

Comments on the UN High-Level Panel Report on Access to Medicines

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“So long as men are governed by unexamined prejudices and led away by sounds, it is natural for them to regard Patents as unfavourable to the encrease of wealth. So soon as they obtain clear ideas to annex to these sounds, it is impossible for them to do otherwise than recognize them to be favourable to that encrease: and that in so essential a degree, that the security given to property can not be said to be compleat without it.”

Jeremy Bentham in about 1792

I have been asked by the International Federation of Pharmaceutical Manufacturers & Associations to comment on the UN High-Level Panel Report on Access to Medicines (“the Report”) published in September 2016.² The views expressed are mine and mine alone. They are based largely on a lifetime of relevant experience.³

1. Summary

In November 2015, UN Secretary General Ban Ki-moon announced the creation of a High-Level Panel on Innovation and Access to Health Technologies (“the Panel”) to “review and assess proposals and recommend solutions for remedying the policy incoherence between the justifiable rights of inventors, international human rights law, trade rules and public health in the context of health technologies.” The Panel comprised a diverse group of 15 eminent individuals⁴ although none had specific expertise in the field of pharmaceutical patent law or compulsory patent licences.⁵ The Panel published its report in September 2016 setting out a number of recommendations aimed at ‘promoting innovation *and* access to health technologies.’

In my opinion:

(a) The Report advocates measures which would certainly reduce the gross income of innovative pharma companies and thereby seriously damage the currently most successful model for encouraging and actually doing pharma R&D;

² Available to download at: <http://www.unsgaccessmeds.org/final-report/>.

³ See Section 2.

⁴ Panel details available at: <http://www.unsgaccessmeds.org/new-page/>.

⁵ Panel member Ruth Okediji is a professor of intellectual property law at the University of Minnesota Law School. The pharma sector was represented only by Sir Andrew Witty.

(b) But the Report contains nothing concrete or practical about promoting innovation. Some of its proposals as regards innovation would have precisely the reverse effect. Others are merely aspirational at best (largely that governments should spend more).

(c) If implemented the Report's proposals will damage existing R&D incentives without replacing them with anything likely to be practical or effective.

I set out here the main Recommendations as they apply to patent protection with my broad comments. The body of my report considers these matters in more detail⁶.

*WTO Members should make full use of the policy space available in Article 27 of the TRIPS by adopting rigorous definitions of invention and patentability to be applied, amending laws to curtail the 'evergreening' of patents and awarding patents only when genuine innovation has occurred.*⁷

My comment. Patent law is already confined to the novel and non-obvious. You cannot re-patent that which is old. Art. 27 TRIPS does not provide any "policy space" relevant to the patenting of medicines. And insofar as it does provide for exceptions to patentability (e.g. for methods of medical treatment) it has not had any benefit. **[See Section 4, below.]**

Governments should apply 'rigorous public health-sensitive patentability criteria'⁸ and, with the support of WIPO, WHO, WTO et al, 'strengthen the capacity of examiners ...to apply rigorous public health-sensitive standards of patentability taking into account public health needs'⁹.

My comment. I do not know what is meant by "public health sensitive patentability criteria". "Strengthening the capacity of patent examiners" make no sense. Firstly because public health needs are not relevant to patentability. And secondly "raising the bar" is both

⁶ The fact that I do not comment on any particular recommendation does not mean that I agree or disagree with it. In some cases I agree or have some sympathy with what is suggested (e.g. early and complete disclosure of clinical trials, positive or negative – provided patentability is not thereby imperilled) in other cases not. This comment is long enough already.

⁷ Report p.9.

⁸ Report p.9

⁹ Report p.9

impractical and a mistaken chimera. Later I describe how examination actually proceeds – and that it takes place at a time when no-one knows whether the invention will prove to have any practical use or will even receive marketing authorisation following Phase III clinical trials. [See Section 4, below.]

Governments should implement legislation which facilitates the issuance of compulsory licences for public health needs, and particularly with regard to essential medicines, based upon the provisions of the Doha Declaration¹⁰.

My comment. Compulsory licences may have effect of reducing prices in the short-term but they also make non-innovators rich and reduce the incentive for innovation in the future. The money which goes to make compulsory licensees rich could be surely be better spent. [See Section 10, below.]

WTO Members should revise the paragraph 6 decision in order to find a solution that enables a swift and expedient export of pharmaceutical products produced under compulsory license. WTO Members should, as necessary, adopt a waiver and permanent revision of the TRIPS Agreement to enable this reform¹¹.

My comment. This would result in a further enrichment of those who do not contribute to innovation and a further reduction of income to pharma companies who rely on their income to finance current research. Much better would be to explore better ways of the patentee providing the medicine to the countries concerned. [See Section 6, below.]

Universities and research institutions which receive public money should prioritize public health objectives over financial returns for their patenting and licensing practices,¹² and adopt policies and approaches that catalyse innovation and create flexible models of collaboration that advance biomedical research and generate knowledge for the benefit of the public¹³.

My comment. Universities with important patents make money which itself goes into research. The Report ignores that. It also ignores all the other financial pressures on universities. Moreover and fundamentally, the Report fails to understand that the only way universities can make money out of any pharma invention they may make is by granting exclusive rights in some way (exclusive licence or sale of patent or spin-off company). Only

¹⁰ Report p.9

¹¹ Report p.9.

¹² Report p.10.

¹³ Report pp.9-10

a commercial company which has the resources and is willing to take the risk would have the capacity to take invention from being a possible good idea through trials to market. If you deny universities the possibility of granting exclusivity of their inventions those inventions are much more likely to remain unexplored - stifled for lack of investment. The Report itself refers¹⁴ to the beneficial effect of the Baye-Dole Act in the US which had the effect of vesting university inventions in the university yet fails to see why that was beneficial.¹⁵ [See **Section 6, below.**]

*It is imperative that governments increase their current levels of investment in health technology innovation to address unmet needs*¹⁶.

My comment. This is wholly general and entirely and merely aspirational. I would guess it is wholly impractical in these hard times for governments to spend more. The Report does not examine in any detail current levels of government funding or how that is actually spent¹⁷. My own rough assessment is that governments (e.g. NIH and MRC) and charities (e.g. Gates and Wellcome) collectively spend about \$30 billion p.a. whereas the top 30 pharma companies spend \$120 billion. [See **Section 6, below.**]

*Stakeholder including governments, the biomedical industry, institutional funders of healthcare and civil society, should test and implement new and additional models of financing and rewarding public health R&D such as the transaction taxes and other innovative financing mechanisms*¹⁸.

My comment. This is not spelt out in any way – and seems wholly unrealistic. What have transaction taxes got to do with funding R&D? So far as I know no-one on the panel was an expert in taxation.

In preparation for a binding R&D Convention that delinks the costs of research and development from end prices to promote access to good health for all, governments should form a Working Group to begin negotiating a Code of Principles for Biomedical R&D which would apply to public R&D funds and should also be adopted by private and philanthropic funders, product

¹⁴ Report p.26

¹⁵ For further discussion,

see, <https://www.autm.net/AUTMMain/media/Advocacy/Documents/BayhDoleTalkingPointsFINAL.pdf>

¹⁶ Report p.10.

¹⁷ Including considering how much is about basic research, how much is targeted at specific diseases and how much is early, non-clinical, work.

¹⁸ Report p.10.

*development partnerships, universities, the biomedical industry and other stakeholders*¹⁹.

My comment. What is supposed to be in this Code? Why didn't the Panel produce a draft? How will it increase R&D? If the costs of R&D are "de-linked" from end-prices what would pay for R&D? [See Section 17, below.]

*Governments should establish and maintain publicly accessible databases with patent information status and data on medicines and vaccines. This information should be periodically updated and consolidated by WIPO in collaboration with stakeholders to develop an international, easily searchable database which should include: (1) standard international common names for biological products; (2) international non-proprietary names for products, either as known at the time of application or after the granting of a patent; and (3) dates of grant and expiry*²⁰.

My comment. This is misconceived. Standard international names for biological products are nearly always given well after the patent application has been made. Dates of grant and expiry of patents are readily ascertainable already. And as far as pharma patents are concerned there is unlikely to be any difficulty in finding out who owns them. This is a non-problem. [See Section 15, below.]

My final summary comments are as follows:

(a) The Panel Recommendations were based upon a general consensus, rather than unanimous agreement.²¹ Panel members were afforded the opportunity to record a personal commentary, appearing as Annex 1 of the report. The commentary of Sir Andrew Witty, CEO of GlaxoSmithKline, distances himself from many of the Recommendations, noting that they "suffer from a lack of rigorous testing, sometimes based upon assertions rather than data/evidence"²² I agree.

(b) Witty points out that the Recommendations are founded upon two flawed assumptions. Firstly, the Report assumes "that the value (clinical or financial) of an innovation is clear at the time of discovery..." Secondly, that "national governments will commit, and be able to raise the very substantial funds that are required to incentivize future

¹⁹ Report p.10

²⁰ Report p.11

²¹ Report p.3

²² Report p.56

innovation.”²³ He emphasizes that “it is often forgotten that almost all of the world’s medical technology has come directly from, or with the enormous contribution of, the research based pharmaceutical, biotechnology and medtech industries.”²⁴ I agree with all of this. It is completely unsatisfactory that the main Report ignores what Witty says.. It is no good, ostrich-like, pretending these serious points do not exist.

(c) In addition, and equally worrying, is the Panel’s ignorance of patent law, and how the patent system works. This infects much of the whole Report. The Panel fails to understand that “TRIPS flexibilities” have significant limits. **[See Section 9, below.]** Issues identified, such as “evergreening” and “patent thickets” are wholly over-stated. **[See Sections 11 to 14, below.]**

(d) The Report is almost exclusively concerned with the price of patented medicines. It fails to put that into its proper perspective. In particular:

(i) Around 95% of WHO’s list of essential medicines are out of patent.²⁵

(ii) If one is speaking about “access to medicines” one should surely consider all matters affecting access – local costs (taxes) supply routes and costs , medical staff and so on.

The Report rather brushes all this aside saying in effect its mandate does not extend to it²⁶. That is taking a very narrow view of “access to medicines.” To most people an inability to diagnose disease and supply medicines for it (whether patented or not) would be regarded as a major obstacle to access to medicines.

(e) The Panel fails to consider how the real problems of incentivisation are to be solved in cases where the prospects of a financial reward are for one reason or another insufficient. These include antibiotics and other medicines that cure, rare diseases, second medical use of known medicines and the development of personalised medicine. Rather than recommending undermining that which does work, the Panel should have focused on what does not.

²³ Report p.56

²⁴ Report p.56.

²⁵ Many of course, now generic and low priced, were once generic. There may be a somewhat larger proportion following a current re-assessment of essential medicines, see Gilles Forte, World Health Organization <http://www.ip-watch.org/2015/04/21/who-reviews-its-essential-medicines-list-some-new-candidates-under-patent/>. But the proportion will inevitably always be much smaller than that of generic medicines.

²⁶ Report p.7.

2. My Qualifications and Relevant Expertise

Having first read Natural Sciences at Cambridge and law at LSE, I started as an intellectual property barrister in 1967. I was made Queen's Counsel in 1981. I became a High Court Judge in 1993 and was one of the select few of judges assigned to take patent cases. In 2003, I became a member of the Court of Appeal and was the judge in charge of the intellectual property list. I sat on nearly all patent cases in the Court of Appeal during the next 8 years. Although I decided to leave the Court in 2011 to take up my present appointment, I continued to sit in the Court of Appeal from time to time – last doing so in a pharma patent case in April 2016²⁷.

Based upon my time at the Bar and on the Bench, I have gained a lot of experience of pharma patent cases. This extends beyond a grasp of the legal questions of patent infringement and validity, to a quite deep understanding of how the economics of the pharma industry works, the latter arising from my involvement with compulsory licences and extension of patent terms.

Until 1978, the Patents Act 1949 was in force in the UK.²⁸ Section 41 of this Act contained a provision for the compulsory licensing of patents for food or medicines²⁹ (on terms to be settled by the Patent Office). The Patents Act 1977 (implementing the European Patent Convention) extended the term of all existing patents from 16 to 20 years. While it repealed section 41, it also provided for those patents which had 11 or less years to run and

²⁷ The patent was invalid.

²⁸ The Patent Act 1977 came into force on 1 June 1978.

²⁹ s.41 (1) Without prejudice to the foregoing provisions of inventions this Act, where a patent is in force in respect of- relating to food (a) a substance capable of being used as food or medicine or medicine, g etc. or in the production of food or medicine ; or (b) a process for producing such a substance as afore- said ; or (c) any invention capable of being used as or as part of a surgical or curative device, the comptroller shall, on application made to him by any person interested, order the grant to the applicant of a licence under the patent on such terms as he thinks fit, unless it appears to him that there are good reasons for refusing the application. (2) In settling the terms of licences under this section the comptroller shall endeavour to secure that food, medicines, and surgical and curative devices shall be available to the public at the lowest prices consistent with the patentees' deriving a reasonable advantage from their patent rights. (3) A licence granted under this section shall entitle the licensee to make, use, exercise and vend the invention as a food or medicine, or for the purposes of the production of food or medicine or as or as part of a surgical or curative device, but for no other purposes.

whose term had been extended a system of compulsory licences³⁰ for those last four extended years. The terms of s.41 licences and licences of right were hotly contested, particularly in pharma cases. During my time at the Bar, I represented both applicants and patentees, which required a detailed examination of incomes, accounts and costs.

I also had a lot of experience of patent term extension under s.23 of the 1949 Act. Under this provision, a patentee could apply to the Court for an extension of the 16-year term by up to 10 years in exceptional cases on the grounds that the “patentee has not been adequately remunerated by the patent”.

While I sometimes represented private parties seeking, or objecting, to extension, my main experience of patent extension was acting on behalf of the UK Patent, acting as an *amicus curiae* to safeguard the public interest.³¹ A lot of these patent extension cases were pharma cases because of delays in gaining market authorisation.³² As with the compulsory licence and licence of right cases, patent extension cases involved a very detailed examination of the remuneration received by the patentee from the invention– as well as a detailed history of the patent and attempts to commercialise it. One got a unique view – from the making of the invention right through the life of the patent. The economics and technical side all came into it. There is nothing like that sort of examination of the life of a patent and its commercialisation anywhere in the world today as far as I know. One of the things I learned then was that there is a lot more to bringing a medicine to market than just the initial idea contained in the patent. That remains true today, indeed with stricter regulatory control, with even more force.

My more recent experiences with pharma patents came whilst I was a judge at first instance and then later as an appeal judge. Of the pharma cases which came before me, I found 11 times for the defendant and 12 times for the patentee. In one of the cases my finding of invalidity was reversed by the Supreme Court. No one should be surprised by these figures – particularly by the success rate of defendants. I will explain why more below.

3. Some examples

³⁰ Called a “licence of right”.

³¹ In that capacity I appeared in all extension cases for about the last 2½ years before they were abolished.

³² Regulatory controls of new medicines were introduced following the thalidomide disaster of the early 1960s, meaning that a patentee could not sell until marketing authorisation was given.

One can learn a lot from particular cases – generalising up from particular facts, evidence in the true sense. Here I tell a few.

3.1 *Phenothiazine*

Very soon after starting practice I became involved (as a lowly second junior) in a case about a powerful psychotropic drug called phenothiazine³³. A generic medicine company called Biorex wanted to import from a non-medicine patent country³⁴ and sell it here. But the patent, owned by a company called Olin Mathieson and exclusively licensed to Smith Kline and French (“SK&F”) stood in the way. Biorex said the invention was obvious and so the patent was invalid. Phenothiazine differed from a known drug called chlorpromazine only slightly. Both had a three benzene ring “head” with an alkyl tail. On what was called the 2-position of the ring chlorpromazine had a chlorine atom. Phenothiazine had a tri-fluoro, -CF₃, in that position instead. Biorex said it was obvious to substitute the -Cl with -CF₃. Arguments raged. For instance, Biorex said you could work out what the -Cl was doing - electron attracting. So, it said, that a stronger electron attracting group such as -CF₃ would probably work better and was thus obvious. SK&F said not so – the whole electron-attracting theory was (a) unproven and (b) an idea only developed with hindsight. SK&F won³⁵ – which meant that the money from phenothiazine sales continued to flow in.

