clinical contexts may also be beneficial. However, the justification for this is often difficult for observers such as politicians and medical and other prescribers to accept. It relates to the fact that the main value of innovative medicines does not lie in producing the substances of which they are made, but rather in the costs and challenges of their development and the benefits conferred on users.

As described in the main text, newly identified pharmaceutical treatments frequently have more than one potential application. But the resources available often allow only research on the clinically most important and/or commercially most promising indication to be taken forward. Allied with this, innovators sometimes fear that if the drug volumes needed to generate a given unit benefit are significantly different in contrasting therapeutic settings (or if the numbers of patients with one condition are much more or less than those with

another) this will lead to pricing problems. In today's regulatory environment the clinical research costs of developing each separate indication for a medicine are likely to be broadly similar. Yet variations in the volumes of active ingredient needed may mean that the price per gram of drug supplied would (at least during the period before IPR expiry) have from an economic perspective to vary by several orders of magnitude between contexts.

It is not in patients' or the public's long term interest that factors like these should impede innovation. Progress in orphan and paediatric drug licensing has started to resolve such difficulties. Yet in other areas involving possible second and subsequent uses of established medicines problems remain. When confronted with different prices for the same medicine prescribers and others may well feel that an attempt is being made to defraud health care funders. Given this situation, patients' organisations could in future seek to understand and explain this field to doctors, managers and others responsible for making and influencing prescribing and allied decisions.

Likewise, once medicines have become available as low cost generics this can be a major barrier to developing new clinical trial validated indications for them, even though 'second use' patents or other forms of IPR are in theory already available. As suggested above, some purchasers see paying significantly above the commodity level for an 'old' drug as being at best unnecessary and at worst wasteful. A message to stress from the standpoint of patients who would benefit from the development of new indications for 'mature' medicines is that, over and above IPR based incentives being nominally in place, research investors are likely to require robust reassurances that they will in practice be able to establish income streams adequate to justify the investment decisions needed.

The public's interest in providing the latter rests on the desirability of stimulating future spending on productive innovations. There is a case for the future introduction of strengthened forms of IP protection for second and subsequent uses of off-patent drugs, designed to build on and extend incentives already provided for in the current orphan and paediatric medicines legislation (Jacob, 2013). The extent to which further adjustments in the scope and duration IPRs for medicines and allied products might be both justified and politically possible is touched on again later in this report. But the conclusion to stress here is that although governments may impose price controls on pharmaceuticals with the objective of curbing costs,¹⁴ there is from a patient and global public interest standpoint a counterbalancing need to ensure that spending on developing innovative technologies is not unduly restricted.

Could and should the financing of biopharmaceutical research be completely separated from the commercial sale of medicines?

There are many other patient and public interest questions to be asked about the interfaces between innovation, IP law and medicines pricing, quality, safety and access in, for instance, areas like medicines counterfeiting. Yet as far as this report is concerned the most important issues relate to the options available for delinking research funding from the commercial market place. While for reasons already indicated the abolition of patents and other IPRs is unlikely to offer a viable way forward, reducing innovator's financial dependence on IPR exploitation may be desirable in some circumstances. Opening specific new funding streams can – as the Gates Foundation has demonstrated in fields such as malaria medicines development – offer valuable additions to global investment in medical and pharmaceutical innovation.

¹⁴ Price controls can have undesired consequences as a result of market distortions. For example, generic manufacturers seeking increased returns may stop making essential medicines if the price limits imposed are unduly low, and focus their activities in other less important areas. A better approach is to wherever possible foster competition via informed medicines purchasing and good prescribing.

The performance of the regulated, mixed public and private market for pharmaceuticals that in its current form developed in the US and Europe in the aftermath of the 1939-46 war, has – as individuals such as Bill Gates have emphasised – been robust as far as the immediate interests of most people in the developed world have been concerned. But for others in poorer developing regions there is still a need for further improvement. The task ahead is not to dismantle arrangements which have delivered to good effect in more advantaged environments. It is rather to create an extended system that is more capable of meeting the needs of rich world minorities together with the particular requirements of populations in less developed economies.

With respect to this debate the Wellcome Trust has recently produced statements that highlight the positive role played by IPRs, and warn against removing the benefits of market competition in the medicines research and development funding process. (See, for example, Wellcome Trust, 2012, 2013). In practical terms commercially driven processes are often of value in pushing forward innovations, and encouraging their uptake via marketing and product and service support activities.

However, James Love and other reform advocates have suggested the introduction of prizes to encourage the development of new medicines in high priority fields (Love and Hubbard, 2007; Stiglitz 2006a, 2006b; Vastag 2012.) This concept can be dated back to and beyond initiatives such as the British Admiralty's efforts in the early 1700s to incentivise the creation of a reliable nautical clock to aid navigation. This was a notable success, albeit that on that occasion the promised prize was not paid until its winner James Harrison was very close to bankruptcy.

There is a logical case supporting the view that an extended use of prizes for the introduction of successful treatments could in some areas usefully augment research funding arrangements. But in complex and fast evolving fields there is a danger they may lack the flexibility needed to maintain their relevance to changing public and patient needs. The extent to which such an approach could be scaled up beyond the occasional 'once-off' level is also uncertain, and there is no evidence to suggest that a prize based approach could ever fully replace existing IPRs.

