



REGULATORY INSTITUTIONS NETWORK (RegNet)
Centre for the Governance of Knowledge and Development

H.C. Coombs Building Extension
Cnr Fellows & Garran Roads
The Australian National University,
Canberra, ACT, 0200
Australia

M +61 400 606 263

E luigi.palombi@anu.edu.au

<http://www.regnet.anu.edu.au>

Friday, 23 March 2012

Saurabh Vishnubhakat
Attorney Advisor
Office of Chief Economist
United States Patent and Trademark Office
Washington D.C.

Genetic Testing Study

My submission to this review panel has been prompted by certain evidence given in oral testimony on February 16, 2012 by Dr. Mercedes Meyer.

In response to her evidence I wish to bring the following facts to the attention of the review panel:

- 1) The Australian Law Reform Commission's (ALRC) review of genetic testing was not without controversy, indeed, apart from the fact that the Commission itself lacked any in-house expertise, either, in the field of patent law, or, the relevant biological sciences, a most controversial issue surrounding the ALRC's review was the decision to appoint an advisory committee to provide the expertise which the ALRC inherently lacked. This advisory board, in so far as the patent attorneys and lawyers appointed to it were concerned, consisted solely of patent attorneys and lawyers whose firms had a direct or indirect interest in the outcome of the ALRC's review. In other words, their firms had represented or were representing clients that had applied for or were granted patents over isolated biological materials, including genetic materials, and the use of these materials in various applications including diagnostic assays, kits or tests. Of the academic lawyers appointed to this board all had published papers inclined to the view that Australian patent law was essentially permissive of the practice adopted by IP Australia, the Australian patent office, of the granting patents over isolated or purified biological materials.
- 2) In the course of its review the ALRC virtually ignored, without a plausible explanation, a substantial body of evidence presented to it over the adverse impact on the Australian healthcare system and caused directly by the grant of patents by IP Australia over the hepatitis C virus nucleotide and amino acid sequences, nucleic acids and proteins, and the use of these materials in virtually any medical, scientific or clinical application, either existing or speculative. In fact, a number of the granted claims were over the use of such materials in HCV vaccines. This evidence overwhelmingly demonstrated that the grant of the HCV patents and the decision by the patent owner, Chiron Corporation (now fully owned by Novartis), to adopt an exclusive licensing business strategy harmed the Australian healthcare sector both financially and clinically by restricting access to the HCV nucleotides and amino acids to Chiron's licensees. The restriction of access to these materials became problematic in Australia because the anti-HCV diagnostic assays produced under license from Chiron were inaccurate, particularly in regard to a low risk cohort, such as, blood donors. Among this cohort, scientific studies showed that the false positive rate was as high as 75%. Associate Professor Stephen Lorcarnini, then Director of one Australia's specialist infectious diseases hospital, gave sworn testimony in the Australian Federal Court. He said:

In a letter recently published in the *Medical Journal of Australia* Vol. 163, 2 October 1995 entitled "**A positive hepatitis C enzyme immunoassay antibody test in a low risk population: what does it mean**" the authors state as follows:

"The introduction of screening of all blood donations for antibodies to the hepatitis C virus (anti-HCV) by enzyme immunoassay (EIA) has reduced the number of cases of post transfusion hepatitis C. Current third generation EIAs typically include antigens from the structural region (capsid) as well as one or more antigens from the non-structural region of the virus (NS3, NS4 or NS5). Such assays are highly reliable among individuals with risk factors for or symptoms and signs of hepatitis C virus infection, but the false positive rate remains a significant problem when a low risk population (such as blood donors) is screened....A definitive diagnosis cannot be made from a positive anti-HCV EIA test result in a healthy asymptomatic individual with no risk factors for HCV infection and a normal ALT." (emphasis added)

A significant finding by the authors of the said letter was that with third generation anti-HCV EIA a repeatedly reactive test result was "interpreted as false positive reactions in approximately 75% of cases". Blood banks in Australia and elsewhere are losing blood donors permanently. This means that the source of blood needed on a daily basis by the Australian community and other communities, is being seriously threatened. Once a blood donor is labelled as an HCV-indeterminate or HCV positive, their blood is excluded from the blood supply, even though they maybe truly negative for HCV. In other words, blood donors are being falsely labelled as "HCV positive" when in fact they are not because of the inadequacies of the present anti-HCV test kits.