3.2 *Cimetidine*

It was that money which SK&F could and did use to invest in more research. Whilst the phenothiazine war was going on, SK&F had engaged James Black as head of research. At his previous company, ICI, James Black had invented a new drug – propranolol, the first beta-blocker. At SK&F he had an idea about a drug for stomach ulcers – a serious problem as those old enough can remember – my grandmother suffered from one. It had been realized that an increase in stomach acid (which caused ulcers) was associated with the release of histamine. Black hypothesised that there were chemical sites in the stomach to which histamine would bind and when it did, it was that which caused acid secretion. There was reason to doubt that: after all anti-histamines were known and were commonly used for instance for reducing inflammation from insect bites and for reducing cold symptoms, both of

³³ It has long since been superseded by better drugs with less side effects – those drug of course will themselves have been patented.

³⁴ Italy, I think, which did not allow patents for medicines at all on the basis of the sort of thinking in the Report.

³⁵ *Olin Mathieson v Biorex* [1970] RPC 157.

which were also associated with increased levels of histamine. The known anti-histamines had no effect on stomach ulcers. But despite that, Black surmised that there was a different sort of site in the stomach, one to which the known anti-histamines would not bind. He pursued this idea relentlessly for years. What paid for this? Why the profits SK&F were making with phenothiazine and some other patented drugs. Black eventually (his work took around 8 years) came up with a new class of drug called the H₂-receptor antagonists. These blocked the histamine receptor sites in the stomach.

I visited SK&F in Welwyn Garden city the day after the first human test of the first one of these. The subject went to University College Hospital where he had a pipe put down to his stomach to take samples of the acid there. He was given an injection of histamine. You could see from the graphical print out the acid level go up (pH fall). Then the subject was given the antagonist and the acid level went down. That first human subject was James Black³⁶. Clinical trials (at least 6 years) followed. The actual drug used by Black in that first trial later proved to have some side effects and another product, cimetidine, made it to the market in 1976. It quickly became the biggest selling pharmaceutical in the world in money terms. And operations and hospital admittance for stomach ulcers virtually ceased.

The moral of this story is important – nay vital - to understand. The moral is simply this: the patented inventions of today pay for the research and development of the new medicines of tomorrow. I am afraid the authors of the Report entirely miss that. Proposing, as they do, measures which will cut the income of research based pharma companies is, however well meant, a proposal to reduce R&D into new medicines. I will elaborate on both these points below.

Returning to cimetidine, there is more to tell, something which illustrates another effect of the patent system. Eyeing SK&F's success with cimetidine was Glaxo. Someone there asked: is it possible that there could be an H₂ antagonist, perhaps a better one or at least one as good as cimetidine? And could it be outside the scope of SK&F's patent? Costly research led to just such a compound, ranitidine. It was superior in some respects (or said to be) to cimetidine. Glaxo patented it and it too became a blockbuster medicine. The incentive for Glaxo had been to invent around the SK&F cimetidine patent and get its own patent. The patent incentive had given doctors a new weapon against stomach ulcers.

³⁶ Sir James Black was later awarded the Nobel prize – the only person to have invented two major classes of medicine.

One final story about cimetidine. The patent was one of those whose term was extended by four years by the Patents Act 1949 but subject to licences of right for those four years. Two generic companies applied for such licences in the Patent Office. There were appeals about the rate of royalty first to the High Court and then to Court of Appeal. In the end a fixed royalty was determined. It amounted to 46% of SK&F's price before generic entry³⁷. An outsider might think that sounds a lot, but it was not in reality – it was a bargain. Manufacturing costs were, as is typical for medicines, very low. So selling even at 80% of SK&F's price would give a huge margin for profit – after all the generic companies had virtually no costs – no R&D costs, no promotion costs, slight importation and distribution costs. And no risk. The entire market for generic prescriptions of cimetidine³⁸ went to the generic suppliers within three months.³⁹ The owner of those generic companies (who also got licences of right for other medicines) became rich⁴⁰ without, as far as I know, ever contributing anything to medical research.

Of course when the patents for cimetidine and ranitidine ran out, like all other formerly patented medicines, they became cheap. As an individual you can buy 60 200 mg tablets from Amazon for about US\$10. No doubt it would be much cheaper still for a government, NGO or hospital to buy in bulk. And both medicines are on WHO's list of essential medicines.

The pattern is exactly the same for all or practically all new medicines. A high initial price whilst still under legal protection followed by a generic price.⁴¹ And it is only the high price which generates the substantial gross profits needed for future R&D.

³⁷ [1990] RPC 203. This case is well worth studying by anyone who has an interest in compulsory licensing,

³⁸ Doctors could prescribe "cimetidine", the generic name, or Tagamet, the trade mark. If they did the latter the pharmacist had to supply the SK&F product but if they used the generic name either the generic product or SK&F's could be dispensed.

³⁹ Who got his supplies from a country where SK&F had no patent.

⁴⁰ As is generally the case for owners of generic companies who have low costs and compete with high price originator companies who have high costs. The High-Level Panel never even inquired into the money made by generic drug companies without who have, as a class, contributed nothing or little to the search for new medicines.

⁴¹ Actually there is a short period immediately after first generic entry when the generic price is only a little below that. Generic companies are motivated by profit. If you can be the first generic competitor to the patentee you can price yourself initially at just below that of the patentee. And that is exactly what happens.

3.3 *Carboplatin/cisplatin: Research Corporation's (Carboplatin) Patent*⁴²

The carboplatin patent case is very instructive about costs of a drug and of treatment. The patent was one of those whose term had been extended from 16 to 20 years, subject to the last four being licence of right. An Australian generic company applied for a licence. As is inevitable in any compulsory licence dispute there was a fight about the royalty rate. The applicant said that the patentee's price for carboplatin was too high. It cost eight times as much as the generic product, cisplatin. Medically speaking they were very similar; they were both platinum containing used principally for the treatment of ovarian cancer. However, cisplatin required the patient to be in hospital for 3 weeks after treatment – the drug caused dreadful side effects such as severe vomiting. Carboplatin did not have these side-effects; Patients could be treated and go home that same afternoon, returning only for the next treatment. There were no hospital treatment costs. The applicant said that made no difference for two reasons. Firstly, the pharmacy budget was a different budget from the general hospital budget, and secondly, even if this bed was not used for three weeks with a patient being treated with cisplatin there would be no saving. Why? Because another patient would occupy it being treated for something else – such is the logic of medical economics. This is what Mr Justice Hoffmann said:

The evidence is that current annual sales of carboplatin in the United Kingdom amount to 8 kg. which is sold for between £2.5 and £3 million, almost exclusively to hospitals. An average 600 mg. dose of carboplatin costs the hospital about £400. This price may be contrasted with that of cisplatin, now out of patent, where competition and price cutting has reduced the cost to about £22 for a 150 mg. dose. These dramatic figures illustrate the frequent disproportion in the drugs industry between the research and development costs and the actual cost of manufacture of the drug once it has been proved and tested. Companies engaged, whether as patentees or licensees, in the research and development of drugs are therefore very dependent upon being able to exercise their monopoly power during the period of the patent in order to recoup their research and development expenditure and make a profit.

Although carboplatin is approved for ovarian and small-cell cancers, its principal use is for the former indication. The number of patients suffering from this cancer is about 4,500, of whom some, on account of the stage of their disease or for other reasons, are not suitable for platinum chemotherapy. Those available for such treatment are probably not much in excess of 2,500, of whom about 2,000 are being treated with carboplatin and the rest with cisplatin. On the other hand, further clinical trials being supported by Bristol-Myers at a cost of

⁴² [1990] RPC 663.

£250,000 a year may lead to the approval of carboplatin for other indications. It estimates that if such approvals were obtained, about 7,500 more patients now being treated with cisplatin might benefit from treatment with carboplatin. At present, however, the scope for expansion of the United Kingdom market is relatively small. A very substantial fall in price might induce some hospitals to undertake more clinical trials, but would at the same time remove the incentive for Bristol-Myers to support such trials. The applicants, on the other hand, have funded some cancer research on a small scale in Australia but make no contribution to carboplatin research.

Evidence from hospitals shows that, because of its cost, they are careful about prescribing carboplatin. Carboplatin has what in a rational economic system might be thought to be the cost advantage that it can be used to treat out-patients whereas the side effects of cisplatin mean that the patients usually have to be admitted to hospital. Even at present prices, therefore, it appears from a letter to *The Lancet* in December 1988 that carboplatin actually costs less to use than cisplatin. But this is not how it appears to hospitals, which have a limited drugs budget and gain no financial advantage by not having to admit one patient when there is always a waiting list of others. At Royal Marsden Hospital expenditure on carboplatin is about 10% of the drug budget. At Newcastle General Hospital the head of the pharmacy department says that a reduction of about 20% in the price of carboplatin led to a small increase in use but that cisplatin is still used on a general basis because it is very much cheaper. This suggests that, given the way the National Health Service budgets work, substitution of carboplatin for cisplatin is unlikely to happen on any large scale until the price differential is substantially reduced. Unless the royalty is fixed at a rate which enables the applicants to undercut Bristol-Myers by a very considerable margin, this is unlikely to happen. In the Manchester area it appears that a fixed annual sum is allocated by the regional health authority to carboplatin.

3.4 *Hepatitis C*

My last case as a barrister was about this vile disease. By around 1980, two forms of hepatitis were known. They were called A and B. They had been identified by so-called “classical” techniques involving the raising of antibodies in rabbits and the like. Kits for testing for A and B were used on all blood donations to prevent the passing of these diseases. But some blood donees were still getting hepatitis. It was serious. And Factor VIII, made from a lot of donations, was given to haemophiliac children. Lifesaving though the treatment was, it came at a high price: nearly all such children got hepatitis as the price of their life being saved. Doctors called this non-A non-B hepatitis— for no one knew whether there was just one more agent or many. All they knew was it was not A or B. That was the position for over 10 years

In the early 1980s the new techniques of genetic engineering were coming in. “Aha said everyone. It will be easy to find the virus or viruses now”. A massive hunt started, with many big companies (and universities and non-profit research institutes) using the new techniques in the hunt. But no one could find anything. By 1988 some scientists had even begun to doubt that there was a virus at all— maybe the agent(s) was or were a prion not a virus. Not much was known about prions, proteins which somehow carried quasi-genetic information even though, unlike DNA or RNA they had no nucleotide sequence of genetic code. But one Californian company called Chiron, funded by speculative venture capital, was convinced that there was at least one virus to be found. A Nobel prize-winner, no less than Harold Varmus⁴³, told them to give up. But the small team at Chiron, headed by a very obstinate Englishman, and consisting of himself, an American, a Taiwanese Chinese and a Singaporean Chinese had other ideas. They persisted and persisted. The risk money paid for them and their laboratory. The Taiwanese had an idea, a small variation from the standard technique of genetic engineering then being employed. The Singaporean spent about 17 hours a day for months inspecting radiological images. And in 1989 the little blighter was found! It was indeed a virus and was called, not surprisingly, Hepatitis C. It turned out to be the main non-A non-B culprit, though there are also D and E.

Once the virus had been found it was possible to get its genetic code and protein sequence. It was then quite easy to produce a testing kit – to find out if the hepatitis C virus was in in a blood donation⁴⁴ or hepatitis patient. The first kit was on the market within a year or so of the detection of the virus. The kit of course made a huge difference. Blood donees were no longer getting hepatitis. And haemophiliac children getting factor VIII were not getting it either.

Chiron sold its kits at a cost of £2 per blood donation. That price was four times higher than the cost for tests for other blood borne diseases. Hepatitis A, Hepatitis B and HIV kits were 50 pence per test. Chiron was making substantial profits, their cost of manufacture being much the same as for these other kits. A person with Bentham’s “unexamined prejudices”, one who is “led away with sounds” would say this level of profit is outrageous.⁴⁵ But rationalists, those who can “annex clear ideas to those sounds” would react differently.

⁴³ Discoverer of the oncogene.

⁴⁴ Some people are just carriers and do not develop symptoms.

⁴⁵ The public debate about patents is old and never stops. See the opening quotation from Jeremy Bentham.

Think of (a) the lifesaving and (b) the true economic effect. Lifesaving speaks for itself but the economic effect is worth considering more: calculations at the time suggested the average cost of treating those who got non-A non-B hepatitis from blood donations was roughly £10 per donation. On that basis the £2 per donation test kit was very well worth it indeed. And that £10 did not include the other costs to society of large numbers of severely ill patients who otherwise would have been infected by blood donations contaminated with the virus.

Chiron's level of profit of course attracted copyists, those who wanted to sell hepatitis kits at something rather less than £2 but still way above the 50p price of other test kits⁴⁶. Chiron responded by suing in the UK for patent infringement the day their first patent was issued anywhere in the world⁴⁷. The copyists said, as they often do "oh but your invention was obvious". Chiron said not so – look at the real world, why could no-one find this virus despite the long search by so many? Can that which a Nobel prize-winner advised was too difficult really have been obvious? Not surprisingly Chiron won.

There is a follow-up. Hepatitis C is a quite a common serious disease. It is said to be the cause of 27% of cirrhosis cases and 25% of liver cancer worldwide. Research into the disease immediately flourished around the world as a result of Chiron's work, disclosing as it did the existence of the virus and its aminopeptide and genetic sequences. Scientists now had a tool to access to the gene of the virus and could do all sorts of research – into different forms⁴⁸ of the disease, for a vaccine and even for a cure. The work has been long and difficult. But recently a vaccine has been undergoing test and at least two drugs which actually cure have come on the market. They came in at a high price – was it worth it? See the further discussion below.

One can be quite sure that but for the patent system, no-one would have invested the intense effort, cost and risk which went into trying to find the agent(s) which were the cause(s) of non-A non-B hepatitis. I daresay the virus would have been found one day, but certainly not in 1989 and probably not for many years later. So also for the new curative medicines. The incentive of the patent system, put simply, was responsible for saving millions of lives. And it advanced both pure science and practical medical knowledge.

⁴⁶ They all cost about the same to make.

⁴⁷ The UK Office was, and still is, one of the fastest patent offices in the world.

⁴⁸ There are six known genetically distinct types.

4. Basics of Patent Law – the ‘Patentability Criteria’ and the Application Process

It is evident from the Report that the Panel, at a number of points, failed to understand both some basic substantive patent law and how the actual procedure of getting a patent works. Nor did it consider how parties in practice can deal with granted patents which are nonetheless invalid. A number of the Panel’s recommendations are based on these misunderstandings. They are either simply impractical or more seriously contrary to law. Here are some basics.

In a nutshell there are just five basic conditions for the grant of a valid patent. Not all patent laws use these names but, by and large, they all amount to the same thing. They are:

- (a) The subject-matter must be of the kind which is eligible for patent protection;
- (b) The subject-matter must be capable of industrial application⁴⁹;
- (c) The subject-matter must be new;
- (d) The subject matter must be “inventive” – which equates to non-obvious;
- (e) The patent must be enabling.

There is no requirement that the invention be better or more efficient or superior or cheaper than anything that has gone before. Such a requirement would be both completely impractical and subversive of the incentive to invent. It would be particularly damaging if any attempt were made to apply this sort of notion to pharma patents. This is because pharma inventions are made years before the medicine reaches the market. As a rule, no-one will or could know - as of the date of filing of the patent - whether the medicine will be safe or how effective it will be. Not until Phase III clinical trials are over and marketing permission is given is it possible to assess with confidence how effective and safe it is in practice.

Next there is this. In all cases and in all countries, patentability is a question of law. It is not a matter for government decision or discretion. In disputed cases, ultimately it is for the national courts, not politicians, to decide. National courts make their decision by applying national patent law – not government policy. The same goes for national patent offices. They also, of course, have to decide whether the subject-matter is patentable, (i.e. whether it is patent eligible, capable of industrial application, new, non-obvious and enabling) as part of

⁴⁹ The notion also goes by the name “useful”. This is a very low threshold requirement. As it is of little relevance to the subject of the Report, I say no more about it here.

the patent examination process. But again this is a matter of law and in most countries, if not all, the office decision is subject to challenge in the courts⁵⁰.

It is thus simply not legally possible for governments or politicians to instruct patent examiners or judges as to what they must decide about patentability – they are bound to apply the legal rules as to patentability to the facts of the case before them. Actually this is part of something rather fundamental. Deep down it is about the rule of law. Patents, like all other legal rights, are created by law, not rulers⁵¹.