Examples of related concepts include:

- **Pogge and Hollis's Health Impact Fund (HIF).** This would, if introduced, offer pharmaceutical innovators an opportunity to register their products with a central Fund and to receive a financial reward commensurate with the projected world-wide benefits generated, in return for supplying at the cost of production wherever the treatment in question is needed (Hollis, 2008). This may be seen as a variant of Love and Hubbard's proposals, coupled with a form of 'value based pricing'. From a theoretical perspective it has a number of attractive aspects, albeit that in practical terms the level of reward requirements and the most appropriate timing of payments due may be difficult to determine.

- **Advanced Market Commitments.** AMCs typically involve public agencies agreeing to purchase given volumes of products such as new drugs or vaccines at a guaranteed price from companies prepared to fund the research programmes needed to develop them (Glennester et al, 2006, Sonderholme 2010c.) AMCs also have a similar but more specifically targeted role to that of drug development prize offers.

Additional ideas range from the establishment of patent pools to facilitate research in neglected disease areas through to the possibility that governments could in selected situations ‘buy out’ patents or other IPRs and then either encourage free ‘price plus quality’ based generic competition, or commission local or global producers to supply in bulk at the lowest sustainable cost. A large body of literature on the viability these and other opportunities exists. But for the purposes of this study key observations include:

- **A fundamental question at the heart of the present IP debate relates to the extent to which poorer countries should have a ‘free ride’ with regard to funding pharmaceutical innovations.** Authors such as Pogge have argued that more affluent nations should be prepared to permit them such an advantage. Others, such as Sonderholme (2010b), have pointed out that the current cost of private pharmaceutical research in the developed world is about \$70 billion per annum and that the balance of world economic power is shifting away from Europe and perhaps the US. In such circumstances the political/social will needed to move significantly further in the direction of the OECD economies being the exclusive funders of high risk pharmaceutical research may prove lacking, other than in very particular instances of special need.
- **In the absence of strong intellectual property rights, governments and other agencies may markedly under-estimate the full value of biopharmaceutical and other medical innovations in the face of immediate political priorities like keeping taxes low.** This could lead to major long term welfare losses. Some public conflicts over access to IP protected medicines may reflect institutional purchasers’ unwillingness to pay premium prices for innovations, even in circumstances where both public opinion and long term economic logic may in fact favour use.

In a variety of countries ongoing political concerns about anti-cancer drug access and efficacy illustrate this problem. It has been estimated that the capitalised value of being able to effectively treat all cancers could be in the order of \$50,000 billion in the US alone (Morphy and Topel, 2006). That is some 50 times the current world annual consumption of all pharmaceuticals. Aspects of methodology underpinning this and similar estimates may be questioned. Yet they underline the potential importance of further biomedical advances, not only in oncology but areas such as, say, the prevention of neurological and musculoskeletal disorders. The ultimate worth of sustained investment in areas like these is likely to far exceed the values implied by fragmented ‘health economic’ calculations made to inform short term health sector resource allocation decisions.

Patient Centred Progress

A central message of this report is that successfully fostering medicines and wider health care innovation while pursuing national and international patient and public interests in the improved delivery of care is likely to require coordinated effort on a wide variety of fronts. Both new medicines development and established treatment access issues need to be understood in their broad social and economic contexts, rather than as isolated challenges.

The extent to which provisions like IPRs protect or negate local and/or global public interests is not simply a function of variables such as patent term durations. It is determined by interactions between the latter and factors such as the degree to which health care funding arrangements permit financial risk sharing and so assure universal care delivery. Without robust, well designed and regulated public or private health care systems which protect against catastrophic health care costs falling on individuals and families no population, affluent or poor, can be assured consistent and equitable access to modern health care technologies (Wong-Reiger, 2013).

Other key variables range from the existence (or otherwise) of efficient pharmaceutical purchasing systems to the way medicines pricing schemes are implemented, and the quality of governance in both publicly and privately funded research institutions. The nature of international agreements on aid and trade relating to products like diagnostics, vaccines and medicines is another important consideration. Bodies representing patient and public interests in health and health care have responsibilities relating to all these fields, and many more besides. However, the topics briefly discussed below are particularly relevant to medicines users concerns’ about treatment costs and the degree to which innovators can for limited periods be protected from the effects of unchecked market competition without harming public interests in affordable care delivery.

Ensuring safety without impeding innovation

In the half century since the Thalidomide tragedy, which at the start of the 1960s caused 10,000 babies to be borne with physical impairments, sophisticated systems of medicines safety regulation have been established to protect populations across the world. Few commentators would question the importance of such advances. But for people facing serious illness and/or premature death, taking even highly significant therapeutic risks is not necessarily unacceptable. It is also not automatically the case that current approaches to regulating the pharmaceutical sector in general and medicines safety in particular will be either economically efficient (not least as judged by the HTA criteria used by bodies such as Germany’s IQWiG or Britain’s NICE) or commensurate with the amounts of spent to reduce the risks of harm in other areas.

From a global public interest perspective, for instance, it is relevant to observe that – as compared with the avoidable harm caused by Thalidomide outside the US,

where the FDA denied it marketing approval¹⁵ – better application of knowledge about the role of folic acid in protecting against spina bifida could today prevent up to 10,000 cases of lifelong disability across the globe every year. Similarly, there is evidence that throughout the world millions more deaths could be prevented via an extended use of relatively safe and very low cost medicines for the reduction of blood pressure and low density cholesterol levels (Wald, 2013). But professional interest and time is often more focused on areas such as vascular disease ‘risk testing’.