The fact that third generation anti-HCV test kits are giving such results is really saying something: it means in a low risk group such as blood donors, the present generation anti-HCV tests are detecting something other than HCV and giving false positive results in up to 75% of cases. It has been five years since the first anti-HCV test kits were first used in Australia and the manufacturers of these kits have not yet produced a kit which is as sensitive and specific as the test kits for HIV. This is clearly unsatisfactory.

Associate Professor Locarnini's testimony was supported by virologists and clinicians from the United Kingdom. Professor Peter Simmonds, then with the Department of Medical Microbiology Medical School of the University of Edinburgh, gave sworn testimony that his laboratory received some 16,000 samples for HIV, HBV and HCV testing each year. He also said that his research had shown that different strains of HCV were relevant to the performance of the Chiron licensed HCV anti-HCV diagnostic assays. He concluded:

The results from this type of research largely reflect the practical results that various users of the early generation testing kits found. When the first generation assays were released the problem observed by my colleagues and I when using the kits was not their sensitivity for type 1a HCV genotypes but their inability to reliably detect HCV infections by genotypes other than type 1a.

The significance of our serology data and our examination of the kits is really placed in perspective when one considers countries such as Australia and South East Asia which do not predominantly contain HCV type 1 infected individuals. A high proportion of the blood donors in Australia are infected with HCV type 3. I am aware from discussions with my colleagues in Australia that there is a clinical suspicion that the present diagnostic assays are actually missing many HCV type 3 infected individuals. This is not a major issue in the United States, most of Southern and Western Europe and Japan, where the screening assays appear to be most extensively used because these countries generally only have type 1 HCV infected individuals.

The issue which Associate Professor Locarnini and Professor Simmonds had to confront was how to reduce the incidence of false positives in low risk populations. This was extremely difficult to do given that the patents granted to Chiron Corporation throughout the European Union and in Australia gave control over the genetic and protein materials of *all* HCV strains, not just to the 1a strain identified by Chiron scientists. By 1995 the only serotyping HCV assay available anywhere in the world was that produced by Murex Diagnostics Limited, a British company, which had been sued by Chiron Corporation for patent infringement in the United Kingdom and other European countries. The availability of the Murex serotyping assay was therefore uncertain. In

Australia, the Australian subsidiary of Murex Diagnostics Limited was embroiled in patent litigation over the supply of the Murex HCV serotyping assay as well as the supply of a secondary anti-HCV diagnostic assay. Before the Australian Federal Court Professor Simmonds gave the following sworn testimony:

The use of the serotyping assay as a research tool would establish whether antigen derived from non-type 1 genotypes can enhance the sensitivity of existing blood screening tests. This is especially important in parts of the world where the predominant genotype is not type 1 (such as Australia, North West Europe, Africa, parts of the Far East). Antigenic characterisation of HCV, and research into the immune response to type-common and type-specific epitopes is central to this sort of work.

Different individuals immune response to HCV is highly variable. It is possible that one or all of the available assays will not detect the existence of antibodies raised by infection of other HCV variants. With other viruses, such as hepatitis B, it is easy to predict the stage of infection by reference to the antibodies raised in the patient to the different regions of the genome. This is not possible with HCV. One infected individual will not necessarily seroconvert to the same regions and in the same order as another infected individual.

The evidence presented to the ALRC included the sworn testimony of Professor Baruch Blumberg of the Fox Chase Cancer Center in Pennsylvania. Professor Blumberg was awarded the Nobel in Medicine and Physiology in 1976 for his work on hepatitis B virus. During the course of the patent litigation between Chiron Corporation and Murex Diagnostics Australia Pty Ltd, Professor Blumberg said this about the impact of the Australian patent:

I have reviewed Chiron's Australian Patent No. 624105 for the purposes of these proceedings. In my opinion, the claims in this patent are very broad. These claims represent a view in scientific thought, i.e., that knowledge of the nucleotide sequence of the virus genome, let alone part of it, tells one all that needs to be known about the functions of the proteins produced by the virus and hence all that needs to be known about the virus. I do not subscribe to this view. Such a view infers that all other information about the proteins and their effects, including post-translational changes in the gene-produced proteins, interactions of viral proteins with each other, interactions of the viral gene products with the host, the biology of the virus and its host, demonstration of effectiveness, etc. is redundant. It states in effect: "Anything that is done with the HCV virus is covered by this patent and all research and development on the virus is subservient to it." The issue can also be stated in scientific terms. This patent essentially does not distinguish between genotype and phenotype, whereas geneticists are very aware that such a distinction should be made. It is the reductionism argument taken to the extreme and it is not supported by the great weight of the history of scientific discovery in biology and medicine. To the extent that this extreme view is backed-up by broad claims, which it is in this patent, the effect will likely be inhibition of research on HCV.

Based on the unusually broad nature of the patent, if I were a research director for anti-virals and had the option of working on several viruses, the existence of this patent would weigh against my deciding to undertake HCV research. A company, or even an academic laboratory, might well be deterred from conducting research on HCV because the patent is, in effect, intimidating. With the patent as it stands, any investigator, particularly in commercial laboratories (where much of the work on hepatitis has been done) would have to seriously consider that Chiron would bring an action against them if they attempted any commercialization of anything related to HCV. (emphasis added)

- 3) That this evidence was practically¹ ignored by the ALRC may be attributable to the fact that a member of the ALRC's advisory committee was the patent attorney who prosecuted the Chiron HCV patent in Australia and which was the subject of the patent litigation referred to in the preceding paragraph. Moreover, it is particularly concerning, given the extensiveness of the evidence submitted over HCV, that the ALRC concluded that such evidence was "equivocal" in regard to the impact on "any present or future ... research". Whether the advisory

¹ Para 12.78 ALRC's Report "The ALRC believes that there is little evidence that gene patents have had any significant adverse effect to date ...".

committee did or did not influence the ALRC's conclusions is not, however, the issue. What is the issue, is that the ALRC allowed itself to appear to be compromised by a serious failure to adhere to principles of good governance.

- 4) In regards to Dr. Meyer's reference to the two Australian Senate inquiries conducted, first, into the issue of gene patents and their impact on Australia's healthcare system and, secondly, into the *Patent Amendment (Human Genes and Biological Materials) Bill 2010*, her evidence not only confuses the two, but, in an attempt to lump them together manages to misdescribe them.
- 5) The first of these two inquiries was conducted by the Senate Community Affairs References Committee. The Committee's reference to instigate this inquiry was in response to the Senate's concerns over a threat issued by the exclusive licensee to Myriad's Australian BRCA patents. That threat, which was directed to all clinical laboratories providing BRCA genetic testing, was highly publicized. The Australian government was also very concerned by this threat, which was, in the end not actioned. The Senate Community Affairs References Committee held public hearings and was presented with credible evidence of how gene patents were impacting upon Australia's health system. They were also presented with submissions from IP Australia to the effect that the patenting of isolated biological materials derived from natural sources was patentable subject matter. In regards to the latter, the Committee rejected IP Australia's submission entirely. The Committee's Report, tabled in the Australian Senate on November 26, 2010 stated:

While the Committee acknowledges IP Australia's defence of the current approach as being analogous to other classes of patents, such as chemical products, the Committee **strongly rejects** the reasoning which says that, for the purposes of the Patents Act 1990 (the Act), genetic information that is 'isolated' from its naturally occurring state in the human body may be classed as an invention, and therefore properly be the subject of a patent (where the other requirements of patentability are satisfied). (emphasis added)

Furthermore, the Committee stated, in so far as the *Patent Amendment (Human Genes and Biological Materials) Bill 2010*, which was sponsored in the Senate by four Australian non-government senators, that:

The Committee considered [the rejection of this reasoning] to be the strongest justification for recommending that the Act be amended to include an express prohibition.

The Committee did not go so far as to make a recommendation to this effect for four reasons:

- (a) uncertainty around the potential effectiveness and effect of such a prohibition;
- (b) the potential for legal clarification of the issue through pending court decisions both in Australia and the United States (with express reference to the Myriad patent litigation);
- (c) a review by the Advisory Committee on Intellectual Property, which at the time was in progress, of the legislative language used in the Australian patent legislation defining patentable subject matter; and,
- (d) the potential for the *Patent Amendment (Human Genes and Biological Materials) Bill 2010*, which if passed into law, would introduce a statutory ban on the patenting of isolated biological materials derived from natural sources.