The Report says:

These multilateral organizations [they are listed – none are patent examining or granting authorities] should strengthen the capacity of patent examiners at both national and regional levels to apply rigorous public health-sensitive standards of patentability taking into account public health needs⁵².

But it is not for any of the organisations concerned to tell patent examiners how to perform their task – nor do they have the capacity to do so if they wanted to. Moreover, what is suggested is completely impractical. I am not sure what the authors mean by “Public health standards of patentability” – perhaps something along lines of an invention which, when it has finally got through its regulatory procedures (passed its Phase III trials and got marketing authorisation). But that is years later than the patent application – all you are apt to find in that is some slight indication of a desirable medicinal effect. Seldom is there even any disclosure of effects on humans. What are patent examiners supposed to make of that? Deny the patent because it does not prove that public health needs will be met? That would be the end of all pharma patents, the research-based pharma industry and the stream of new important medicines the patent system has made possible.

⁵⁰ Article 62(5) of TRIPS mandates the possibility of judicial or quasi-judicial review of, inter alia, decisions about the acquisition of intellectual property rights.

⁵¹ In mediaeval times absolute rules did grant patents, some indeed for inventions (Brunelleschi’s patent for some kind of barge to bring Carrera marble to Florence is the most famous example. It was the Republic of Venice which was the first to create a law for the grant of patents for inventions in 1474.

⁵² See p.9 of the Report. Contrast with Witty’s observations on p.57: “Patentability must be based on clear, rationale and predictable criteria. The Report proposes that Member States should have the right to define these criteria in the best interests of public health without in any way describing how that is to be judged. This would create complexity and unpredictability for all stakeholders involved in the innovation process.”

4.1. *Eligible subject-matter – the type of things that can or cannot be patented*

This is about the *type* of thing (product or process) which may or may not be patented. Most, perhaps all, patent laws, contain provisions about this. Some types of subject-matter are simply expressly excluded from the patent system. It does not matter whether they are new, enabled and inventive, the law says they cannot be patented. A simple non-controversial example would be a new symphony or painting.⁵³ More “industrial” examples, away from medicines, are that under the European Patent Convention, computer programs and business methods “as such” are not be regarded as inventions⁵⁴. In the US there is no corresponding statutory provision, but the Supreme Court has in recent times been active in finding that some inventions (particular for computer program and business methods) are excluded subject matter.⁵⁵ Again the US judge-made exclusion is far from clear.

As regards the field of medicine there are some express exclusions which are pertinent. In earlier times the exclusions were wider in scope than they are now. For instance, when I came to the Bar, Italy along with many other countries, did not permit the patenting of medicines at all – it was from Italy that the applicants for s.41 compulsory licences intended to source their product. It is worth noticing that there was no or virtually no research in Italy into new medicines at this time.

Currently in Europe Art.52 of the EPC provides:

European patents shall not be granted in respect of:

(a) inventions the commercial exploitation of which would be contrary to ‘ordre public’ or morality; such exploitation shall not be deemed to be so contrary merely because it is prohibited by law or regulation in some or all of the Contracting States;

(b) plant or animal varieties or essentially biological processes for the production of plants or animals; this provision shall not apply to microbiological processes or the products thereof;

(c) methods for treatment of the human or animal body by surgery or therapy and diagnostic methods practised on the human or animal body; this provision

⁵³ Considered to be protectable, if at all, under the standards provided by copyright law.

⁵⁴ EPC Art. 52(c). These exclusions are far from clear – much ink has been spilled on decisions and articles about the limits of the exclusions for reasons which it is not necessary to go into here.

⁵⁵ See *Alice Corp.v CLS Bank* 573 US S.Ct 2347 (2014).

shall not apply to products, in particular substances or compositions, for use in any of these methods.

The most important of these exclusions is that the actual method of treatment by a doctor cannot be patented in any of the countries of the European Patent Convention. That is so in many other countries, although the USA is a notable exception. But in practice, patentees in the US have not tried to take legal action against individual doctors⁵⁶. There are other exclusions but compared to this exclusion they are of lesser overall significance⁵⁷.

There is also room for some judge-made law about patent eligibility. This is because in most if not all laws the word “invention” is not defined. The line between “a mere discovery” (unpatentable) and an “invention” is apt to be fuzzy. Thus courts in different countries can come to different conclusions about this (e.g. in the US an “isolated” gene is unpatentable as a discovery whereas the cDNA is patentable,⁵⁸ whereas in Australia neither are⁵⁹).

On the other hand, and very importantly, it is not possible in my opinion for a country to restrict the concept of “invention” so far as to exclude the patentability of a new and inventive medicine. The modern pharma industry could not exist without such patentability. And no or very few of the new medicines created since the Second World War would have been invented, or even if invented would have been researched and developed so as to be safely brought to market⁶⁰. Those who negotiated TRIPS knew that, and if they had wanted

⁵⁶ Or at least to any great extent. The politics and adverse publicity of suing actual treating doctors is obvious.

⁵⁷ Another exclusion is provided by the Biotech Directive, 98/44/EC. Article 6(1) repeats EPC Art.52(a) and then adds an interpretation of this in Art.6(2). Art 6(2) includes “(c) uses of human embryos for industrial or commercial purposes.” Controversially the CJEU interpreted this exclusion very widely so as exclude from patentability not only products or processes which actually involved the commercial use of human embryos but also such products or processes whose invention or use involved the destruction of a single such embryo. It was said to be contrary to human dignity but many, including me, find it very difficult to see why destruction of a single embryo, which would have legally destroyed anyway, is contrary to human dignity. At my University, UCL, for instance, Professor Pete Coffey is investigating the use of a treatment for the cure of macular degeneration (7 million Europeans suffer from this). His work involved at the outset the destruction of a single embryo which in due course would have been lawfully destroyed anyway. Is relieving this major source of human misery and diminishment “contrary to human dignity?” Fortunately it has turned out that research involving the destruction of a human embryo has not become as important as it was once thought to be – other approaches, e.g. the use of pluripotent stem cells from parthenogenetically-activated oocytes, are being used, see CJEU Case C-364/13 *International Cell Corporation v Comptroller of Patents*.

⁵⁸ *AMP v Myriad* 133 S. Ct. 2107 (June 2013)

⁵⁹ *D’Arcy v Myriad* Case NoS28/2015, October 2015).

⁶⁰ And most especially since the 1960s when, following the thalidomide disaster, new medicines needed rigorous regulatory approval for safety and efficacy.

to provide a derogation in the case of new and inventive medicines they would surely have so provided.

Once upon a time a country was completely free to decide what sort of thing could, or could not, be patented and what rules applied to patents generally. Indeed, they were free to decide not to have a patent law at all. For instance, there was a strong anti-patent movement in the nineteenth century.⁶¹ Holland even abolished patents for inventions from 1869 to 1912. It then changed its mind. The Dutch-based Philips company, which started during the period of abolition, is now the top European patenting company!

TRIPS has significantly limited the former complete legal freedom of a country to have what patent law (if any) it likes⁶². TRIPS is an international treaty. Failure to abide by it can ultimately result in sanctions. I shall discuss further how far TRIPS has limited that freedom as regards medicines below.

4.2. *Novelty*

You cannot patent that which is old. By and large the rule is the same in all countries. The European rule for what is old is about as comprehensive as one can conceive:

The state of the art shall be held to comprise everything made available to the public by means of a written or oral description, by use, or in any other way, before the date of filing of the European patent application.⁶³

This is a stringent and far-reaching definition. Single prior oral disclosures can destroy a patent, wherever made in the world. So also a single publication of a document in whatever language.

Nearly all other countries (including now the USA) have a first to file system, though in some cases with a grace period⁶⁴. As a practical matter in the field of pharma these

⁶¹ See e.g. *Patent Abolitionism*, Mark Janis, Berkeley Technology Law Journal, Vol 17 Article 9, March 2002.

⁶² Even before TRIPS there was of course political pressure on trading countries to have some sort of patent system – and most did, though, not surprisingly, particularly for developing countries, the system was at best rudimentary. You cannot reasonably expect a poor country to have a fully developed patent office and patent courts – they have bigger problems to worry about. That is still the case today. And is of course the case as regards public health. Access to clean water and doctors, nurse and hospitals is much more important than making the very small proportion of essential medicines still in patent available at cheap prices.

⁶³ Art.54(2) EPC.

differences do not matter – for instance most pharma companies do not make use of a grace period because they want patents around the world including in first to file countries such as those of the European Patent Convention⁶⁵.

On p.18 the Report asserts:

“WTO Members may develop their own definitions of ‘novelty’, ‘inventive step’ and ‘industrial application’”

That is wrong – there is nothing in TRIPS or the DOHA Declaration about any flexibility either to strengthen or to water down these patentability criteria. As far as novelty is concerned, it is, I would have thought self-evident even to a non-lawyer, that basically an invention is new or it is not.⁶⁶ Moreover, this is not a matter for Governments – it is a question of law. Of course there may be a legal question about what is new. For instance, if a patent is for a particular specific compound, can a prior disclosure of a large class which includes that compound be novelty destroying? As regards the big picture, however, this sort of minor difference in the application of the law does not matter.

What does matter is the relevance of novelty in the context of so-called “evergreening.”⁶⁷ For the plain fact is that once a product has been disclosed it cannot simply be re-patented. It follows, in particular, that a medicine on the market cannot be validly covered by a later patent. I discuss this more below.⁶⁸

4.3. *Inventive step – obviousness*

Inventive step and non-obviousness are different terms for the same thing⁶⁹. They convey the same notion for the self-evident reason that if an idea is not obvious (to the person skilled in the art) then it requires invention (i.e. an inventive step) to arrive at it. They are opposite ways of saying the same thing.

⁶⁴ This is the popular name for a legal rule which deems a prior disclosure by the inventor within a specific window not to be used as the basis for an invalidity attack.

⁶⁵ E.g. a prior disclosure in the US by the inventor would prevent any valid European patent from issuing, even though the grace period may save the US patent - (it is a little complicated).

⁶⁶ There is only scope to determine which prior disclosures are relevant, when considering novelty.

⁶⁷ See p.22 of the Report, stating that “national authorities ...interpret the criteria broadly, granting secondary patents ...[which] prolong exclusivity (commonly known as ‘evergreening’).

⁶⁸ See Section 11, below.

⁶⁹ TRIPS by note 5 to Art 27(1) says: “For the purposes of this Article, the terms ‘inventive step’ ...may be deemed by a Member to be synonymous with the terms ‘non-obvious’....”

As regards the legal test for obviousness the basic rule is universal – was the invention obvious to a person skilled in the art at the priority date of the patent? It is true that this is not a very precise standard, but it is nonetheless a legal standard, not one for governments to modify. And as I have said the same goes for “invention” itself – governments are not free to say that only inventions which turn out to be real improvements are patentable.

What patent law does not do is to require any more than non-obviousness, for instance that the invention be really important or a great improvement. If patents were only confined to the really important then there would be none for incremental (or alternative) ideas. The incentive to keep on finding new ways would be seriously eroded – yet in the real world much of what happens by way of improved technology is by incremental improvement, not by great seismic changes in technology.

Obviousness is probably the commonest form of invalidity, at least that which is disputed in the courts. It is not a very precise concept. It involves a hindsight question when one already knows what the invention is: the question is was it obvious when the patent was applied for? And apart from technical questions secondary questions may arise too – for example, if an apparently simple invention has proved to be very successful commercially and could have been made much earlier, the seemingly obvious with hindsight may be found not to have been obvious – for if it was, why was it not done before?

Quite a substantial number of granted pharma patents are found on closer examination to be invalid for obviousness. For instance, patents for combinations of two medicines each of which merely has its own known effect, routine new formulations of an existing medicine, self-evident or new dosage regimes which were routine to investigate, or new crystalline forms of known medicines are all apt to be obvious. You get exceptions – for instance a new formulation which unexpectedly enhances the efficacy of the drug⁷⁰. Each case has to be examined on its merits.

⁷⁰ *Napp v Ratiopharm* [2009] EWCA Civ 252. The invention turned a minor known painkiller, oxycodone, into a frontline painkiller similar to morphine.

In this connection, no one should think that the percentage of invalid pharma patents is higher than in other fields of technology. Indeed, if anything, the position is the other way round. For instance, the telecoms industry has many, many more patents than does the pharma industry. They are less readily searched and it is my impression that many more and a greater proportion of telecoms patents are invalid compared with those of the pharma industry.

From time to time⁷¹ economists, competition authorities, and others raise concerns about patents granted by patent offices but which are subsequently found to be invalid, often, but by no means exclusively, on the grounds of obviousness I discuss the question of invalid patents in more detail below⁷².

4.4. *Enablement (sufficiency of description)*

One of the basic justifications for the patent system is that the patentee must disclose not only what he claims as his invention but also how to perform, or enable, it. Early disclosure is part of the trade-off for patent protection. Absent the patent system, people would naturally hold back information as to what they were up to for as long as possible.

Patent law therefore requires an enabling disclosure – how to perform the invention over the full range of the subject-matter claimed. This rule can have some importance in disputes *between* major research-based pharma companies: one says the other has claimed too widely based upon the disclosure made. But it is an objection to validity which has relatively little practical significance as regards competition between generic makers and research based patentees. I say no more about here.

4.5. *Procedural Patent Law*

The Report has little to say about procedural patent law, yet it is vital to understand this if one is to understand the system as a whole. I will endeavour to set out the basics so far as relevant.

⁷¹ Actually from as long ago as the mid-nineteenth century – the Janis article, *supra*.

⁷² Originally published as ‘Raising the Bar: a mistaken Chimera’ in *Concurrence Santé Publique, Innovation et Médicament*, L.G.D.J lextenso editions (2010), and with an updated commentary is Chapter 28 of my Book *IP and Other Things*, Bloomsbury, 2016.

A basic outline of the application process is this:

- (i) The patentee files an initial specification in a particular country or via the PCT system to establish a “priority date”. That application can itself be processed, but generally is used as the basis of a priority claim for applications filed within a year of the priority filing. The patentee must decide within that year which country or region (where there is a regional system – particularly the EPC) where he wants protection, or he can file via the PCT system if more time is needed to make that decision.
- (ii) He then files applications in all the countries or regions where he wants protection. The specification filed forms the basis of search and examination by the patent offices concerned (there may also be searching – not examination – by or for the International Bureau– part of WIPO).
- (iii) The date of the application (not the priority date) is what matters as regards the term of the patent. It is when time starts running – the patent will expire 20 years after this date. Pharma inventions generally take at least 10-15 years to go through full clinical trials and cannot be sold until they receive a marketing authorisation. The effective term of protection is thus much less than the 20 years from filing. So much is the effective term reduced so that it has been necessary to prolong protection by additional schemes such as the SPC⁷³ scheme in Europe and the patent extension scheme in the US.⁷⁴
- (iv) Whatever filing route is used, ultimately (save in some countries) the application will be examined for patentability.⁷⁵ As I explained above, that examination involves an application of the law to the facts of the case – it is not a political or discretionary matter.

⁷³ Supplementary Protection Certificate.

⁷⁴ USC s.156

⁷⁵ The Report, at p.22, notes that some national authorities do not examine for patentability prior to grant, but does not identify whether patentability is considered later at the enforcement stage in these countries, thereby implicitly suggesting that there are no checks and balances in place. I doubt that is so.

- (v) The patent application must both describe the invention for the purposes of enablement, and contain draft patent claims to define the protection sought. A well-advised patent applicant will have draft wider claims than he ultimately expects to get. He will not go so wide as to cover matter which he knows is in the prior art (often he will make express reference to this). But there may be prior art which he will not know about. He cannot tell what the prior art search will reveal. He may narrow down the scope of the claims by amendment but, generally, is not allowed to widen claims.
- (vi) Of particular importance in the case of patents for medicines is that it is sufficient for the patentee to describe the potential use of the medicine and give some, very slight, evidence to justify that assertion. No-one can tell from a pharma patent whether the medicine will eventually be shown to work in humans and be safe or perhaps be more efficacious than existing medicines. At points the Panel seem to think that patent examiners should be able to assess this sort of thing. They can't.
- (vii) After the Office has examined the prior art the patentee may propose amendments to deal with Office objections. In the end (perhaps after further discussion with the office), he will propose an amended specification including amended claims which the Office finds acceptable, and the patent proceeds to grant.
- (viii) In a few countries there is a pre-grant opposition procedure; in others a procedure for challenging the patent in the immediate post-grant period (the EPO has such a procedure). Generic medicine companies do not make great use of this – for the practical reason that by the time the time for opposing the patent has expired there is seldom any medicine protected by the patent on the market at all. The time for opposition expires well before any marketing authorisation is given and often before clinical trials are completed.