Such observations do not deny the importance of safety issues. Nevertheless, from the viewpoint of pharmaceutical consumers they highlight the value of putting established knowledge into practice in timely ways. They also underline the additional need to reduce the avoidable harm that can result from unduly cautious professional and/or regulatory approaches to allowing the public access to beneficial innovations. Pursuing safety at any cost is not desirable, as compared to seeking to maximise benefits relative to unwanted outcomes.

From the standpoint of this analysis it is also important to stress that IPRs in part help to ensure that innovators who test their products carefully are not financially disadvantaged and are not motivated to promote them without due caution. This is especially important when it is difficult to evaluate the full consequences of a medicine’s use in large populations. Seen from this angle it is uncertain that current ‘on the market’ patent protection periods of only a little over a decade are sufficient to serve public interest focused policy ends. If approaches such

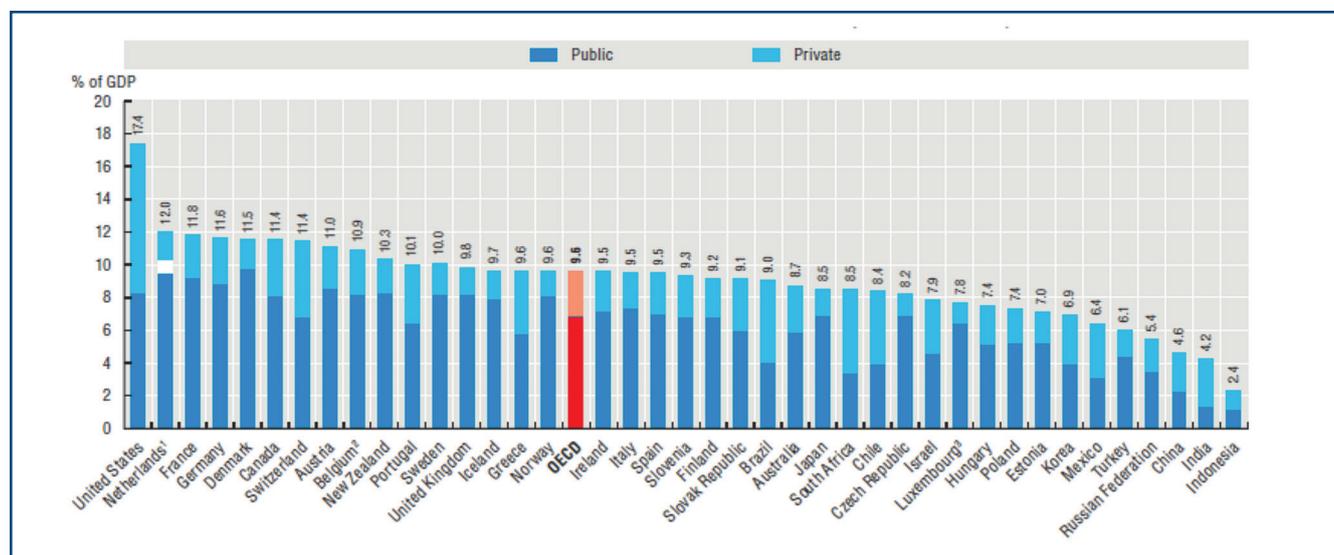
as adaptive medicines licensing are in future introduced the case for extending pharmaceutical IP terms is likely to further strengthen. Ideally, this should not only allow more time for the staged introduction of innovations like, say, new cancer treatments. It could also lower market entry prices, if it permits overall ‘above commodity return’ income generating periods be significantly increased.

Patient organisations whose members could benefit from such reforms might wish to consider questions such as why, for example, modern copyright terms can run for 75 years after the death of an author, while IPRs on medicines that may require in excess of \$1,000 million of public and private money for their development provide only about ten years on the market protection. In the face of questions relating to the possible costs of extending IP term durations and its impacts on the affordability of innovative medicines’ in poorer nations, it is relevant to note the potential for approaches like tiered global pricing to in future help ensure universal access to essential new treatments – see below.

Pricing, value and affordability

Total national outlays on modern medicines (including distribution costs, local taxes and trading mark ups) have when expressed as a proportion of GDP been relatively stable at around 1-2 per cent of GDP in richer and poorer nations alike for about 50 years. Total health care spending is now typically in the order of 5 per cent of GDP in the latter and 10 per cent in wealthier nations, although in the US it is close to 18 per cent (see Figures 8a and 8b).¹⁶

