

Response To The Advisory Council On Intellectual Property Issues Paper Concerning Patents And Experimental Use.

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Question 1 (a) What is your understanding of current law on an experimental use exemption in Australia?

- (a) What is the basis of this understanding and how certain are you of it?
- (b) How has your understanding affected your research and development behaviour?

Beyond s.78 *Patents Act, 1990* [Cth] [*the Act*] there is no express nor implied experimental use exemption in Australia regarding patents. Section 13, *the Act* defines the exclusive rights of a patentee. The words - *make, hire, sell or otherwise dispose of*- include *the use of*. The words, *the use*, are all inclusive and do not encompass any commercial purpose or motive threshold with respect to the exploitation of a product, process or method. They mean precisely what they say. Therefore, any use, including experimental or non-commercial or regulatory use of a patented product, process or method without the authorisation of the patentee is a violation of the patentees exclusive rights in Australia.

The exception provided by s.78 only serves to reinforce this interpretation. If *Freason v Loe* was the law in Australia, then the experimental, non-commercial or regulatory use of a pharmaceutical substance *per se* would not need to be expressly exempted. Moreover, the use of the invention for the purpose of improving upon it so that the improvement may be sold or supplied is a commercial enterprise which has all the hallmarks of exploitation. Accordingly, it is reasonable to suppose that an unauthorised person that used the invention with no intention of selling, hiring or disposing of the invention *per se*, but of doing something to it or with it, even if it is to improve upon the invention, is still interfering with the patentees rights of exploitation. It is possible that an improvement to the invention, even if it is capable of being separately patented, is a violation of the patentees rights to the invention.

Question 2: What lessons, if any, do overseas experience and law hold for an experimental use exemption in Australia? In particular, are any of the overseas approaches to be preferred for Australia?

The decision of the CAFC in *Roche Products, Inc. v. Bolar Pharmaceuticals Co., Inc* and *Madey v Duke* provide support for the answer to Question 1. The narrowness of the US experimental use exception suggests that it is virtually useless given the blurring of boundaries between the universities and commercial enterprises. At what point the experimental use of an invention, by a curious individual or an educational entity such as a university, crosses the line is very difficult to assess. If the threshold is the *sole amusement or strictly philosophical inquiry test* as prescribed in *Madey v Duke*, it is possible that even experiments conducted on an invention for the purpose of demonstrating that it fails to provide the utility described in the patent specification could violate the patentees exclusive patent rights if the university is acting in furtherance of its business interests or of a contracting commercial enterprise. This is especially so if the invention is made or used for the purpose of experiments that are in furtherance of an attack on the validity of the patent or to avoid infringing the patent because the use is (a) in furtherance of the university's

legitimate business or activities and (b) not being conducted for idle curiosity. That type of activity is ultimately shrouded in commerce and contrary to the interests of the patentee.

The approach in the UK and NZ is no less problematic because it is difficult to foresee circumstances where the experimental use of an invention is conducted for 'purely' private or non-commercial purposes.

The problem with the overseas examples of experimental use exceptions discussed in the Issues Paper resides in defining the nature of the activities that are legitimate.

Question 3: What are the constraints for an experimental use exemption (or possible alternatives) under any of the international agreements to which Australia is a signatory?

Articles 28, 30 and 31 TRIPS do constrain an experimental use exemption.

First, art. 28 requires the 'use' of an invention to be one of the exclusive rights of a patentee.

Secondly, art 30 permits '*limited exceptions*' to the exclusive rights provided that the exception does not 'unreasonably' (a) '*conflict with a normal exploitation of the invention*' or (b) '*prejudice the legitimate interests of the patent owner.*'

Thirdly, art. 31 permits government authorised use of the invention beyond art. 30 'limited exceptions' but only on very limited conditions that include the exploitation of a second patent [which suggests an improvement of the first patent but which comes within the scope of the first patent] only if '*the invention claimed in the second patent shall involve an important technical advance of considerable economic significance in relation to the invention claimed in the first patent*' and '*the owner of the first patent shall be entitled to a cross-licence on reasonable terms to use the invention claimed in the second patent*' and '*the use authorised in respect of the first patent shall be non-assignable except with the assignment of the second patent*'.

Given that a supposed 'legitimate' use of experimental use of an invention as per the 19th Century UK case *Freason v Loe* is to improve "*upon the invention the subject of the patent, or with the view of seeing whether an improvement can be made*" the impact of TRIPS on the ability to allow for an effective experimental use is significant.