The application and examination procedure is inherently rather crude and superficial, but it serves as a first filter for clearly unpatentable subject matter⁷⁶. Patent Offices have enormous workloads and, given the very broad definition of potentially relevant ‘prior art’ and limits placed upon official fees levied, their searches are inevitably somewhat limited. It is no good saying patent offices should do better – they can’t. Anyone who says otherwise should try it first⁷⁷! There are other factors at work here. In the end, most patents have no or little importance – the inventions turn out not to be commercially useful. They seemed a good idea at the time but that turned out not to be. Yet patent offices have to examine all of the vast number of applications, treating them all the same before the law. They have no idea which ones really matter – indeed very often no-one knows at that early stage.

Pre-grant examination can be but a crude filter. The only practical conclusion is that one needs to focus on the relatively few patents that really matter – and only when it is known that they *do* matter. That means a court working on much more detailed examination than is possible in patent office proceedings. And it means a detailed examination well after grant⁷⁸.

5. The effective term of protection is falling

The Panel does not examine this in detail. It clearly ought to have done because the term of exclusivity of an originator company is the effective period for which it can charge a premium price. Once the medicine falls out of protection it normally can be made by anyone and prices normally fall⁷⁹. Much of the Report’s discussion is about compulsory licensing – irrelevant as soon as there are no rights to be licensed. You cannot really begin to evaluate the effect on R&D funding, the Report’s proposals about compulsory licensing, “evergreening” or much else until you have a good idea of the term of protection. For it is that term which crucial in the balance between high initial prices for new medicines and commercial R&D funding.

⁷⁶ Again I have written about this, see: ‘Raising the Bar: a mistaken Chimera’ in *Concurrence Santé Publique, Innovation et Médicament*, L.G.D.J lextenso editions (2010).

⁷⁷ I think they do very well considering their limited time.

⁷⁸ Unless the grant has been delayed – as can happen in some Offices.

⁷⁹ Particularly when several generic companies enter the market.

As is well known the basic term of a patent is 20 years from filing. But because regulatory approval takes so long the period from first marketing of a medicine, much of that time is, commercially speaking, lost. In various parts of the world it has been necessary to extend protection⁸⁰. That can be done by simple patent term extension.⁸¹ In the EU it was done by creating a “sui generis” right called a Supplementary Protection Certificate.⁸² When it was introduced in 1992 effective patent term for protection of pharmaceuticals had fallen from about 15.5 years in 1980 to 12 years in 1990. The SPC system created an overall potential maximum period of protection of 15 years⁸³ (patent plus SPC) from first marketing authorisation in the EU. But the maximum term of an SPC is 5 years. The maximum term of protection is thus 20 years patent plus 5 years SPC. If the marketing authorisation is given at say 15 years from filing, then the maximum term of protection is 10 years.

Tony Rollins⁸⁴ recently did a study of how the SPC regime is working in practice⁸⁵. He did a detailed analysis of the UKIPO SPC, looking at all the SPCs for pharmaceuticals. He was able, using this hard data, to ascertain the average actual market exclusivity term and how that has changed since the SPC system started up until 2011⁸⁶. His conclusion is stark and precise. The effective term has been falling. In 2011 it was 11.52 years which is to be compared with the 15 years the EU Commission thought appropriate when the SPC system started and the just over 14 years he found was the position in 1994. The term of protection is falling. Why is that so? Because the process of marketing authorisation is taking longer – a point Dr Rollins also examines in some detail.

Dr Rollins’ overall conclusion is worth quoting:

If the trend observed in decreasing patent and SPC term continues then it is debatable if the financial return provided in the future in Europe will be sufficient for pharmaceutical companies to develop new medicines using the traditional big pharma model, particularly with the advent of personalised medicines. Personalised medicines are those where a diagnostic test or marker is used to determine a subset of the population for which a specific medicine is suitable (or potentially not suitable). Personalised medicines, by definition, will

⁸⁰ The US in 1984 (the Hatch-Waxman Act), Japan in 1988.

⁸¹ As was the position in the UK before 1977 and in several other countries following the same system, e.g. Australia.

⁸² Supposed to be simple it has proved to be complicated with many questions being asked of the CJEU.

⁸³ Plus a possible extra 6 months if there is a paediatric extension.

⁸⁴ Immediate Past President of the UK Chartered Institute of Patent Attorneys and former managing counsel for European and Japanese patent portfolios.

⁸⁵ <http://www.managingip.com/Article/3560853/HowEuropesSPCregimeworksinpractice.html>

⁸⁶ Later years were not included because many applications for SPCs were pending.

treat much smaller patient populations than the blockbusters of today and yesteryear. However, their development costs may not be significantly lower than those for blockbuster drugs⁸⁷.

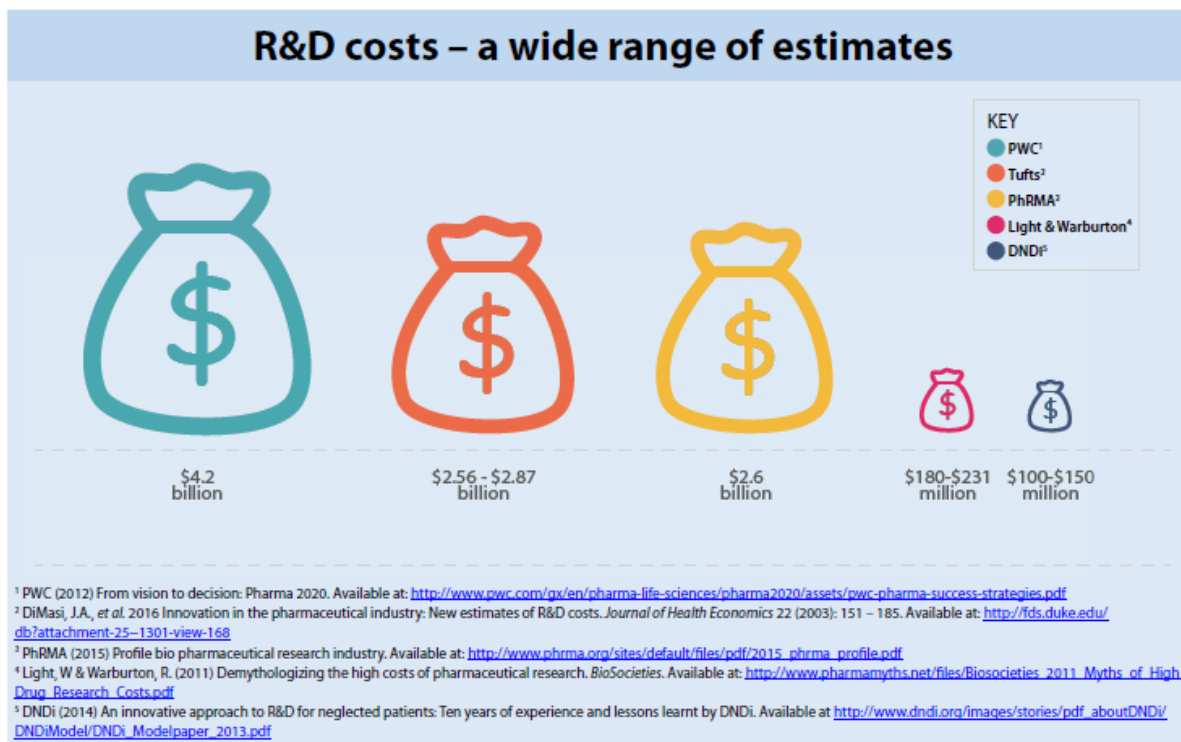
Dr Rollins recommends that the term of SPCs should be increased to seven years to make up for the increased time it takes to get marketing authorisation. And there is a wider overall conclusion: if, by “access to medicines” we include access to future medicines, to medicines yet to be invented, proved and developed, it is more than dangerous to interfere with the major source of funding for these future medicines.

6. Money for R&D: where does it come from now?

The Report considers this. On p.36 there is a nice picture of bags of money of different sizes representing various estimates of how much it cost historically to bring new medicines to market⁸⁸

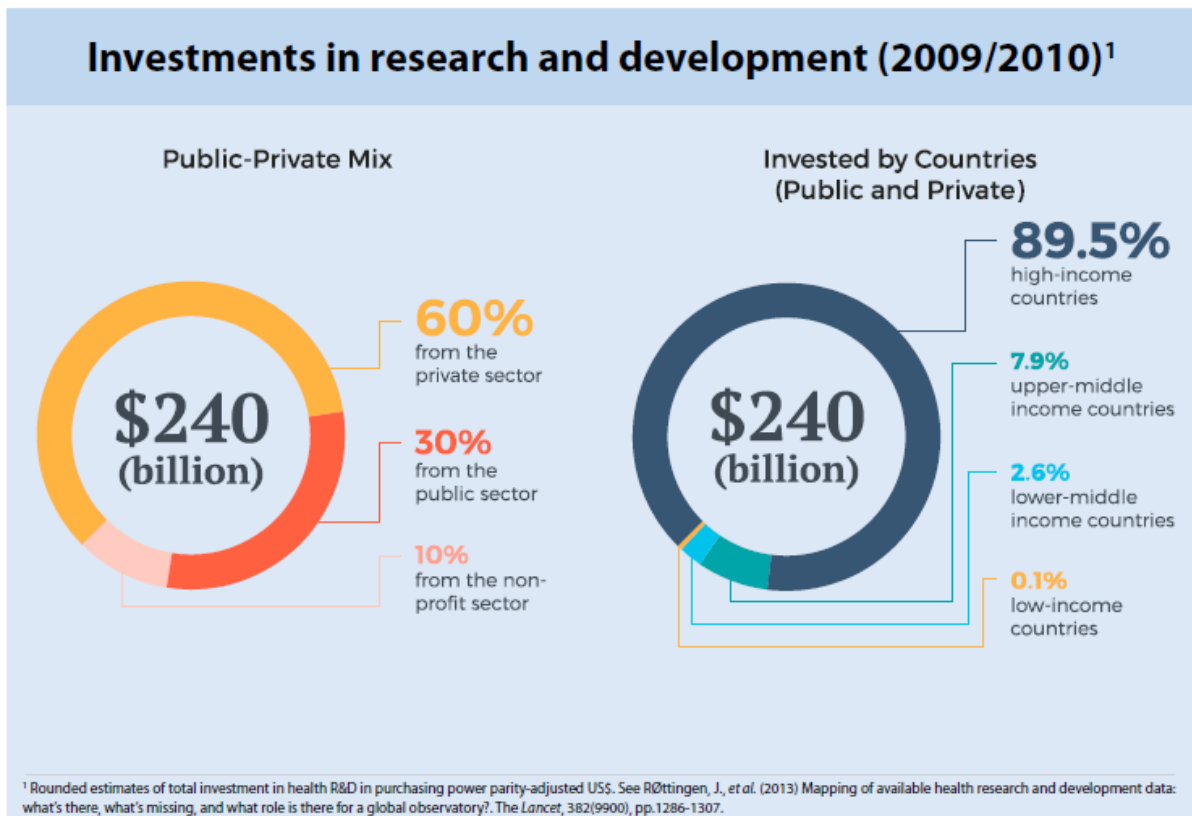
⁸⁷ See also Taylor and El-Saeed, ‘Can (and will) governments afford personalized medicine?’ *Future Medicine* September 2010. Vol 7 No. 5 pp. 587-595.

⁸⁸ Estimating this for a particular invention was the key exercise in UK (and some other countries) patent extension cases until they were abolished in 1977 – see above. I always thought the exercise was rather artificial, depending as it did on very arbitrary cost allocations.



The Report says the figures are disputed – the differing bag sizes graphically representing this. But as I pointed out under the perspective of the CEO of a research based big pharma company, the figure does not really matter. Whatever the true figure, it is all in the past – spent money, or ‘sunk’ as the economists say. What matters now is what can be spent *now* on R&D. That depends on current and projected gross margins. So I think the Report’s consideration of the past is at best of no value and, probably to an uninitiated outsider, a misleading distraction.

Of much more interest are the numbers in the picture on p.14:



Picking out the bit of that which really matters the study shows that in 2009/10 US\$240 billion was spent on pharma R&D. Of that, 60% was from the private sector, 30% from the public sector and 10% from the non-profit sector (I suppose that means charities and universities though the latter are in part public). I rather suspect this underestimates the proportion from the private sector.

I did a rough study of my own for a talk I gave at the University of Durham in 2015.⁸⁹ The next few paragraphs are largely taken from that talk. Some of it I have already said above, but the importance of the points I make well bear repetition.

(a) Pharma's R&D spend

Research and consulting firm GlobalData⁹⁰ reported that the 30 biggest drug companies spent US\$112bn on R&D in 2013. Here are a select few:

- Novartis: \$9.8bn

⁸⁹ The conference was entitled *Incentivising Innovation and Higher Standards in Regulation and Liability Relating to Medicines- The Society of Legal Scholars Annual Seminar 2015*. Papers from the conference are planned for publication in September 2017 by Hart Publishing.

⁹⁰ GlobalData, *PharmaLeaders: Global Pharmaceutical Market Benchmark Report – Retrospective and Forward-Looking Analysis of the Leading Pharmaceutical Companies* (October 2014).

- Hoffmann-La Roche:	\$10bn
- Johnson and Johnson	\$8.2bn
- Pfizer:	\$8.3bn
- Eli Lilly:	\$5.5bn
- GSK:	\$5.3bn
- Merck:	\$7.5bn

There will also be a lot spent by start-ups, risk companies, probably with the hope that they will be taken over by ‘Big Pharma’ if they come up with something promising. ‘Big pharma’ are the only bodies with the resources to take a medicine from being a promising candidate to the market via all the expensive regulatory compliance trials.

The EU Commission Sector Inquiry 2009⁹¹ into the Pharma industry – hostile to drug companies though it was - said:

From 2000 – 2007 originator companies spent on average 17% of their turnover from prescription medicines on R&D worldwide (approximately 1.5% of turnover was spent on basic research to identify potential new medicines and 15.5% of turnover was spent on developing the identified potential medicines through trials into products sufficiently safe and efficacious to be marketed. Expenditure on marketing and promotional activities accounted for 23% of their turnover during the period. In the year 2007 manufacturing costs accounted for 21% of originator companies' total turnover.⁹²

Using that as the basis, roughly speaking, every prescribed medicine carries a contribution for future research of about 17% of its cost. But even that underestimates the real effect of medicines still under patent or equivalent protection. That is because most prescribed medicines are out of patent and are unlikely to carry the price premium they did when patented. What you really want is the figure for patented medicines – they will give you a much better estimate of the premium included in the price of patented medicines by way of contribution to research. It is probably not far wrong to say it is about 25%.

The key to all this is that it is the fruits of research (patented medicines) which pay for future research. They do not go on paying forever – far from it. Generally, the period of exclusive protection of a patent, plus protection in the way of a Supplementary Protection Certificate, will be in the order of 10 years. Current successful drug companies will all be out

⁹¹ Available at: http://ec.europa.eu/competition/sectors/pharmaceuticals/inquiry/staff_working_paper_part1.pdf.

⁹² EU Commission Pharmaceutical Sector Inquiry Final Report (2009), p.30.

of business – or mere commodity medicine makers - if they do not find new medicines within ten years.

Critics of the industry point to the figure for marketing activities – as though the marketing of medicines is akin to advertising soap powders or cosmetics. But, in reality, it is largely education of the medical profession⁹³ rather than glitzy ads of the ‘*because you’re worth it*’ type. The education is how to use the new medicines, what they can be used for, including follow-up and backward feedback about what is happening when they are used. As a matter of fact, the advertising spend in the cosmetics industry is higher than promotion in the pharma industry. It is more like 25% of turnover. Furthermore, in Europe, we do not allow advertising of prescription medicines to the public (but they do allow it in the USA)⁹⁴.