Figure 8a. Total health spending as a % of GDP



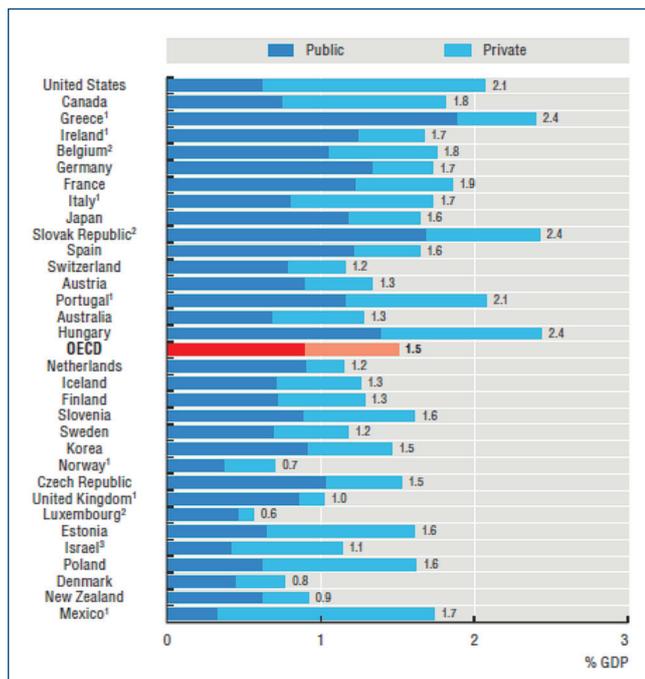
Source: OECD 2011 (2009 data)

15 In 1960 Dr Frances Kelsey, a medically qualified pharmacologist serving as an FDA drug reviewer, prevented the approval of Thalidomide in the US as a sedative pain killer and anti-emetic for use in pregnancy. This was because she had concerns about a lack of data on the drug’s ability to cross the placenta, and an absence of clinical trial results. Some pharmaceutical scientists in Europe shared concerns related to hers in the late 1950s. But the lack of a rigorous approach to medicines licensing at that time meant that it was nevertheless marketed for use by pregnant

women in countries such as the UK and Australia, as well as in Germany. Much later, the drug was found to be appropriate for use in areas such as the treatment of leprosy.

16 It is sometimes claimed that 50% or more of health spending in countries such as India is accounted for by medicines spending. But in reality spending on allopathic medicines accounts for only about 20% of total Indian health spending. The latter is, as a proportion of GDP, lower than that recorded in nearly all other major nations.

Figure 8b. Pharmaceutical spending as a % of GDP



Source: OECD 2011 (2009 data)

For some observers, the fact that pharmaceutical costs represent a limited and in some instances falling part of health spending may be surprising. The factors underpinning this include not only the effects of patent expiries but also purchaser led savings programmes coupled with the increased

relative cost of medical and other health service labour. The sometimes paradoxical impacts of price controls may have been of some additional significance (Box 9), as has the trend towards new medicines being targeted towards relatively small numbers of patients. Even an innovation costing \$50,000 a year will in overall terms be an order of magnitude less expensive than one costing \$500 per annum, should the former only be being taken by 1,000 people while the cheaper medicine is used by a million.

Because the costs of developing new medicines are largely fixed regardless of their potential market sizes, the trend towards a declining number of patients benefiting from each new medicine has had the effect (at least in this phase of the innovation cycle) of driving up the unit cost of innovative therapies. This has in turn focused increasing attention on pharmaceutical prices and costs, even in countries where overall spending on medicines and allied goods has declined in relation to health outlays. Patient groups and representatives can play important parts in helping decision makers to judge the affordability of newly available therapies. Those representing people with conditions that are not yet satisfactorily treatable may also wish to take an active role in building awareness of the value of incentivising continuing spending on high risk research and development.

Accepting this reasoning may on occasions expose patients' organisations to allegations that they are

merely defending commercial interests, or are insensitive to the needs of people living in poor and unprotected settings. Such concerns deserve attention. In inherently uncertain circumstances there are inevitably going to be disputes about how much should be spent on innovative treatments. Yet if anything humanity's characteristic (and perhaps eventually fatal) error has probably been to 'risk' too little on spending for a better future as opposed to enjoying present consumption.

Failing adequately to defend the interests of patients in developing treatments that may directly or indirectly deliver better health outcomes in the years ahead could have costs that will far exceed those associated with the possibility of paying 'too much' for innovations. At the end of the day profitability regarded as excessive is something that if necessary can be recovered by 'claw backs'. By contrast, avoidably lost or harmed lives can never be regained.

Medicines price stratification in a global marketplace

In theory, global public and patient interests in medicines innovation and equitable treatment access could best be protected if affluent people with access to good health care are required to make (either out of pocket or via taxation or insurance funding) 'full' contributions to the costs of new medicines wherever they happen to live, while members of less advantaged groups are supplied with essential treatments at their marginal cost or free of charge. The welfare based case for free supply rests on evidence that for people living at (or to varying degrees above) poverty levels even small price barriers can act as a serious deterrent to appropriate treatment uptake.

If this view is accepted, then an ideal way forward would be to combine a standardised world-wide system of intellectual property rights with robust national and where necessary international funding arrangements for meeting the pharmaceutical care needs of less advantaged sections of the community. The latter ought it may be suggested to be backed by more research based industry action to differentiate the prices charged to health services for innovations, in accordance with variables such as regional GDP levels. This would help ensure that all those able to enjoy health care of a quality comparable to that available in the developed nations contribute fairly to ongoing research and development costs. At the same time members of less advantaged groups in need of either generic medicines or innovative treatments that have IP protection but are appropriately classified as essential could be affordably treated.