It is difficult to imagine a situation where the experimental use of an invention that has the effect or end result of a) destroying the validity of first patent, b) avoiding infringement of the first patent or c) improving upon the first patent, would not i) '*unreasonably conflict with a normal exploitation of the invention*' or ii) '*unreasonably prejudice the legitimate interests of the patent owner.*' Furthermore, in the context of an improvement to the invention of the first patent and one which comes within the scope of the first patent, the requirement that the improvement be '*an important technical advance of considerable economic significance*' is a very high threshold to satisfy.

It seems that the CAFC decision in *Madey v Duke* supports the very limited scope of an experimental use exception, not only under US patent law, but also under TRIPS.

Question 4: Is there any *empirical* evidence that the balance between the incentives for innovation and the ability to use innovations, particularly for research and development, is being significantly affected by the absence of an explicit experimental use exemption [or some other provision] in Australian patent law?

Yes, there is. The evidence referred herein was given before the Federal Court of Australia in the case of *Murex Diagnostics Australia Pty Limited v Chiron Corporation and Ortho*

Diagnostics Systems, Inc (NSW District NG 106 of 1994) which was heard in Sydney before the Honourable Justice Burchett between June 24, 1996 and August 28, 1996. This case and issues relevant to it received media attention, e.g., ABC Lateline in 1994, Channel 9 Sunday in 1995, ABC Quantum in 1996 and ABC The 7.30 Report in 1996. It was also featured in the Sydney Morning Herald in 1996. Evidence of expert witnesses filed in the proceedings included two of the named “inventors” of HCV, Drs Houghton and Kuo from Chiron, Dr. Bradley formerly of the Centers for Disease Control, U.S.A., Dr. Stephen Locarnini then the director of Victorian Infectious Diseases Reference Laboratory, Nobel Laureate Professor Baruch Blumberg of the Institute for Cancer Research, Fox Chase Cancer Center, U.S.A, Dr. David Kemp then of the Menzies School of Health Research, Professor Sir Gustav Nossal then the director of the Walter & Eliza Hall Institute for Medical Research, Professor John Shine of the Garvan Institute of Medical Research. There were other noted scientists and experts, but rather than mention them all individually at this point, it suffices for the purposes of this introduction if those mentioned here gives some indication of the high level of science considered throughout this case.

The issues which were germane to this case centred on the validity of Australian Patent 624,105 granted to Chiron Corporation. The patent AU 624,105 was granted by the Australian Patent Office in 1992 and is entitled “NANBH diagnostics and vaccines”. Chiron cross-claimed that Murex infringed its patent by importing and selling in Australia an HCV immunoassay and an HCV serotyping assay. However, evidence was given relating to continuing, albeit reduced, spread of post-transfusion HCV and the immediate need for a variety of HCV immunoassays designed for Australia.

There was no judgment of the Federal Court of Australia because the proceedings came to a sudden halt when on August 28, 1996 Murex and Chiron settled their worldwide differences in confidence. Although Murex did succeed in obtaining a license to manufacture and sell its HCV immunoassay, this was a license that was restricted to certain areas of the world – fortunately Australia was one of those countries included within the license. However, Murex’s HCV serotyping assay became available on a worldwide basis. Within two years of this settlement, Murex was fully acquired by Abbott Laboratories [U.S.A.], one of the original Chiron licensees.

Why is this relevant? Because the spread of post-transfusion HCV was not halted in Australia with the introduction of Chiron licensed HCV immunoassays in the early 1990’s and there is evidence that people who received blood or blood products during the 1990’s contracted HCV through that route. The 624,105 patent prevented the development of alternative HCV diagnostics assays in Australia when there was a well documented vital medical need for alternatives which the patentee [and its licensees] failed or refused to provide.

The History Of Post-Transfusion Hepatitis In Australia, Including When Non-A, Non-B Hepatitis [Hepatitis C] Was First Identified As A Risk To The Safety Of Blood Supplies In Australia And Internationally.

(a) before 1990

The first affidavit of Professor Stephen Locarnini explained,

2.5. My involvement in hepatitis research began in March 1974. I was a member of a research team at the Department of Microbiology, Monash Medical School, Monash University at the Alfred Hospital. This was the first research group in the world to detect the Hepatitis A virus in the faeces of patients with naturally acquired disease, and to prove conclusively that the particle was both disease-associated and serologically specific for naturally acquired Hepatitis A infection. Even though my

Ph.D. was focused on hepatitis A, because my work was part of a prospective study of consecutive admissions of patients to Fairfield, it allowed me and my colleagues to define hepatitis as it was occurring in Melbourne at the time. **We were then able to break down patients into either hepatitis B, hepatitis A or non A, non B hepatitis (NANBH). Of the 118 consecutive patients admitted to Fairfield Hospital in 1975, 75 patients were hepatitis A, 31 patients were hepatitis B, 18 patients were non viral hepatitis, i.e., miscellaneous, and 16 patients were hepatitis of undetermined etiology which would be classified as NANBH.**