(b) Government spending

A brief look in to how much governments spend on research in treating various diseases reveals the reliance on big pharma investment. For example:

- The British Government has announced it will double funding for research in to dementia disease in the next ten years – from £66m to £122m per annum in 2025.⁹⁵
- The British Government spending on cancer research was £267m in 2007/8⁹⁶
- Medical Research Council gross research expenditure was £845m in 2013/14⁹⁷
- The grant of the United States Government to the National Institute of Health was set to be \$31.3bn in 2016⁹⁸
- University spending does not greatly add to these figures as their spending largely derives from government such the MRC or NIH, and the position is similar in continental Europe.

⁹³ The over-luxurious glitzy era of medical conferences sponsored by pharma companies has been over for some time now – and a good thing too.

⁹⁴ I am reasonably sure Europeans are right: consumer advertising of medicines is apt to overly optimistic – we have all seen commercials for painkillers showing pain free arthritic grandparents dancing with jolly grandchildren and people whose cold symptoms have miraculously disappeared completely after taking the advertised drug. The danger is that doctors will be pressurised to prescribe that which does not really work.

⁹⁵ Prime Minister’s Office Press Release, *PM Launches next phase of Britain’s fight against dementia*, 21st February 2015, < <https://www.gov.uk/government/news/pm-launches-next-phase-of-britains-fight-against-dementia>>

⁹⁶ < <http://www.theguardian.com/society/2013/dec/11/dementia-research-doubled-david-cameron-alzheimers-nhs>>

⁹⁷ Medical Research Council Annual Report and Accounts 2013/14, < <http://www.mrc.ac.uk/news-events/publications/annual-report-and-accounts-201314/>>, p.14

⁹⁸ The Office of Management and Budget, *The Budget of the United States Government Fiscal Year 2016*, < <https://www.whitehouse.gov/sites/default/files/omb/budget/fy2016/assets/budget.pdf>>, p.18

What the Report surprisingly misses are some very simple things. It failed to consider at all how much its proposals would affect pharma R&D or how much it would put into the pockets of generic companies. The Panel had considerably more resources and manpower than I have. It could and should have made a much better study of the current financing and costs of the industry. What is clear is that its proposals if implemented will reduce the income of the big pharma companies. That will in turn reduce worldwide pharma company worldwide R&D spend. And because the private sector is the biggest R&D spender, if the proposals are implemented the world total R&D spend will go down.

The Report says:

It is imperative that governments increase their current levels of investment in health technology innovation to address unmet needs.

Stakeholders, including governments, the biomedical industry, institutional funders of healthcare and civil society, should test and implement new and additional models for financing and rewarding public health research and development (R&D), such as the transaction taxes and other innovative financing mechanisms⁹⁹.

Now it is true that the Report urges governments to spend more on research. Does anyone seriously think that will happen? Or that government research would somehow be better at finding new medicines than private companies? Or that governments or charities would conduct risky large-scale clinical trials? It is no good wishing for the moon. It would be lovely if money grew on trees. It would be splendid if governments had unlimited resources. But that is not the real world. It seems most unlikely that this Panel recommendation would have any effect on any government. The brutal reality is that if the research expenditure of the private sector is cut it will not be replaced by public expenditure. As the dissenting opinion of Sir Andrew Witty¹⁰⁰ says, this assumption, that national governments will commit the substantial funds needed to for future innovation, is unlikely “to prove robust or be broadly deliverable.”¹⁰¹

As to the “new and additional models for financing”, what are they? The Panel does not say. “Rewarding public health R&D”: what does that mean? That governments should act

⁹⁹ See Report, p.10.

¹⁰⁰ I should point out that GlaxoSmithKline makes a small annual donation (£3000) to the Institute of Brand and Innovation Law, part of my Law Faculty. That has in no way influenced my views.

¹⁰¹ See Report, p.56.

like private companies? What are “transaction taxes” and how could they help? Already I suppose R&D companies are entitled to deduct the cost of R&D from their gross profits before coming a net profit figure on which they may be taxed. Are transaction taxes something else? What kind of transaction does the Panel have in mind? And between who? The Report does not say.

Finally, the Report says:

Universities and research institutions that receive public funding should adopt policies and approaches that catalyse innovation and create flexible models of collaboration that advance biomedical research and generate knowledge for the benefit of the public¹⁰².

This seems alarming. It is suggesting that government (for where else should public funding come from) should somehow get involved with dictating what research is done at the university and indeed how it goes about. Much university research is fundamental – not aimed at producing medicines at all. It is vital that scientists are free to pursue such knowledge but it is fundamentally down to them to decide: academic freedom really matters. Governments controlling research, however indirectly, would be a handicap on knowledge. That is not to say that there cannot be targeted research by universities – my own University, UCL, has a £250 million programme concerned with Alzheimer’s. But that sort of thing is the exception rather than the rule. And note the amount involved for that Alzheimer’s project – it sounds a lot to an outsider but it nowhere near enough to bring a medicine to market.

Beyond that this recommendation is so vague and platitudinous as to be meaningless.

7. The Limits of the Patent System in incentivising R&D

The Panel did not focus on this important subject, though it touched upon it from time to time. I think this subject should have been central to its approach. For the Report accepts that the patent system does promote innovation – the figures I refer to above prove it uncontroversibly. A consequence of that is that the private sector will introduce important

¹⁰² See Report, p.10.

new medicines¹⁰³ initially at prices which are too high for many to pay. Yet the prices will fall – the patented medicine of today will be the generic of tomorrow. That is the trade-off for encouraging innovation through the private sector. It is surely better to have short-term high price for a new drug than no new drug at all. Access to medicines in the widest sense should mean access for the people of tomorrow as well as today.

But the patent system is not a sufficient system for the creation of and access to new medicines and vaccines for all human ailments. It will not and does not work if the commercial incentive to take the risk of those years of substantial expenditure in R&D is not big enough. That is the position in relation to a number of important areas. These include:

- (a) Medicines or vaccines where the market is unlikely to be big enough, even with a patent monopoly, to justify the R&D investment – the so-called “orphan drug” problem. Companies will not invest huge amounts to find cures for only a few people;
- (b) Basic scientific research which has no more than a long-term prospect of leading to new medicines or vaccines. This sort of research is done by universities and research institutes – the researchers themselves are not aiming at new medicines or vaccines though they know that what they may find out may eventually be harnessed for this purpose, and
- (c) In some cases new uses for established medicines. This is such an important topic that I discuss it more fully below. The Report, to my mind regretfully, does not address this topic at all.

I turn to new uses for established medicines. Typically when a wholly new medicine is developed it is for a particular indication only. After successful Phase III trials it will get a marketing authorisation for that indication. It will typically have about 10 years of protection via patent and any extension. And it will have been disclosed in the basic patent. But in many cases the medicine may have other uses – a medicine approved for cancer A may work on other cancers. Sometimes doctors report observations which suggest the medicine has another

¹⁰³ Either invented in house or bought in (which includes under exclusive licence, purchase of start-up company, or the result of collaboration with a research institute or university).

use – a little while ago there was a report in the New Scientist by an oncologist saying that a particular drug he was prescribing for cancer might have a beneficial effect on those patients who also had Parkinson's. No-one followed this up. This type of case is not rare – sometimes the new use is followed up eventually – for instance there are clinical trials of a bisphosphonate for the treatment of breast cancer years after the bisphosphonates came into use for osteoporosis.

To establish that a known drug has a beneficial effect you need clinical trials. These trials are likely to be a lot less extensive than for a wholly new medicine because a lot will be known about the medicine already. In particular its toxicity and side effects will have been investigated in the original clinical trials. The investigation about the proposed new use will largely be about efficacy alone.

Various pharma companies (and this includes some generic companies as well as big pharma) think this area is very important. But who is to pay for the research? If the new use is proved and the drug for the old use has become generic the medicine may command only a generic price. For that reason often potential new uses are simply not followed up – the same goes for any substance which is old or obvious and so cannot be patented.

To some extent in some cases the position is ameliorated by some legal fictions.¹⁰⁴ You can in Europe patent “X for the treatment of Y” where X is a known substance and Y is a medical indication. If X is not already a medicine it works well. But if X is a medicine already on the market there are complex legal and practical problems. It is not necessary to say more here other than two things: that the system, so far as it works at all has both legal and practical uncertainties and that in many cases it does not work to provide any protection.

The result is that new uses for established medicines are not researched nearly as fully as it could, and should, be. So also for substances (medicines or not) which are old or obvious.

There is a formidable lesson to be learnt here – that the availability of only weak or non-existent patent protection has a direct negative impact on research. I cannot see that message anywhere in the Report.

¹⁰⁴ This is one form of “evergreening”, discussed in more detail below.

In my opinion the Panel ought to have left well alone – those kinds of case where the patent system does incentivise research. The Panel should not have recommended steps which reduce that incentive (e.g. weakening protection and advocating compulsory licences). The Panel should have focussed much more on the kinds of case where the patent system does not provide an incentive sufficiently or at all. How can governments and the charitable sector do better in this vital area¹⁰⁵?

The Report speaks much of de-coupling the commercial incentive¹⁰⁶. But before you uncouple an engine from its coaches you had better be sure that something else will pull them. Otherwise the coaches will cease to move. You need to be sure that the alternative engine is at least as good as the old one, and you have to be sure it will take over at once after decoupling. Merely saying Governments and charities should take over is nowhere near good enough.

8. Vaccines which work and Medicines that cure: what are they worth?

I suppose few would quarrel with the following as list of priorities for a disease:

- (1) Prevention – which means a vaccine¹⁰⁷;
- (2) Cure – which means a medicine;
- (3) Alleviation if there is no cure – this will mean a medicine which has to be taken regularly – blood pressure controlling, cholesterol lowering or antidepressants are the sort of thing.

We would also think it self-evident that if a medicine is to be used on a patient it should be as specifically targeted as possible – it is no good (at best) prescribing or injecting something which won't work¹⁰⁸. Increasingly we are getting better at diagnosis and

¹⁰⁵ Similarly, Witty notes that while the Report identifies that in many parts of the world there is limited access to essential medicines which are not patented and which are sold at generic prices, yet the Panel makes no recommendations to address this issue, see Report, p.56.

¹⁰⁶ 'Delinkage', discussed further below.

¹⁰⁷ I am here talking about treatments to the body – of course there are other ways of preventing diseases e.g. clean water supplies prevent cholera or bed nets against malaria carrying mosquitoes.

¹⁰⁸ A simple recent example in the UK is the encouragement to take a test if you have cold-like symptoms to see whether you have a viral or bacterial infection. It is no good prescribing an antibiotic if the patient only has a viral infection – indeed it is worse than no good because the medicine may well cause unwanted side effects

identifying those patients or diseases who will, and those who will not, respond positively to treatment with a particular medicine –customised treatment.

So far so good. But one needs to consider the implications of these self-evident truths. As is so often the case it is helpful to start with some examples.

a. Vaccines

The Report discusses these well. It appreciates the problem that very minor, local, diseases can suddenly and unforeseeably mushroom into something much bigger – Ebola and Zika are well-known recent examples. The potentiality of “bird-flu” to mutate into a world pandemic such as that of the “Spanish flu” of 1919¹⁰⁹ is also well-known.

The Report rightly focusses on the need for research to develop new vaccines (and diagnosis tools) and realises that this will cost. The Report proposes more government funding for research. Indeed, it is difficult to see where else it could come from. You can’t expect a commercial company to invest a huge amount in a vaccine for an obscure disease – indeed mass vaccination programmes for rare diseases would probably not happen even if there was a vaccine simply because of the cost of the programme itself.

The Report also recognises the need for what might be called rapid response readiness. If (probably when) another Ebola emerges (or Ebola itself mutates and spreads again) what will be needed, and needed fast, are diagnostics and a vaccine.

Some progress has indeed been made since the Report was written. The following is a quotation from a thoughtful BBC News report of 18th January 2017.

A coalition of governments and charities has committed \$460m to speed up vaccine development for Mers, Lassa fever and Nipah virus. They are asking funders at the World Economic Forum Davos for another \$500m.

The Coalition for Epidemic Preparedness Innovations (Cepi) aims to have two new experimental vaccines ready for each disease within five years.

New vaccines usually take about a decade to develop and cost hundreds of millions of dollars.

such as in the digestive system. In any event it is overprescription which has contributed so much to antibiotic resistance.

¹⁰⁹ My own grandfather died in this – in his mid-forties leaving my grandmother with 7 children, youngest 4.

The Ebola outbreak in West Africa, closely followed by the Zika epidemic in Latin America, exposed just how "tragically unprepared" the world is for new outbreaks. Jeremy Farrar, director of the Wellcome Trust, one of the founding members of Cepi, said:

"Before the 2014 outbreak we only had very small Ebola epidemics that were in isolated communities that we were able to control. But in the modern world with urbanisation and travel, 21st Century epidemics could start in a big city and then take off the way Ebola did in West Africa. We have to be much better prepared."

Ebola killed more than 11,000 people in Liberia, Sierra Leone and Guinea. The arrival of the Zika virus in Brazil in 2015 has left thousands of children brain-damaged.

During both outbreaks, there were no treatments or vaccines to prevent people getting sick...Scientists scrambled to resurrect research on these obscure diseases.

Effective vaccines were eventually developed during the Ebola outbreak, but only as it started to wane. Nevertheless, governments, scientists and regulators all came together with unprecedented speed, and managed to expedite the notoriously complex development and regulatory processes.

Cepi wants to continue that momentum and develop vaccines for other viruses so that by the time an outbreak hits, experimental vaccines are ready to be sent to affected areas for large human trials that can establish how effective the vaccine is.

Lassa, Middle East Respiratory Syndrome (Mers) and Nipah virus are 'top of the list' of 10 priority diseases that the World Health Organization (WHO) has identified as potentially causing the next major outbreak. Dr Marie-Paule Kieny, assistant director-general of the WHO, said:

"Besides the known threats - such as Ebola and others - there are also all those viruses that are known but are thought to be very benign."

She said they could mutate and become more dangerous for humans. "Then there are the things that are completely unknown to us at the moment," said Dr Kieny.

The lottery of viruses that could hit us next makes it very difficult to plan for the future. Pharmaceutical companies aren't lining up to invest in these little-known viruses because there is no commercial market for them.

However, some have come on board with this new alliance, including GSK and Johnson and Johnson.

"We've got lucky so far," said Jeremy Farrar, "because recent outbreaks haven't become airborne." But he said a far more contagious version of an Ebola like virus could emerge. "I could cough it over you today and you could cough it

over someone tomorrow and it could spread very quickly. That puts the world in a very vulnerable place.¹¹⁰

The Report makes no mention of generic vaccines – it sees the way forward as via partnership between big vaccine companies. There is no suggestion in relation to vaccines that prices are too high and should be undercut by generics or compulsory licensing of any relevant IP. That makes sense.

b. Medicines which cure.

(i) Hepatitis C

I take first as an example, the Gilead Hepatitis C drug¹¹¹ – the cost of a treatment which cures was when it was introduced, £35,000¹¹². The societal value of this cure extends not only to the personal health of the patients, but their ability to work and pay taxes, their cost of medical treatment in other ways and the cost on their families. The cost of a liver transplant is £70,000¹¹³. Is the Gilead drug really too expensive?

In the UK NICE approved the Gilead drug Solvadi (sofosbuvir) in February 2015. Broadly speaking NICE approval means that the medicine is good value, measured by QALYs.¹¹⁴ Despite that the UK National Health Service said it would not pay and delayed funding. It thought it would cost £1bn¹¹⁵ to provide treatment for 20,000 people. There is a rival Janssen drug, Olysio,¹¹⁶ so we may not expect the prices to stay this high for all that long.

The Report discusses these hepatitis C curing¹¹⁷ medicines: It goes out of its way to emphasise a contribution from the Ministry of Foreign Affairs of the Netherlands by highlighting it in Box 6. This reads:

¹¹⁰ Available at: <http://www.bbc.co.uk/news/health-38669584>.

¹¹¹ Brand name Hirvani, generic name sofosbuvir.

¹¹² < http://www.pmlive.com/pharma_news/gileads_harvoni_gains_nice_yes_-_but_wont_face_funding_delay_666916>

¹¹³ This is the figure for 2015 given by the Statista database.