It is possible that some if not all of the architects of the 1994 TRIPS agreement had the evolution of such a system in mind when it was originally established, and that the world will in future move further in this direction. However, there are a number of major barriers to such vision being achieved. These most importantly relate to perceived and actual national differences in industrial interests as they affect the pharmaceutical sector, and

Box 9. The limits of ‘value based pricing’ for medicines

Since the 1960s health economics has made much progress. This was initially related to pharmaceutical industry support, linked to companies’ efforts to communicate the value of innovations. More recently, it has been strongly associated with government bodies’ efforts to control costs and optimise the use of the public resources spent on health care in general and medicines in particular. One key step forward was, from the 1980s onwards, the introduction into widespread use of the Quality Adjusted Life Year (QALY) and the parallel concept of the Disability Adjusted Life Year (DALY). Although in practice very difficult to assess with accuracy, ‘cost per QALY’ measures are used to estimate the relative utility of interventions and so to permit ‘value for money’ comparisons within the health arena.

Throughout the world public and private health spending on health and allied services rose as a percentage of GDP during the last half century, primarily because of increased outlays on health sector labour. In association with this trend QALY based calculations have become progressively more widely employed as a means of guiding the allocation of health sector funds in ways which will increase service efficiency. However, in the US in particular objections have been raised to valuing one life more than another because of a person’s age or health status.

While acknowledging the importance of efforts to ensure that limited resources are used wisely in attempts to improve welfare, it is in addition true that traditional health economics techniques have had little to offer in areas such as understanding how social relations within the health sector influence productivity

and outcomes. Further, they cannot address questions such as *‘how much of its income ought a nation to spend on health services?’* or *‘what is the long term value of investing in areas such as biopharmaceutical innovation as opposed to improving the provision of existing means of care?’*

There are major uncertainties involved in trying to assess how new technologies will in future develop, and in predicting how in the long term advances in areas such as, say, genetics, the neurosciences and bio-engineering will impact on not only health and health care but other aspects of human development and survival. The scale of the unknowns involved discourages mainstream academics and other analysts from speculating about broad questions such as *‘what would developing technologies that enable health professionals to prevent or cure all cancers and/or complaints such as Alzheimer’s Disease be worth to humanity over the course of the twenty first century?’*

However, patients and the public have a vital interest in recognising the importance of investing for the future. Patient organisations seeking to defend their members’ interests in sustaining innovation should be aware of the possibility that apparently objective approaches such as cost per QALY linked ‘value pricing’ for medicines and other innovations could systematically under-value the long term community returns to be derived from spending on high risk research and development. They should also be able to communicate to decision makers why this is so, and how such risks can be minimised through the balanced pursuit of better access to care today and better treatments tomorrow.

to local capacities and willingness to develop health care systems that respond adequately to varying patient needs and abilities to pay.

It is therefore more likely that (subject to the terms of the ‘free trade’ agreements being negotiated between, for instance, the EU and America on the one hand and India on the other) IPRs and the ceiling prices of pharmaceutical innovations will for the foreseeable future remain stronger and higher in the richer countries of the world than in poorer nations. Accepting this uncritically could in some circumstances increase inequities within emergent economies, particularly when better off people benefit from low medicine prices but fail to make ‘transfer payments’ sufficient to support the health services needed by less fortunate citizens. Yet global patient and public interests in the continued private (and public) sector funding of biomedical innovation need not be undermined if price boundaries between regions do not deteriorate. This might happen because of illicit trading, or if political forces undermine the willingness of people in countries like the US and those of the EU to accept higher prices for medicines than those paid individuals elsewhere in the world.

People and organisations seeking better treatments for themselves, for their contemporaries and/or future generations would on the basis of the assessment offered here be well advised to recognise the value of and defend IPP based incentives for innovation, while at the same time advocating well targeted medicines access support for less advantaged people. In summary, the approach suggested here is that in addition to considering the advantages of further extending the duration of IPRs for new pharmaceutical products in the OECD nations, patient organisations and others interested in both continuing biomedical progress and assuring appropriate global access to effective treatments should:

- **press for the establishment of internationally agreed criteria for identifying ‘public health emergencies’ and situations in which there is an urgent need to enhance access to IP protected and/or generic medicines.** The purpose of this would be to help prevent arbitrary government interventions that in effect confiscate or transfer intellectual property rights away from innovators, while at the same time improving the global community’s

ability to identify and correct life endangering and avoidable pharmaceutical market and wider health care system failures; and

- **seek to ensure that mechanisms for, and the extent of, price stratification between markets are also systematically based on transparent principles.** Patients and the wider public also have an interest in arrangements that prohibit ‘leakages’ of low cost IP protected pharmaceutical products from lower to higher GDP regions. Progress in this area could also serve to reinforce the integrity of medicines licensing systems, and the global quality of pharmaceutical products.

From a global public interest standpoint a related issue to clarify is the extent to which international companies offering patented or other IP protected medicines at a low cost in poor settings remain able to charge higher prices in more affluent contexts. The history of ‘parallel trading’ (or in US terms re-importing) in the European Union suggests that it may be difficult if not impossible to maintain the commitment to social justice and human welfare needed to make price differentiation based strategies deliver desired outcomes. But without such arrangements the global introduction of preventive and clinical applications of the major advances currently occurring in areas such as genetics and molecular biology could be needlessly slowed.

Conclusion

Supplying pharmaceuticals of any sort is rarely, if ever, enough by itself to solve complex public or personal health problems. Yet along with other health protecting and promoting interventions, improved diagnostics, vaccines and medicines supply and use can make important differences to the health of not only individuals but entire populations. Seen from this viewpoint, assuring access to modern pharmaceuticals is *‘one of the most pressing and morally compelling problems we face as humanity’* (Williams, 2012).