These reasons do not, with great respect to Dr. Meyer, justify her evidence. Indeed, her statement that "these ... studies ... have failed to demonstrate a net negative impact of intellectual property" and that "[r]ather, they each determine exactly the opposite", comes very close to being a misrepresentation.

- 6) The second of the inquiries was conducted by the Senate's Legal and Constitutional Affairs References Committee. This inquiry was specifically over the *Patent Amendment (Human Genes and Biological Materials) Bill 2010*. And while it is true that that Committee did not support the Bill, the reasons provided in the Report for not doing so, do not, by default, support Dr Meyer's summary. Indeed, what is very clear from the Report's conclusion is that the Committee believed that the Raising the Bar Bill, another piece of legislation introduced by the Australian government in response to other inquiries over other unrelated aspects of the Australian patent system, would provide better "solutions" to the problems caused by gene patents.

That said, this was not a conclusion shared by all Committee members. Three senators dissented. In their dissenting report they referred to the evidence presented by Cancer Council Australia, the Royal College of Pathologists of Australasia, the Human Genetics Society of Australasia, the Royal College of Physicians, the Australian Department of Health and Ageing, the Australian Medical Association, the South Australian State Government and the Generic Medicines Industry Association, all of which supported the intent of the *Patent Amendment (Human Genes and Biological Materials) Bill 2010*.

The South Australian State Government submitted:

... broad patent claims specifically related to human genes and biological materials, as they exist in nature, have been shown to have an adverse impact on the provision of health care, including medical research, the scope of the provision of training and accreditation of health care professionals and the cost of performing certain genetic tests within South Australia.

The Australian Department of Health and Ageing submitted:

Free access to genetic material, including the normal genome and its mutations (as well as information relating to the association of genes with disease), is essential to promote continued innovation in the prevention, diagnosis, prognosis and treatment of disease.

A U.S. generic pharmaceutical company, Mylan, Inc also filed a submission supporting the Bill. In its submission it reasoned:

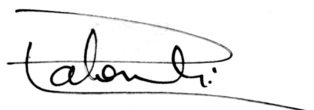
The patenting of naturally occurring biological materials is stifling medical and scientific research as well as the diagnosis, treatment and cure of human illness and disease. Such patenting prevents doctors, clinicians and medical and scientific researchers from gaining free and unfettered access to these materials, however made, that are identical or substantially identical to such materials as they exist in nature.

The Australian Medical Association argued:

Allowing doctors, clinicians, and researchers free and unfettered access to such biological materials has the very real potential to facilitate greater, more competitive research into the development of genetic technologies. This would benefit patients, health care professionals, and the broader health care system by allowing more equitable access to a wider range of genetic tests and related technologies.

In closing may I just add that the *Patent Amendment (Human Genes and Biological Materials) Bill 2010* has yet to be voted on by the Australian Parliament. That the majority of the Senate Legal and Constitutional Affairs References Committee recommended against this Bill does not mean that ultimately the Parliament will not pass it or some other legislation to the same or similar effect. Recent developments in the United States, particularly with the U.S. Supreme Court in *Prometheus v Mayo Clinic*, suggest that isolated naturally occurring genetic materials are patent in-eligible subject matter. Should the U.S. Supreme Court grant certiorari in *Association of Molecular Pathology et al v USPTO and Myriad Genetics*, the resolution of this longstanding debate in the United States will most likely influence developments on the same issue in Australia. In this regard, it is important to note the caveat in U.S. Supreme Court's decision in *Prometheus v Mayo Clinic* to the effect that the law is the law and whatever the consequences the Court "must hesitate before departing from established general legal rules lest a new protective rule that seems to suit the needs of one field produce unforeseen results in another". It seems likely, in view of *Prometheus v Mayo Clinic*, that the USPTO and those that champion the patenting of genetic materials isolated from natural sources have made that very mistake.

Yours sincerely,



Luigi Palombi LL.B (Adel), B.Ec (Adel), Ph.D (UNSW)