¹¹⁴ Quality of Life Years. The NICE system has its critics but is nonetheless probably as good as one can get in objectively measuring the value of a medicine. The critics are largely those who think a medicine should have been approved when it was not.

¹¹⁵ <http://www.theguardian.com/society/2015/jan/16/sofosbuvir-hepatitis-c-drug-nhs>.

¹¹⁶ Simeprevir. And there may be others in the not too far future.

¹¹⁷ Actually it depends on which geno-type of Hepatitis C. This is about the commonest forms.

Sofosbuvir is an important breakthrough in the treatment of patients with chronic hepatitis C. The problem is that a one-time treatment costs between 46,000 and 96,000 Euros. The Netherlands has an estimated 20,000 patients with this disease. The supplier defends this price in part by pointing to the great value to the patient and to those affected by the patient's illness. But such costs make healthcare unaffordable. If the Netherlands continues in this way, it will become nearly impossible to reimburse patients for these medications¹¹⁸.

This cost of a cure is undeniably a real problem. The Netherlands analysis is not adequate however. A better test is to compare the total cost of the disease absent the medicine and with it – before and after. The total cost of the disease absent the medicine consists of the actual medical treatment costs (such as hospitalisation, liver transplantation and so on). But there are societal costs too, such as lost taxes, cost of care by the family etc. Only this comparison provides a fair test. And even that would not be completely fair – cured means no more contagion – no spread of hepatitis C from cured patients. These are the calculations which ought to be made before one even considers whether a medicine is “too expensive”.

However that is not an end of the discussion. Even if a medicine is not “too expensive” on the basis of a fair calculation, the problem remains that the cost of curing all patients with hepatitis C may be beyond what governments or insurance systems can realistically pay. That is perhaps what the Netherlands had in mind – just as the UK government initially said it would not pay the cost of curing the British population of hepatitis C. One is faced with the choice of either a rationing system or a price reduction. The latter ought to be possible but only if the population to be treated is large enough. What is needed is a rational price setting system for this sort of medicine – one that will provide enough gross margin fully to fund future R&D and provide a good profit for those who invested in the company which invented and invested in the cure. The Report does not discuss how such a system might work at all.

One final comment about hepatitis C. I have already described how the discovery and elucidation of the virus itself by Chiron in the late 1980s was driven by the patent incentive and how that discovery led to the ability to test blood donations for what had previously been called non-A-non-B hepatitis. The discovery of course led to a flowering of hepatitis C research (e.g. the elucidation of different geno-types). And would surely have been a starting point for the R&D which eventually led to the curative medicines of Gilead and Janssen. That

¹¹⁸ Report, p.21.

R&D itself would have been expensive and risky – and only undertaken because the patent system provided the incentive. It is surely plain for all to see how the patent system benefitted mankind. No-where does the Report acknowledge this. No-where does the Report recognise that but for the patent system we would not have the cures whose price is under attack. Nowhere does the Report consider this: that it is better to have a cure at an initial high price¹¹⁹ than no cure at all.

(ii) Cancer cures

Siddhartha Mukherjee's brilliant Pulitzer prize-winning book *The Emperor of All Maladies* was published in 2010. It vividly describes the history of cancer(s) and the vast amount of research which has gone into trying to find cures down the ages. The effort and expense, including numerous blind-alleys, is all graphically described. A fair summary would be that improvement in therapy has been significant but achieved largely by incremental steps. Excitingly things may have moved on even since the book was published. Significantly immunotherapies are beginning to reach the market, e.g. Bristol-Myers-Squibb's Opdivo (nivolumab)¹²⁰ for melanoma and Merck's Keytruda (pembrolizumab) for non-small cell lung cancer. They may not only provide a cure where there was really none before, but they may save huge amounts on hospitalisation and so on. A few administrations of the drug may replace the crude and debilitating techniques of chemo- and radio- therapies.

These two new and powerful medicines simply could not have come to market without the incentive of the patent system. The story is not uninteresting. A relatively small Japanese pharmaceutical company, Ono, which concentrates on drug discovery made a breakthrough invention through Professor Honjo and Mr Shibayama of Kyoto University. It was that anti-PD-1 antibody could plausibly be used as a treatment for cancer – all cancers. It applied for patents and BMS saw enough potential to take an exclusive licence. The application was filed in July 2003. There was a long way to go still. BMS spent a huge effort in developing nivolumab, getting its first FDA approval (for advanced melanoma) in December 2014. Approvals for other cancers (some in combination with ipilimumab) have followed.

¹¹⁹ Moreover one that will fall over time.

¹²⁰ Which in combination with its Yervoy (ipilimumab) has got NICE approval meaning that it is good value.

The patent claim is wide indeed - in effect for the use of an anti-PD-antibody for the treatment of cancer¹²¹. Merck developed its Keytruda anti-PD-1 antibody for use against non-small cell cancer. Merck challenged the patent, saying it was obvious or insufficiently enabling and was too wide. Ono and BMS sued for infringement. The High Court rejected all attacks on the patent and found infringement¹²².

For present purposes there is a further point. Recognising the importance of Merck's product, Ono/BMS did not ask for an injunction. Instead they asked the court to fix a royalty rate if one could not be agreed. Although Merck launched an appeal, before it came on the parties agreed worldwide terms of settlement which included a substantial royalty to Ono/BMS. The important take home point is that the Ono patent in no way deterred Merck from doing research into and making a very substantial investment in pembrolizumab.

An estimate for the potential market for cancer immunotherapies was quoted by the Judge – US\$35 billion. Is that too much? If they work, I doubt it. The price will be high. NICE has approved the use of nivolumab for melanoma even though it costs around £60,000 per patient – good value compared with prior largely ineffective treatments. Again the question forces itself forward: if there is no initial high price who will be incentivised to make and develop the invention?

(iii) Antibiotics

The Report discusses the well-known problem: that increasingly disease bacteria are developing resistance to known antibiotics. The Report correctly identifies the problem: that developing a cure may not pay – even with the possibility of patent protection a medicine which cures may not have enough predicted sales to justify the R&D. The Report proposes collaborative approaches – and “de-linking” the costs of R&D from the end product. What that boils down to is more public/charitable money. Easy enough to say, but sadly a cynic might say it is unlikely to happen. The UK proposal to levy the pharmaceutical sector makes little sense – diverting as it would funds from other important R&D.

¹²¹ Because it is not permissible in Europe directly to patent methods of medical treatment the claim has to be to the purpose bound substance. Thus the “EPC 2000” type claim actually reads: “Anti-PD-1 antibody which inhibits the immunosuppressive signal of PD-1 for the use in cancer treatment”.

¹²² *Merck Sharp & Dohme v Ono* [2015] EWHC 2973.

What the Report does not consider is strengthening the patent incentive – granting 30 year patents for new antibiotics is the sort of thing which could work and surely ought to be considered. The problem is urgent – otherwise there is little one can do but hope that a new antibiotic might turn up¹²³.

The case of antibiotics is an example of what happens when patent protection is unlikely to provide enough money to justify the risk of RA&D.

(iv) Alzheimer's

Yet another problem. As life expectancy increases this disease becomes more and more important¹²⁴. A particularly informative and perceptive article about it appeared in the *New Scientist* as I was writing this¹²⁵. The article points out that in 2015 46.8 million people worldwide had dementia and that the number was set to double every 20 years, mainly because of increasing life expectancy in developing countries. Billions of dollars have been spent on trying to find a cure – to no avail. Eli Lilly alone has spent £3 billion over the last 30 years and their latest hopeful product failed phase III clinical trials last year.¹²⁶ Other trials are in progress but nothing is sure.

Suppose a medicine which cured Alzheimer's could be found? What would society be willing to pay for it now? Proposals such as that of the Report (de-linking, compulsory licensing and so on) would reduce the reward of the finder – which is hardly an incentive now for more research. The Report looks backward not forward. All a bit like the Pied Piper of Hamelin:¹²⁷:

“If I can rid your town of rats
Will you give me a thousand guilders?”
“One? fifty thousand!” -- was the exclamation
Of the astonished Mayor and Corporation.

Later, when the rats had all been drowned, the Mayor said:

¹²³ There are 2016 reports it may have – found in the human nose! We will have to see. But unless there is some form of patent protection it will be difficult to justify the necessary R&D and nothing may come of it.

¹²⁴ It is surprising that the Report does not consider this disease at all.

¹²⁵ “The Alzheimer's problem” Andy Coghlan *New Scientist* 28th January 2017, p.22.

¹²⁶ Causing a 14% drop in the share price – which demonstrates the link between investment and prospect of financial return.

¹²⁷ I cited this at the public presentation of the Preliminary Conclusions of the EC Commission Public Sector Inquiry.

“So, friend, we're not the folks to shrink
From the duty of giving you something to drink,
And a matter of money to put in your poke;

But as for the guilders, what we spoke
Of them, as you very well know, was in joke.
Beside, our losses have made us thrifty.
A thousand guilders! Come, take fifty!"

If a cure were found, there would again be the problem of what can governments and insurance companies afford to pay? Again the solution would be in sensible pricing arrangements not compulsory licensing.

9. TRIPS Flexibilities

Countries who are members of the WTO¹²⁸ are signatories of the 1994 TRIPS Agreement (‘TRIPS’). By this agreement, members have all agreed to implement patent laws which provide for minimum standards of protection for patentees.

The Report makes much of “TRIPS flexibilities”.¹²⁹ It speaks of these as though member states were free to depart from the basic principles of patent law in almost any direction. Thus on p.8 it says:

TRIPS flexibilities – for example the freedom to determine patentability criteria and further define concepts such as “novelty”, inventive step and “industrial applicability” can ensure that patents are only awarded for genuine innovation.

And on p.18 it asserts:

WTO Members may develop their own definitions of ‘novelty’, ‘inventive step’ and ‘industrial application’.

¹²⁸ Only a few countries are not members.

¹²⁹ See also pp.22-28 of the Report.

I think the Panel is mistaken in law. TRIPS does not confer extensive rights to deviate from the basic principles of patentability. I discuss novelty and obviousness (inventive step) above.¹³⁰ As regards the type of thing that may be patented (which I am calling “patent eligibility”¹³¹ – the same word is used in the US), the general rule in TRIPS is set out in Article 27(1)¹³². In effect it says that patents *must* be available for an *invention* covering any subject-matter. It is true that that “invention” is not defined and that things like musical or literary creations, however creative¹³³ cannot be patented. The only limitation in the general TRIPS rule is that it must be for a “field of technology”. Medicines and vaccines are clearly within that concept. There is no flexibility in the general rule.

I am of course aware the India has a special provision about patentability of improvements of known medicines, s.3D of the Patents Act 1970.¹³⁴ It declares that the following are not ‘inventions’:

the mere discovery of a new form of a known substance which does not result in the enhancement of the known efficacy of that substance or the mere discovery of any new property or new use for a known substance or of the mere use of a known process, machine or apparatus unless such known process results in a new product or employs at least one new reactant.

Explanation. -For the purposes of this clause, salts, esters, ethers, polymorphs, metabolites, pure form, particle size, isomers, mixtures of isomers, complexes, combinations and other derivatives of known substance shall be considered to be the same substance, unless they differ significantly in properties with regard to efficacy...

In my opinion, the better view is that this provision is not within any “TRIPS flexibility.” It is saying that even if a medicine is new and inventive it cannot be patented. It is casuistry to say that such a medicine is not an invention at all because it is a mere discovery. You could say the same about a wholly new medicine. I can find nothing in TRIPS

¹³⁰ See part 4.2 and 4.3, above.

¹³¹ See part 4.1, above.

¹³² Art. 27(1) TRIPS reads:

‘Subject to the provisions of paragraphs 2 and 3, patents *shall* be available for any inventions, whether products or processes, in all fields of technology, provided that they are new, involve an inventive step and are capable of industrial application. Subject to paragraph 4 of Article 65, paragraph 8 of Article 70 and paragraph 3 of this Article, patents shall be available and patent rights enjoyable without discrimination as to the place of invention, the field of technology and whether products are imported or locally produced’ (emphasis added).

¹³³ Which is not the same thing as “inventive”.

¹³⁴ Discussed briefly in the Report on p.21.

justifying this section. The Panel must have known that there are arguments about the compliance of s.3D with TRIPS. It ought at least to have mentioned these – one day it may reach a WTO Panel.

I would add this: that one of the justifications for s.3D is to prevent “evergreening”. That does not stand up. Once the basic patent has expired competitors are free to make the basic compound – what they can’t make is the medicine the subject of the follow-on patent. That does not matter if the latter does not in fact amount to a therapeutic or dosage regime improvement, see the discussion on “Evergreening”, below.

Article 27(2) and (3) TRIPS provides for some exceptions to the general provision of Art 27(1). Arts. 27(2) and (3) provide, so far as it material:

2. Members may exclude from patentability inventions, the prevention within their territory of the commercial exploitation of which is necessary to protect *ordre public* or morality, including to protect human, animal or plant life or health or to avoid serious prejudice to the environment, ...

3. Members may also exclude from patentability:

(a) diagnostic, therapeutic and surgical methods for the treatment of humans or animals;

(b) plants and animals other than micro-organisms, and essentially biological processes for the production of plants or animals other than non-biological and microbiological processes.

These are the permitted exclusions: none cover s.3D or anything like it. Does the Doha Declaration¹³⁵ make any difference? This is what we might call a gloss on TRIPS. It reads:

1. We recognize the gravity of the public health problems afflicting many developing and least-developed countries, especially those resulting from HIV/AIDS, tuberculosis, malaria and other epidemics.

2. We stress the need for the ...TRIPS Agreement to be part of the wider national and international action to address these problems.

3. We recognize that intellectual property protection is important for the development of new medicines. We also recognize the concerns about its effects on prices.

¹³⁵ The Doha Declaration on the TRIPS Agreement and Public Health of 2001.

4. We agree that the TRIPS Agreement does not and should not prevent Members from taking measures to protect public health. Accordingly, while reiterating our commitment to the TRIPS Agreement, we affirm that the Agreement can and should be interpreted and implemented in a manner supportive of WTO Members' right to protect public health and, in particular, to promote access to medicines for all. In this connection, we reaffirm the right of WTO Members to use, to the full, the provisions in the TRIPS Agreement, which provide flexibility for this purpose.

5. Accordingly and in the light of paragraph 4 above, while maintaining our commitments in the TRIPS Agreement, we recognize that these flexibilities include:

In applying the customary rules of interpretation of public international law, each provision of the TRIPS Agreement shall be read in the light of the object and purpose of the Agreement as expressed, in particular, in its objectives and principles.

Each Member has the right to grant compulsory licences and the freedom to determine the grounds upon which such licences are granted.

Each Member has the right to determine what constitutes a national emergency or other circumstances of extreme urgency, it being understood that public health crises, including those relating to HIV/AIDS, tuberculosis, malaria and other epidemics, can represent a national emergency or other circumstances of extreme urgency.

The effect of the provisions in the TRIPS Agreement that are relevant to the exhaustion of intellectual property rights is to leave each Member free to establish its own regime for such exhaustion without challenge, subject to the MFN and national treatment provisions of Articles 3 and 4.

6. We recognize that WTO Members with insufficient or no manufacturing capacities in the pharmaceutical sector could face difficulties in making effective use of compulsory licensing under the TRIPS Agreement. We instruct the Council for TRIPS to find an expeditious solution to this problem and to report to the General Council before the end of 2002.

7. We reaffirm the commitment of developed-country Members to provide incentives to their enterprises and institutions to promote and encourage technology transfer to least-developed country Members pursuant to Article 66.2. We also agree that the least-developed country Members will not be obliged, with respect to pharmaceutical products, to implement or apply Sections 5 and 7 of Part II of the TRIPS Agreement or to enforce rights provided for under these Sections until 1 January 2016, without prejudice to the right of least-developed country Members to seek other extensions of the transition periods as provided for in Article 66.1 of the TRIPS Agreement. We instruct the Council for TRIPS to take the necessary action to give effect to this pursuant to Article 66.1 of the TRIPS Agreement.

The answer is a clear “no.” Whilst there is clear encouragement of compulsory licensing there is simply nothing whatever suggesting TRIPS flexibilities extend to rendering unpatentable new and non-obvious medicines on the grounds that they do not amount to an improvement. As I discussed above, some courts draw the line between mere discovery and patent-eligible inventions in different ways. But that is largely peripheral to most new medicines or vaccines – they are miles from that fuzzy line. There is no TRIPS flexibility to deny patentability to inventions which satisfy the requirement of patentability according to the basic rules set out in TRIPS Art. 27(1).