Similar conclusions can be drawn in relation to ongoing pharmaceutical and other forms of biomedical innovation and world health, even though ensuring that sufficient resources are allocated to activities like research is an inherently more uncertain task than seeking to make existing care arrangements more efficient. There is in the first half of the twenty first century an historic opportunity for humanity to complete the global processes of demographic and epidemiological transition that began in Europe at around the start of the 1800s. Given continuing biomedical and pharmaceutical innovation coupled with extended health care coverage and delivery, child and ‘working age’ adult mortality due to infectious and many forms of non-communicable disease could be virtually eliminated by 2050 (Peto, 2012).

It is also possible that by then average healthy life expectancy at birth will be extended to over 80 years in every world region, and that technologies linked to current biopharmaceutical progress will be making

important contributions in fields ranging from food and fuel production to the management of atmospheric and oceanic pollution. But translating the promise of such benefits into realised health gain will not only demand the national and international political will needed to, for example, further extend universal health coverage. It will in addition require the maintenance and strengthening of the economic and social mechanisms required to channel resources into costly high risk research and generate productive innovations.

A central message of this report is that intellectual property rights have a vital role to play in this last context. Even if in future additional incentives such as State or private donor backed prizes for the development of therapeutic solutions to priority problems were to be funded, and proposals such as Pogge and Hollis’s Health Impact Fund given large scale international support, it is unlikely that such initiatives could replace provisions such as patents or regulatory data protections in a way that will benefit rather than harm international welfare standards.

Some observers may genuinely believe that the global system for conferring IPRs is ‘broken’, and should be dismantled. But the conclusion offered here is that preserving and in some contexts strengthening intellectual property rights has an essential role to play in facilitating continuing private and public investment in pharmaceutical and other forms of innovation. This is so despite the fact that it in effect involves imposing a temporary ‘tax’ on the use recent developments in order to encourage desired spending on ongoing research.

This is not to say that agencies such as patient organisations that have a remit to foster the development of better treatments should ignore the needs of people living in economically less advantaged communities for better access to today’s life saving and enhancing medicines. It is instead to argue that additional provisions and reforms should be introduced alongside traditional approaches to IP law to ensure that sometimes conflicting global public interests in present access and future innovation are met as effectively as possible.

Some commentators may argue that providing universal global access to good quality health care and effective modern pharmaceuticals is an unaffordable, utopian, goal. However, a second key finding of this analysis is that although skilled health professionals are at any one time a finite and relatively expensive resource, products like medicines are – once they have been developed for use in clinical or wider settings – normally relatively inexpensive to make. As manufacturing technologies improve this could increasingly be the case with large molecule biopharmaceuticals, as well as with small molecule ‘chemical medicines’. Although innovative treatments are initially expensive because of the need to test them thoroughly and to maintain the economic conditions required for further investment, their supply costs in time fall significantly. The fact that in some less advanced markets combinations of prescriber and consumer loyalty and sometimes questionable marketing practices might on occasions allow branded mature medicines to make margins that appear close

to those earned by patented innovations should not be permitted to obscure this truth.

The final message of this analysis is therefore that patients and the public should be confident that after the expiry of IP rights pharmaceutical innovations normally become permanently available low cost resources. This is in marked contrast to other health care factor costs, which typically increase over time as societies increase their wealth. It represents a powerful reason for continuing to invest in new pharmaceuticals. Innovative medicines do not only incrementally improve upon established treatments. They can open up fundamentally new and cost effective opportunities for the relief of suffering, the elimination of disease and the enhancement of life. Communicating this reality to policy makers and electorates is from a patient standpoint likely to become a progressively more vital task as the twenty first century unfolds.