The Report points to Articles 7 and 8(1) of TRIPS, providing, respectively that IP rights should advance technological innovation and dissemination “to the mutual advantage of producers and users ...in a matter conducive to social and economic welfare and to a balance of rights and obligations” and “Members may, in formulating or amending their laws and regulations, adopt measures necessary to protect public health and nutrition, and to promote the public interest in sectors of vital importance to their socio-economic and technological development, provided that such measures are consistent with the provisions of this Agreement.”¹³⁶ It is suggested that these provisions also provide “flexibilities” which enable members to derogate in various ways from the basic obligation to provide patent protection provided for in Article 27. Not much is spelt out however. Yet if you are going to say there is a flexibility to do this that or the other, you should surely spell out exactly what you have in mind.

I certainly do not read these provisions as allowing members to derogate from specific requirements of TRIPS for instance as to patentability criteria. I do not, for instance, see it as permissible for a member simply to abolish patents for medicines altogether. That would not be “mutual advantage of producers and users”.

The Report makes particular reference to competition law¹³⁷ as a possible means of preventing the abuse of IP rights. But competition law has significant limitations. In

¹³⁶ Report, p.17.

¹³⁷ Report, p.22.

particular it cannot be used simply to say “we think your price is too high¹³⁸”. I have some sympathy with recent cases where competition authorities fined generic companies which had “bought” a product from a big pharma company and raised the price massively – but that is nothing whatever to do with patents – indeed the products concerned were no longer protected. The generic company took advantage of the fact that the local drug pricing regimes did not control the price of generic drugs and because they were the only suppliers of the drug they had a *de facto* monopoly over a medicine which patients were already taking..

To conclude, in the words of Sir Andrew Witty’s dissent: “The report overstates the extent of the TRIPS flexibilities. TRIPS does not permit ...unlimited discretion to determine what is and is not patentable.”¹³⁹

10. TRIPS and Compulsory Licensing

It is undisputable that TRIPs permits individual members to have a system of compulsory licensing for medicines. So much is clear from Article 30 – and in this connection Doha spells it out more in Article 5(b). TRIPS itself rather confined compulsory licensing to the home market¹⁴⁰. Doha has changed that somewhat¹⁴¹. In principle a compulsory licence in country A may now permit export to countries who the lack production capacity of their own. In practice compulsory licences may not be granted to export to developed countries and the Report says the system of export of compulsory licensed produce does not work well.

It is a pity that the Panel did not investigate fully what actually happens when there *is* compulsory licensing. Who makes the money, how much do they make, what is the actual effect on prices and availability? It is not sufficient to show that that in one case (efavirenz

¹³⁸ And think about the carboplatin story above.

¹³⁹ Report, p.56.

¹⁴⁰ see Art. 31(f).

¹⁴¹ see paragraph 6 of Doha and the subsequent waiver of Art 31(f) by the TRIPS Council on 30th August 2003.

in Brazil) the price fell. What else happened? Surely one needs to know all that before promoting compulsory licensing as the (or a way) forward¹⁴²?

Indeed compulsory licensing is an old idea which has never worked well. The real problem is twofold: the rate of royalty has never been enough properly to compensate the patentee fully and secondly it enriches a party who makes no contribution to the future and has taken no or virtually no risk.¹⁴³ He only comes in once the originator company has invented the drug, developed it to marketing authorisation and established it in the market by education of the medical profession.

The Report favours compulsory licensing on the grounds that it will lower prices of patented medicines. So it will in the short term, but to my mind there must be better ways of doing it than making licensees rich. The Report does not consider this or even consider how much compulsory licensees can make, and have in the past, made. Diverting money to those who make no contribution is probably not the best way of achieving better access to medicines.

11. “Evergreening”

The Report defines “evergreening” as:

A term used to describe patenting or marketing strategies to extend the period of patent protection or effective period of market exclusivity, which are considered unjustifiable and therefore abusive. In some cases for example, this might involve the filing of multiple, often successive, patent applications on minor and insignificant variants or indications of the same compound¹⁴⁴.

The word is emotive – to accuse a company of “evergreening” is to condemn them. The very definition used by the panel uses the word “abusive” which ought to raise in the rational mind “abusive of what?” Because the word is so emotive – containing as it does the

¹⁴² Witty also notes, on p.56 of the Report, that in 2015, only 34 of the 409 medicines on the WHO Essential Medicines List were patented, and of that 34, few were patented in LDCs or many of the poorer countries. He concludes that “IP plays no role in the lack of access for these medicines and these countries, so IP-based ideas such as CLs are extremely unlikely to help.”

¹⁴³ See e.g. Reed Beall, Randall Kuhn and Amir Attaran ‘Compulsory Licensing Often Did Not Produce Lower Prices For Antiretrovirals Compared To International Procurement’ 2015 34(3) *Health Affairs* 493-501.

¹⁴⁴ See Report, p.5.

notion that whatever it is it ought to be stopped – I think it is very important not to be swayed by unreasoned emotion but focus instead on the realities. In particular there is a danger of demonising incremental advances in medicines.

The first and most important point I have discussed already under the heading “novelty”. That which is old – lacks novelty – cannot be validly patented. So if a medicine is patented it cannot be re-patented. You can’t “evergreen” what is in the prior art¹⁴⁵.

In my career I have only known one case where a pharma patentee tried to do this. I gave the main judgment¹⁴⁶ in the Court of Appeal upholding the High Court’s decision to revoke the patent. I said “it is the sort of patent which can give the patent system a bad name”. And so it was. But one bad egg does not mean that all or indeed any other eggs are bad – and, as I say, I know of no other case like it. The law has its remedies in such a case. The patentees have been and still are embroiled in litigation about the consequences of obtaining and enforcing a patent which, it is alleged, they knew or ought to have known, was invalid.¹⁴⁷ It would be a huge mistake to draw any general conclusion about “evergreening” from this isolated case (save this – that a patentee who tries this sort of thing is likely to regret it!).

Turning back to the basic rule, that you can’t re-patent an old medicine, what are the consequences? They are simple, when the patent or any extension or protection based on the patent runs out, third parties are free as far as patent law is concerned to make the old medicine. They may not be able to make some validly patented special form of it (dosage, crystalline form etc.) but no-one can stop them making the old medicine.

¹⁴⁵ I should qualify that, however in a respect which does not matter for present purposes. If the prior art is in general terms e.g. a Markush claim, then it may be possible to patent something within that general claim but which is more specific. Such was the case, for instance, in *Dr Reddy’s v Eli Lilly* [2009] EWCA 1362 where the court (I was a member of it) upheld a claim to a single chemical, olanzapine even though it was member of two prior disclosed bigger classes, one of 10¹⁹ and the other of 86,000 compounds. The prior art never suggested the specific use of olanzapine as an antipsychotic whereas the patent did and provided some evidence that it might work. It was not in any sense a case of “evergreening” since the prior art had never lead to a medicine.

¹⁴⁶ *Laboratoires Servier v Apotex* [2008] EWCA Civ 445. Servier had previously patented the medicine perindopril by an application of 1980. It had put it on the market in 1988. The later patent (date 2000), identified and claimed a particular crystalline form of perindopril. But what it was actually claiming was the form of perindopril which, unless you took special precaution, is the one which would normally be made. Servier had been selling this form for years.

¹⁴⁷ The cases are to be found on the Bailii website – and there is an ongoing EU Commission investigation. Servier also had to compensate the generic company Apotex for the losses it suffered by reason of an interim injunction restraining it from selling perindopril. The losses were its lost UK profits of £17.5m less the damages which it had to pay for infringing a Canadian patent when it made perindopril.

In some cases I understand that patentees have tried to stop generic entry by withdrawing their own marketing authorisation for the old form of the medicine – the generic company then cannot use the data for that. I see no sense in that being possible. The information given to obtain a marketing authorisation should be open to all to use after the initial period of exclusivity. If that were properly in place, no-one could evergreen a medicine which is out of patent.

That is not an end of the discussion however. For after a new medicine is invented and patented the patentee (and others) will endeavour to find better ways of making it, better forms of delivery (which may include new crystalline forms which provide better bio-availability), better dosage regimes and so on. Patentees often seek to patent these new developments – I will call such inventions and patents “follow-on” inventions or patents. This may be called “evergreening” by some. It is nothing of the sort - once the patent on the medicine has gone, people can make it. They may not be able to make the new development if the follow-on patent is valid. But that is always the case when you have a patented improvement on an earlier invention.

Some are troubled by this. They ought not to be for two reasons:

- (a) Firstly, it may indeed be the pharma company’s intention to change from the old to the new form to extend protection, but unless the follow-on invention is important enough to amount to an advance in treatment, there is no need for generic companies to make it or for payor’s to pay any price higher than the generic price for the new product. They can buy the old one. The market and the medical profession, not the law of patentability, should decide on whether the variant has any significance.
- (b) Secondly many follow-on inventions of this sort cannot be validly patented. For instance it is normally rather obvious to investigate whether there are various crystalline forms of a medicine and to see whether they have different properties such as solubility. Similarly it is generally obvious to investigate different dosage forms. So if any patent for the result of objectively routine/non-inventive work is obtained nonetheless it should be readily challengeable in the courts.

The Report labels “the filing of multiple, often successive, patent applications on minor and insignificant variants or indications of the same compound” as “abusive”¹⁴⁸. But what is the matter with that? If those variants are new and inventive they are patentable – patent law does not require major advances as I pointed out above. Normally the position is likely to be more subtle – that the variant is not merely an exact equivalent of the old medicine but is an incremental improvement. If it is and is inventive then there is absolutely nothing wrong with the improvement being patented. On the contrary it should be patentable because society needs improvements in existing medicines.

Of course it may be asked that if a new form provides no real improvement, why would the pharma company want to patent it? The answer is simple: when the variant is first identified it will probably not be known if it in fact provides an improvement – for that you would need clinical trials. It is difficult to run these (especially on a large scale for Phase III) while keeping the product confidential. Yet if the product is disclosed prior to applying for a patent, the opportunity to obtain a patent may be lost. Therefore, it is simply impractical to delay the decision to patent until the value of the new form is known.

The Report asserts that:

Secondary patents can, however, prolong exclusivity (commonly known as evergreening). In order to do so entrance of generic or competing products can be curtailed and prices remain high, thereby limiting access to health technologies¹⁴⁹.

I just do not understand how the Panel can have concluded that. A secondary patent can interfere only with sales of the product protected by the later patent. Any generic company can make and sell the original. Inventing and selling improvements is a huge part of innovation. But the Report is saying by implication there should not be a patent incentive for making improvements.

In short I consider the whole “evergreening” thesis to be flawed and that it leads to conclusions dangerous for the future of innovation.

I would add an important postscript, however. Quite a large proportion of granted “follow-on” patents turn out on the close scrutiny given by a court in revocation proceedings

¹⁴⁸ Report, p.5.

¹⁴⁹ Report, p.22.

to be invalid. No blame should be attached to innovator companies for applying for them unless they know or ought to know for sure that the patent would be invalid. Applying for a patent for an incremental improvement which might have a 30% chance of being held valid is in no way discreditable – it is prudent business policy. The remedy is not to blame the companies but to have a good system of adjudication on the validity of the patent. The Report does not, as in my opinion it ought to have done, discuss or make recommendations in this regard.

I can offer some suggestions. Theoretically it would be lovely if developing countries had efficient and well qualified patent courts. Indeed some do (China particularly is creating specialist IP courts). But obviously this is not a practical possibility in many, many countries. One way to surmount the problem is for the parties (originator and generic company) to litigate the validity in an arbitration. Another way would be to litigate the validity of the parallel patent¹⁵⁰ in the court of a country which does have an established and respected patent court and for the parties to agree to abide world-wide by the decision of that court.

It might be objected that both of these suggestions involve considerable litigation expense. But that is not really so. Although the costs sound large¹⁵¹ they are small, indeed almost trivial, compared with the large sums at stake for both originator and generic companies. Indeed we already have quite a lot of litigation about the validity of follow-on patents where the case is simply about the market in the developed country concerned.¹⁵² The costs of litigating a single market are no deterrent to litigation. Adding an agreement that the result would apply in other countries would add little.

¹⁵⁰ There will almost certainly be one in practice.

¹⁵¹ In the UK perhaps £1-2m

¹⁵² In the UK for example, *Actavis v Merck* [2008] EWCA Civ 444 (patent in Swiss form for a new use of old medicine using a different dosage form held valid); *Actavis v Novartis* [2010] EWCA Civ 82 (patent for sustained release form of known medicine fluvastatin invalid); *Richter Gedeon v Generics* [2016] EWCA Civ 410 (new dosage form of post-coital contraceptive, patent invalid – incidentally this was my last judgment); *Lundbeck v Generics* [2008] EWHCA Civ 311 (patent for escitalopram, the (+) enantiomer of a known medicine citalopram held valid); *Generics v Daiichi* [2009] EWCA Civ 646 patent for the (-) enantiomer of a known medicine valid); *Novartis v Ivax* [2007] EWCA Civ 971 (formulation patent not infringed); *SmithKline Beecham v Apotex* (patent for novel forms of paroxetine hydrochloride held valid but not infringed); *Teva v Leo* [2015] EWCA Civ 779 (patent for two component cream for treatment of psoriasis valid – the cream was a valuable medical advance even though the components were known individually); *Ranbaxy v Warner-Lambert* [2006] EWCA Civ 876 (patent for particular chiral form of atorvastatin invalid).

The Report in my opinion should have considered this sort of solution to the problem of machinery for attacking the validity of patents. There may well be other ideas along similar lines.

12. Patent Thickets – a non-problem

So-called patent thickets are non-problem. The Report suggests that many pharmaceutical products are covered by a mass of patents. But the Panel has done no research to show this is so – instead it draws on some figures given by the EU Pharma Sector Inquiry. That inquiry itself did not research the alleged problem either. Moreover it went in for massive overcounting because it counted parallel patents in different countries as separate patents, rather than focussing upon the number of patent ‘families’¹⁵³. I believe that the reality is that in any particular country most patented medicines are protected by a single patent. Sometimes there may be a patent for a “follow-on” invention but the broad picture is one patent per product. The industry is not like the telecoms industry where there are thousands of patented inventions from many companies embodied in a single product.

I have good grounds for my belief. Throughout my career at the bar and on the Bench pharma patent fights have largely been about a single patent, it being that patent alone which stood or was alleged to stand between the (normally) generic company and the market. The patentee did not have an armoury of weapons to use – he had just one. The Panel could have asked a few companies how many patents they had for important products in say, UK, Germany and the USA.

There is a limited exception to what I have just said, but it is reality of no significance. During the prosecution of a patent the patentee is normally allowed to break his original application out into smaller pieces – to divide out¹⁵⁴. This can result in a number of patents stemming from the original application. Most importantly for present purposes it is

¹⁵³ So if an invention was patented in all 38 countries of the European patent union that would be counted as 38 patents, rather than one patent family.

¹⁵⁴ This is the European expression – the US and other countries have a somewhat similar system.

vital to understand two things¹⁵⁵. Firstly, that such divided out patents cannot have a longer term than the original parent application. Secondly, by filing a divisional application, you cannot claim anything you could not have claimed in the original parent application. The technical disclosure justifying the claim of the divisional must have been in the parent application. Indeed, the claims of a divisional are in effect no more than extra claims which could have been in the original. Thus, you cannot use divisional applications to broaden the scope of protection claimed. You can't prolong protection and you can't add subject-matter.

Divisional application ought not to have caused trouble but for the fact that the prosecution process can be so long. As a result, there can be divisional applications still in prosecution by the time the protected product gets marketing authorisation and generic companies which to compete. Such companies may take the view that no valid patent can be obtained on the product, no matter how much the patentee seeks to divide up. In the UK at least the courts have devised a remedy – a declaration that generic company's proposed product could not be the subject of a valid patent because it is old or obvious at the date of the parent application. This is called an "Arrow" declaration, recently affirmed by the Court of Appeal¹⁵⁶. As is often the case the answer to a problem lies in a good working court system.

The patent thicket problem was graphically described by one of its chief proponents, the economist Carl Shapiro thus:

A dense web of overlapping intellectual property rights that a company must hack its way through in order to actually commercialize new technology¹⁵⁷.