References

- Agarwal P., Sanseau P. and Cardon L. R. (2013) Novelty in the target landscape of the pharmaceutical industry. *Nature Reviews Drug Discovery* Volume: 12, Pages: 575 – 576
- Anderson R. (2013) personal communication Year published:
- Attaran A and Gillespie-White L. (2001). Do Patents for Antiretroviral Drugs Constrain Access to AIDS Treatment in Africa? *Journal of the American Medical Association (JAMA)* 286(15): 1886-1892
- Banerjee A., Hollis, A. and Pogge T. (2010). The health impact fund: incentives for improving access to medicines. *Lancet* 375, 166-169
- Berndt E. R., Glennerster R., Kremer M. R. et al (2007). Advance market commitments for vaccines against neglected diseases: estimating costs and effectiveness. *Health economics*, 16, 491-511.
- Bijker W. E., Bal R. and Hendriks, R. (2009). Paradox of Scientific Authority: The Role of Scientific Advice in Democracies. Boston: the MIT Press
- Boldrin M. and Levine D.K. (2013). The Case Against Patents. *Journal of Economic Perspectives*, 27, 3-22.
- Boseley S. (2012). *Does eu/india free trade agreement spell the end of cheap drugs for poor countries?* Available at www.guardian.co.uk/society/sarah-boseley-global-health/2012/feb/10/hiv-infection-pharmaceuticals-industry Last accessed September 2013
- Chang, H. J. (2002). *Kicking Away the Ladder – Development Strategy in Historical Perspective*. Anthem Press, London
- Charles C., Gafni A. and Whelan T. (1997). Shared decision-making in the medical encounter: What does it mean? (Or it takes at least two to tango). *Social Science & Medicine*, 44(5), 681-692.
- Coffman T.M. (2011). Under pressure: the search for the essential mechanisms of hypertension. *Nature Medicine* Volume: 17, Pages: 1402 – 1409
- Davies J.E., Neidle S. and Taylor D.G. (2012) Developing and paying for medicines for orphan indications in oncology: utilitarian regulation versus equitable care? *Br J Cancer* 106 (1): pp 14 – 17
- Dikshit R.P., Nagrani R., Yeole B. et al (2011) Changing trends in Chronic Myeloid Leukaemia in Greater Mumbai, India, over a period of 30 years. *Indian J Med Paediatr Oncol* 32(2): 96 – 100
- DiMasi J.A. and Grabowski H.G. (2007a). The cost of biopharmaceutical R&D: is biotech different? *Managerial & Decision Economics* 28: 469-479.
- Dimasi J. A. and Grabowski H. G. (2007b). Should the patent system for new medicines be abolished? *Clinical pharmacology and therapeutics*, 82, 488-490.
- Drummond M., Tarricone R. and Torbica A. (2013). Assessing the Added Value of Health Technologies: Reconciling Different Perspectives. *Value in Health* 16(1), S7-S13.
- Elberse J. E., Pittens C. A. C. M., Buning T. D. C. and Broerse J. E. W. (2012). Patient involvement in a scientific advisory process: Setting the research agenda for medical products. *Health Policy*, 107(2-3), 231-242.
- EU (2012). The 2012 Industrial R&D Scoreboard. Luxembourg: Publications Office of the European Union
- FDA (2013) Patient Network News. Available at: <http://patientnetwork.fda.gov/> Last accessed September 2013
- Flynn J.R (2009) What is intelligence? Beyond the Flynn effect. Cambridge: Cambridge University Press
- Gates B. (2005). <http://www.gatesfoundation.org/speeches-commentary/pages/bill-gates-2005-world-health-assembly.aspx>. Last accessed September 2013
- Gagnon M. P., Desmartis M., Lepage-Savary D. et al. (2011). Introducing patients' and the public's perspectives to health technology assessment: A systematic review of international experiences. *Int J Technol Assess Health Care*, 27(1), 31-42
- Hailey, D. and Nordwall M. (2006). Survey on the involvement of consumers in health technology assessment programs. *International Journal of Technology Assessment in Health Care*, 22(4), 497-499
- Hollis A. (2008). The health impact fund: a useful supplement to the patent system? *Public Health Ethics* 1: 124-133.
- Jacob R. (2013) Personal communication
- IFPMA (2012) Ending Neglected Tropical Disease. Geneva: International Federation of Pharmaceutical Manufacturers Associations
- IMS Consulting Group (2013). Securing IP and Access to Medicine: Is Oncology the Next HIV? Available at http://www.imsconsultinggroup.com/deployedfiles/consulting/Global/Content/Our%20Latest%20Thinking/Static%20Files/IMSCG_Compulsory%20Licensing%20-%20Securing%20IP%20and%20Access%20to%20Medicine_March%202013.pdf Last accessed October 2013
- Kaitin K. (2010). Deconstructing the Drug Development Process: the new face of innovation *Clin Pharm Ther* 87 (3): 356-361
- Kanavos P., Costa-Font J. and Seeley E. (2008). Competition in off-patent drug markets: Issues, regulation and evidence. *Economic Policy* 23: 499-544
- Kanavos P., Sullivan R., Lewison G. et al (2010). The Role of Funding and Policies on Innovation in Cancer Drug Development. London: The London School of Economics and Political Science
- Kaplan W., Vartz V.J., Teeuwisse A. et al (2013). Priority Medicines for Europe and the World, 2013 update. Geneva: World Health Organisation
- Kaye J., Curren L., Anderson, N. et al. (2012). From patients to partners: participant-centric initiatives in biomedical research. *Nature Reviews Genetics* 13(5), 371-376.
- Kent A. (2006). Patients and IP – should we care? *Script-ed* 3,4, 260-264
- Kuhn R. and Beall R. F. (2012). The time for pharmaceutical compulsory licensing has expired. *Nature Medicine*, 18, 1168-1168.
- Love, J. and Hubbard, T. (2007). The big idea: prizes to stimulate R&D for new medicines. *Chicago-Kent Law Review*, 82, 1519 – 1554.
- Love J. (2011). The production of generic drugs in india. *British Medical Journal* 342: d1694
- Light D. W. and Lexchin J. R. (2012). Pharmaceutical research and development: what do we get for all that money? *British Medical Journal*, 345:e4348