It sounds a plausible theory – particularly for industries like telecoms where there are so many thousands of patents that in the real world it is difficult to suppose anyone could even read them all. But the theory is not borne out by reality. Telecoms have many new

¹⁵⁵ Some do not seem to appreciate the very significant limits of the divisional procedure. I wrote about this: 'Pharmaceutical Patents: Competition Law Goes Too Far' in *Competition and Intellectual Property Law in the Pharmaceutical Sector An International Perspective*, Giovanni Pitruzzella and Gabriella Muscolo (eds.), Kluwer, 2016. I think it is pretty evident that the Italian Competition Authority, ultimately upheld by the Supreme Court, simply did not understand the Divisional system and in particular that it could not provide protection beyond the 20 years of the basic parent application and that any claim of a divisional is one that could have been in the parent because there was enough information in the parent to support it.

¹⁵⁶ *Fujifilm v AbbVie* [2017] EWCA Civ 1 and see *Fujisfilm v Abbvie* [2017] EWHC 395 (Pat) (declarations that what the defendants wanted to do was old or obvious and hence could not be the subject of any later patent).

¹⁵⁷ C Shapiro, 'Navigating the Patent thicket: Cross Licenses, Patent Pools, and Standard-Setting' in AB Jaffe et al (eds), *Innovation Policy and the Economy* (MIT Press, 2001).

entrants and despite the numbers of patents actually increasing prices fall. That is partly due to the FRAND system which has no counterpart in pharma. It is also due to the fact there simply are no thickets.

I should mention here that the so-called problem was examined by the European Patent Office Economic and Scientific Advisory Board¹⁵⁸ which produced a report after a Workshop at the University of Leuven. Its report said:

Arguments were presented as to whether or not those thickets represented an insurmountable problem. Another presentation contrasted that situation with the pharmaceutical industry, where thickets were thought to be less prevalent and less problematic, as was also borne out by the data analysis of von Graevenitz et al¹⁵⁹.

Just as I said above. The Panel's overall conclusion is worth stating too:

The final plenary session was designed to reach conclusions about patent thickets. There was extensive debate about whether patent thickets are a problem per se, and the experts could not agree on that issue. Generally speaking, industry-based experts were less concerned about patent thickets as an insurmountable problem.

Saying industry experts were less concerned suggests that the practical view was less worried than the theorists. I cannot but agree.

In my opinion the Panel and report should have stayed well away from the thicket debate, still less sided with those theorists who think it is a problem. It has nothing to do with access to medicines.

13. The myth of “hold-up”

Critics of the patent system use the pejorative term “hold-up” in two quite distinct senses:

¹⁵⁸ I was a member.

¹⁵⁹ *How to measure patent thickets –A novel approach. Economics Letters*, 111(1), 6-9. doi: 10.1016/j.econlet.2010.12.005

- (a) In the context of FRAND committed patents in the telecoms and other electronic industries¹⁶⁰. This kind of “hold-up” is not applicable in the world of pharma which does not have this interdependence in final products of inventions of many different companies. Besides, pharma companies hold many many less patents than telecoms companies.¹⁶¹ I say no more about this kind of “hold-up”. The Report, rightly, does not mention it.
- (b) “Hold-up” is also used in a quite different sense. The hypothesis here is that an important patent in the hands of powerful commercial company may actually deter research: paradoxically that a system intended to incentivise research actually has the opposite effect. The hypothesis has been espoused by some theoretical economists – for instance Boldrin and Levine suggest that the development of the steam engine was held up the patent owned by James Watt and Matthew Boulton. However close examination of the detailed facts of such cases does not support the hypothesis¹⁶².

The Report does not refer to “hold-up” by name. But it clearly asserts that it exists in the world of pharma:

¹⁶⁰ In these industries it is vital that the products of different companies work together – e.g. that the phone of one company will talk to that of another. The industries have set up standard setting bodies and everyone agrees to licence others on Fair Reasonable and Non-Discriminatory terms. The “hold-up” hypothesis is that if a patentee of a patent which covers a standard seeks an injunction, the defendant will be so frightened of an injunction that he will agree to pay more for a licence than the proper FRAND rate. The hypothesis gained some traction a few years ago but more recently has somewhat faded. So far as I know it has no basis in fact and there are strong legal reasons for thinking it flawed – in particular if the patent is FRAND committed no court is likely to grant an injunction if the patentee is willing to arbitrate (or have the court settle) FRAND terms. I discuss this in an article I wrote jointly with Alexander Milner, *Lessons from Huawei v ZTE* commissioned by 4IP. It is available on the 4IP website and is shortly to be published in Italy as part of a volume *Rivista Italiana di Antitrust* (Italian Antitrust Review) and by Tongi University’s (Shanghai) IP and Competition Law Review.

¹⁶¹ A big telecom company may hold 10,000 or more patent families which are FRAND committed and many more which are not. The patents in each “family” have the same priority date so that the parallel patents in different countries are broadly for the same invention.

¹⁶² E.g. *Fallacies of Patent Hold-up Theory* Galetovic and Haber Hoover IP2 Working Paper Series No 16009; *An Empirical Examination of Patent Hold-Up*, Galetovic, Haber and Levine. *Journal of Competition Law and Economics*, 0(0), 1–30 doi:10.1093/joclec/nhv024; *Strong Steam Weak Patents or the Myth of Watt’s Innovation-Blocking Monopoly Exploded*, Selgin and Turner, *Journal of Law and Economics*; *The myth of the early aviation patent hold-up – how a US government monopsony commandeered pioneer airplane patents*, Katznelson and Howells, *Industrial and Corporate Change*, pp. 1–64 doi:10.1093/icc/dtu003. There are more publications of this sort. They show that you have to look at hard facts (e.g. actual patent claims and what really happened in the market).

Patents pile up over time with no indication as to which ones the holder plans to enforce and extend. These factors, as well as excessive patenting, can impede scientific progress and legitimate competition¹⁶³.

This is a quite extraordinary collection of assertions. Patentees never say which patents they intend to enforce. The normal behaviour is to enforce when and if the patent is infringed – otherwise there is no point in having a patent. Patents do not “pile up”. They have a limited maximum term and (particularly because renewal fees increase with time) most sensible patentees have policies of deciding which patents to renew and which not. As far as I know (I have done no research and certainly the Panel did not do any research) the total number of pharma patents in force at any one time has not changed vastly over the years. There is no such thing as “excessive patenting” as far as I know – and how would you decide whether patenting is “excessive” anyway?

The assertion that patents impede scientific progress is an assertion of hold-up. I have never come across a real case where a party contemplating research has been deterred by a patent of another. And why should he? After all it is not an infringement of a patent to do research into the invention of the patent – there is a research exemption at least in Europe¹⁶⁴.

The Report makes a further assertion that patents impede innovation in its discussion of “patent thickets.” It asserts:

Empirical studies of patent thickets show varied results which range from (1) discouraging others from undertaking research on competing products¹⁶⁵.

The Panel did no research of its own to justify this assertion. It relies on the material asserted in the EU Pharma Sector inquiry. That material, if one goes to it, is thin indeed. If a serious charge like this is to be made out it requires hard solid data. It would not have been all that costly actually to conduct a proper survey to ask industry and universities whether patents had really impeded any research and if so to specify exactly how.

For what it is worth I can point to real cases which point the other way. I have already mentioned the fact that the basic Chiron patent – effectively on hepatitis C led to a flowering

¹⁶³ Report, p.36.

¹⁶⁴ Although the Community Patent Convention & 67/6/EEC never came into force most European countries enacted its infringement and exception to infringement provisions. Art.31 provided that the rights conferred by a patent “shall not extend to... (b) acts done for experimental purposes relating to the subject-matter of the patented invention.” Thus for instance the UK Patents Act 1977 so provided by s.60(5)(b).

¹⁶⁵ See Report, p.22

of research, not hold up. Similarly Human Genome Science's patent for neutrokin- α and its antibodies did not deter Eli Lilly from researching for a valuable such antibody and spending a huge amount on trials¹⁶⁶. Nor did Ono's patent for the use of an anti- PD-1 antibody deter Merck from researching and bringing to market such an antibody.

I am not saying that sometimes a company may elect not to do research on a product within the scope of a competitor's patent. He may decide to "design around" as Glaxo did when considering SK&F's cimetidine patent. What I do say is that given the long, long experience of the patent system, if it were really the case that patents impeded innovation, there would be masses and masses of material to prove it. The Panel should not have been so gullible.

14. Royalty Stacking

This is another economists' theory. It goes like this. Where a product is covered by a large number of patents (as in telecoms) if each patentee asks for too much by way of royalty the result will be that the would-be licensee cannot afford to pay all the royalties due to all the patentees ("the stack") and enter the market. I think it has no basis in reality. A high-level American Court¹⁶⁷ said:

A jury, moreover, need not be instructed regarding royalty stacking unless there is actual evidence of stacking. The mere fact that thousands of patents are declared to be essential to a standard does not mean that a standard-compliant company will necessarily have to pay a royalty to each SEP holder¹⁶⁸.

This was a telecom case where the theory might apply. The test the court went for was reality. And that those who assert must prove. Quite apart from lack of proof there is substantial evidence that the hypothetical problem is not a reality¹⁶⁹.

The Panel referred to royalty stacking in the context of patent thickets. It said that a potential impact was:

¹⁶⁶ *Human Genome Sciences v Eli Lilly* [2011] UKSC 51. The patent was upheld but in the end the *Eli Lilly* product failed its phase III trials.

¹⁶⁷ The Court of Appeals for the Federal Circuit, or CAFC.

¹⁶⁸ *D-Link v Ericsson* 7773 F.3d 1204

¹⁶⁹ E.g. *Smart Phone Litigation and Standard Essential Patents*, Gupta and Snyder, Hoover IP2 Series, May 2014; *Holdup, Royalty Stacking and the Presumption of Injunctive Relief: a Reply to Lemley and Shapiro*, Sidak, [2008] Minnesota Law Review, 714; *Is There an Anti-Commons Tragedy in the Smartphone Industry?* Galetovic, Haber and Zaretski, Hoover IP2 working paper 17005, January 18th 2017; *Cumulative mobile-SEP royalty payments no more than around 5% of mobile handset revenues*, Mallinson For IP Finance August 2015.

“competing products potentially infringing on a number of patents and thus requiring multiple royalty payments (known as royalty stacking)...¹⁷⁰”

The Panel failed to consider completely whether this had anything to do with access to medicines. For it even to begin to be relevant you would have to show that important medicines were covered by a “number of patents”. That the Panel failed to do – and I believe is not the case. As far as I know the royalty stacking hypothetical problem simply does not exist in this industry. So from the point of view of access to medicines one need not even get as far as considering whether the hypothetical is a reality. The Panel should have stayed right away rather than espousing an unproven theory which in any event could not apply to pharma patents.

15. Patent Information

The Report asserts:

Procurement decisions and generic manufacturing are often delayed by the absence of clear, accurate and up-to-date information on existing and expired patents¹⁷¹.

It recommends:

Governments should establish and establish and maintain publicly accessible databases with patent information status and data on medicines and vaccines. This information should be periodically updated by WIPO in collaboration with stakeholders to develop and international easily searchable database which should include (1) standard international common names for biological products; (2) international non-proprietary names for products, either as known at the time of application or after the granting of a patent; and (3) dates of grant and expiry¹⁷².

The justification for this appears in the body of the text:

Currently, patent information is often confusing, incomplete and fragmented. A single product may be protected by hundreds of patents and compounds may appear under a brand name or an international non-proprietary name (INN). Patents pile up over time with no indication as to which ones the holder plans to enforce and extend¹⁷³.

I have already commented on the “single product, hundreds of patents assertion”. It is simply wrong for patents for medicines and vaccines unless the Panel means parallel patents

¹⁷⁰ Report, p.22.

¹⁷¹ Report, p.9.

¹⁷² Report, p.11.

¹⁷³ Report, p.36.

in different countries, which is not a fair way to count¹⁷⁴. It is of course true that these products are patented in many countries – that is simply because patents are national rights and there are nearly 200 countries in the world.

I have also commented on the “pile-up” and “no indication as to which will be enforced” assertions. As to “extend” (by which I take it the Panel means something like US patent extension or a European SPC) many countries (particularly developing) have no such system. And where there is a system, there are fixed times for making the application and it can readily be found out from the Office by internet search whether an application has been made. Any competent generic company can find out what it needs to know

The Panel overlooked:

- (1) the fact that the status of a patent is normally very easy to find. Patent Offices maintain a register of patentees. It is true that sometimes this gets out of date when a patent is assigned, or when companies merge or change company name, and these changes are not recorded. That can be a problem in commercial areas where companies regularly assign patents and patentees regularly exploit their patents by licensing. FRAND committed patents are the typical sort of thing. Pharma patents by contrast are not assigned very much because the same company takes them through from invention to marketing.
- (2) the fact that it is very common for originator companies to mark their products with relevant patents.
- (3) the fact that it is not difficult to ask the originator what patents he has covering a specific product. Such a request (if made within reason) ought to be answered and can have legal consequences if not answered or not answered correctly (possibly even amounting to a bar to legal action on the undisclosed patent if the generic company relied upon the answer).
- (4) most astonishingly of all the fact that UN itself via the UNDP has considered this and demonstrated an easy way of find out patent information. This Report¹⁷⁵ was

¹⁷⁴ Even the telecoms industry counts by families of patents.

published in Jul 2012 but there is no reference to this sensible piece of work in the Report of the Panel.

As to the supposed problem of someone not being able to know the patents because they only know the INN or proprietary name, this is fanciful. Generic companies are not naïve or without resources. Every packet of the originator's medicines will have an information leaflet giving the INN so there is no question of only knowing one or the other and not both. It is not difficult for a competent patent attorney to find out what patents are in force relating to a particular compound.

In short the whole of this piece is a non-problem. More worrying is the Panel's ignorance of the patent system which somewhat infects the whole Report.

16. Delinking

The Report says:

Building on current discussions at the WHO, the United Nations Secretary-General should initiate a process for governments to negotiate global agreements on the coordination, financing and development of health technologies. This includes negotiations for a binding R&D Convention that delinks the costs of research and development from end prices to promote access to good health for all. The Convention should focus on public health needs, including but not limited to, innovation for neglected tropical diseases and antimicrobial resistance and must complement existing mechanisms¹⁷⁶.

The talk of "delinking" is potentially very dangerous – what could (and, given the other financial pressures on governments probably would happen) is that pharma companies would lose their research incentive without anything in fact replacing their work. In the real world if implemented to any significant degree, R&D would very likely be reduced.¹⁷⁷

Of course it would be wonderful if neglected tropical disease and microbial resistance were researched more. I discuss antibiotics separately but it is simply unrealistic to say that anyone, private or public, can do large scale research into new medicines for all rare diseases

¹⁷⁵ *Patent Information and Transparency: A Methodology for Patent Searches on Essential Medicines in Developing Countries*, UNDP, July 2013.

¹⁷⁶ Report, p.10.

¹⁷⁷ See Witty's comment, on p.57 of the Report: "Delinkage will likely not be appropriate or useful for many therapy areas. Different mechanisms are needed for different problems as they arise – a one-size fits all approach is not optimal, and is potentially damaging to innovation."

(see what I say about Ebola). R&D money and resources, public or private, are limited and it makes sense for the money to go to the cases of biggest need and with most prospect of success.

17. Code of Principles for Biomedical R&D

The Report recommends:

As a preparatory step, governments should form a Working Group to begin negotiating a Code of Principles for Biomedical R&D. The principles would apply to public R&D funds and should also be adopted by private and philanthropic funders, product development partnerships, universities, the biomedical industry and other stakeholders. Governments should report annually on their progress in negotiating and implementing a Code of Principles as a preparatory step to negotiating the Convention in the United Nations General Assembly¹⁷⁸.

What is supposed to be in this proposed Code?¹⁷⁹ Why did the Panel not produce a suggested first draft so that practicalities could be discussed? How will such a Code increase R&D spending? The idea of such a Code to my mind is at much too high a level. The devil is in the detail.

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April 7th 2017

¹⁷⁸ Report, p.10.

¹⁷⁹ See also Witty's criticism of the vagueness and lack of clarity of this Recommendation on p.56.