- Mestre-Ferrandiz J., Sussex J. and Towse A. (2012). The R&D Costs of a New Medicine. London: The Office of Health Economics
- Murray C.J.L., Vos T., Lozano R. et al (2012) Disability-adjusted life years (DALYs) for 291 diseases and injuries in 21 regions, 1990–2010: a systematic analysis for the Global Burden of Disease Study 2010. *Lancet* 380, 2197-2223
- MSF (2012) <http://www.doctorswithoutborders.org/press/release.cfm?id=6338>, last accessed September 2013
- Nuffield Council on Bioethics (1999). Ethical Issues in Research In Developing Countries. London: Nuffield Council on Bioethics
- Peto R. (2012) Harveian Oration. See <http://www.rcplondon.ac.uk/webstreamed-events/harveian-oration-2012-halving-premature-death-sir-richard-peto> Last accessed June 2013
- Pogge T. W. 2005. Human rights and global health: a research program. *Metaphilosophy*, 36, 182-209.
- Pugatch M.P., Chu R. and Torstensson D. (2012). Assembling the pharmaceutical R&D puzzle for needs in the developing world. The Pugatch Consilium.
- Pugatch M.P., Torstensson D. and Chu R. (2012). Taking Stock: How Global Biotechnology Benefits from Intellectual Property Rights. The Pugatch Consilium.
- Reichman J. H. (2009a). Comment: compulsory licensing of patented pharmaceutical inventions: evaluating the options. *The journal of law, medicine & ethics*, 37, 247-263.
- Reichman J. H. (2009b). Intellectual property in the twenty-first century: will the developing countries lead or follow? *Houst law rev*, 46, 1115-1185.
- Salomon J.A., Wang H., Freeman M.K. et al (2012) Healthy life expectancy for 187 countries, 1990-2010: A systematic analysis for the Global Burden Disease Study 2010. *The Lancet* 380, 2144-62.
- Samant R. and Bennett C. (2008). Decision making in oncology: A review of patient decision aids to support patient participation. *CA: A Cancer Journal for Clinicians* 58(5), 293-304.
- Shahani R. (2013) Personal communication
- Sonderholm J. (2010a). Intellectual property rights and the trips agreement. *Research working papers*, 1, 1-48.
- Sonderholm J. (2010b). A reform proposal in need of reform: a critique of thomas pogge's proposal for how to incentivize research and development of essential drugs. *Public health ethics*, 3, 167-177.
- Sonderholm J. (2010c). A theoretical flaw in the advance market commitment idea. *Journal of medical ethics*, 36, 339-343.
- Stiglitz J. (2007). Prizes, not patents. *Post-autistic Economics Review*, 42, 46-47
- Taylor D.G. & Bury M. (2007) Chronic illness, expert patients and care transition. *Sociology of Health & Illness* 29, 27-45.
- Trotter, a. 2012. Enforcement costs: some humanitarian alternatives to stronger patent rights. *Medico-legal journal*, 80, 22-32.
- UNAIDS (2012). Global report: UNAIDS report on the global AIDS epidemic 2012. New York: Joint United Nations Programme on HIV/AIDS
- Vastag B. (2012). 'Radical' bill seeks to reduce the cost of aids drugs by awarding prizes instead of patents. *Washington Post*, May 19th edition
- Vogel I. (2010). Fund proposed to pay for drugs with greater global impact. *Canadian Medical Association Journal* 182, e231-e232
- Wellcome Trust (2013). Policy on Intellectual Property and Patenting. <http://www.wellcome.ac.uk/About-us/Policy/Policy-and-position-statements/WTD002762.htm> Last accessed September 2013
- Wald N.J. (2013) Personal communication
- Wald N.J. and Misselbrook D. (2011) *The Future of Prevention in Cardiovascular Disease*. London: the Royal Society of Medicine Press
- Wellcome Trust (2013). The approach of the Wellcome Trust in managing intellectual property to maximise public health benefit. <http://www.wellcome.ac.uk/About-us/Policy/Policy-and-position-statements/WTX037150.htm> Last accessed September 2013
- WHO (2006) Public Health, Innovation and Intellectual Property Rights. Geneva: World Health Organisation
- WHO (2012) Good health adds life to years: Global brief for World Health Day 2012. Geneva: World Health Organisation
- WHO (2004) Priority Medicines for Europe and the World. Geneva: World Health Organisation
- Williams O.D. (2012). Access to medicines, market failure and market intervention: a tale of two regimes. *Glob public health*, 1-17.
- Wolff J. (2012). *The Human Right to Health*. New York: W.W. Norton & Co
- Wong-Reiger D. (2013). Personal communication
- Zhang X (1999) Traditional Medicine Worldwide – The Role of WHO. *Drug Information Journal* 33, 321-6

In the world's history certain inventions and discoveries occurred of peculiar value, on account of their great efficiency in facilitating all other inventions and discoveries. Of these were the art of writing and of printing, the discovery of America, and the introduction of patent laws [the most important].

Abraham Lincoln, 1860

Medicines, which may be of the utmost value for poorer countries, can be bought by us only at exorbitant prices, since we are unable to have adequate independent bases of research and production. This apart, sometimes dangerous new drugs are tried out on populations of weaker countries although their use is prohibited within the countries of manufacture. It also happens publicity makes us victims of habits and practices which are economically wasteful or wholly contrary to good health... My idea of a better ordered world is one in which medical discoveries would be free of patents and there would be no profiting from life or death.

Indira Gandhi, 1981

Political systems in rich countries work well to fuel research and fund health care delivery, but only for their own citizens. The market works well in driving the private sector to conduct research and deliver interventions, but only for people who can pay. Unfortunately, the political and market conditions that drive high quality health care in the developed world are almost entirely absent in the rest of the world. We have to make these forces work better for the world's poorest people.

Bill Gates, 2005