The first affidavit of Dr. Daniel Bradley explained,

- 4.1 By 1975, it was understood that a significant number (and perhaps a majority) of cases of post-transfusion hepatitis was not caused by any known human virus including hepatitis A virus (HAV), hepatitis B virus (HBV), cytomegalovirus (CMV) or Epstein-Barr virus (EBV). Rather, these cases appeared to be caused by one or more additional transmissible agents which, for lack of a better term, were known as “post-transfusion non-A, non-B hepatitis” agents (PT-NANBH), or, simply, NANBH agents. At about this time, it was generally agreed among scientists in the field that between 10% and 20% of patients transfused with blood or blood products developed PT-NANBH.
- 4.2 In 1977, I was contacted by Dr. Gary Dolana of Hyland Laboratories in Costa Mesa, California. Dr. Dolana’s company manufactured and sold a Factor VIII product. Factor VIII is required by hemophiliacs to restore normal clotting activity. I learned from him that three lots of Hyland Laboratories’ Factor VIII concentrate had been implicated in causing NANBH in several patients. Two patients had developed NANBH after receiving aliquots of Lot No. D0056A. Two other patients had been afflicted with NANBH after receiving Factor VIII from two other lots. I arranged to have all of the remaining supplies from each of these lots sent to my laboratory. I also arranged for convalescent phase sera from two of the three infected patients to be collected and sent to me.
- 4.3 After receiving the suspect Factor VIII materials, I attempted to visualize virus-like particles in both fractionated and unfractionated materials using standard electron microscopy (EM) and immune electron microscopy (IEM). Despite extensive efforts, no virus-like particles could be visualized with these techniques.
- 4.4 Since the presumed viral agent(s) could not be visualized, I designed a primate protocol to test the Factor VIII concentrates for the presence of a transmissible agent. In early 1978, four chimpanzees from CDC’s primate facility were intravenously inoculated with the suspect Factor VIII concentrates. Two chimpanzees received 30 mls each from suspect lot No. D0056A. The other two received the same amount from a pooled preparation from the other two suspect lots. Over a period ranging from 13 to 70 days, all four chimpanzees experienced an elevation of a liver enzyme called alanine aminotransferase (ALT) which was indicative of hepatitis. Light microscopic examination of liver biopsy materials obtained from all four animals also showed histopathological changes consistent with acute viral hepatitis. However, EM and IEM examination of liver tissue and plasma taken from each of the four animals did not reveal any disease-specific virus-like particles.
- 4.5 **Serological tests were performed to rule out the possibility that the ALT and histopathologic responses were caused by known viruses, i.e. HAV, B V, CMV and EBV. These tests were negative. I therefore concluded that the suspect Factor VIII concentrates indeed contained one or more transmissible agents capable of causing NANBH.**

Professor Terukatsu Arima, of the Second Department of Internal Medicine at the Faculty of Medicine of Kagoshima University in Japan explained,

22. **By the late 1970's I was aware of the existence of NANBH through the clinical treatment of patients suffering from hepatic liver disease. Hepatitis A virus (HAV) infections were excluded by the absence of infection in the intestinal-oral route. Hepatitis B virus (HBV) infections were excluded by diagnostic testing using test kits commercially available at that time. I was aware of many patients that were suspected of being infected with the putative agent for NANBH.** In Japan, about 60% of chronic Hepatitis patients (about 720,000 patients), about 40% of Liver cirrhosis patients (about 100,000 patients) and about 40% of liver cancer patients (about 7,000) were patients having NANBH. Further, the mortality rate attributed to NANBH reached 16 thousand per year. Nearly 1 to 6% of all blood donors in Japan were NANBH carriers.

(b) After 1990

The first and second generation Chiron licensed HCV immunoassays in Australia were not as accurate as they should have been in detecting HCV in donated blood. Dr. Locarnini explained,

- 6.6. An important issue that is emerging relates to the geographical distribution of hepatitis C genotypes. The most important study on the various genotypes of HCV to date comes from the Edinburgh University. A research team supervised by Dr. Peter Simmonds, published the results of their research in McOmish et al., *Geographical Distribution of Hepatitis C Virus Genotypes in Blood Donors: An International Collaborative Survey* Journal of Clinical Microbiology, April 1994, 884-892. ... This ... shows that there are at least 6 genotypes of hepatitis C, classified by the McOmish Simmonds system. Genotype 1 is a common one. The original Chiron clone 5-1-1, is from genotype 1a. All these six genotypes, show strong reactivity to at least the core protein, which is the c22-3. The next most important protein in terms of antibody response is the c33c (the helicase protein). Clearly it is important in respect to genotype 1, genotype 2, 4, 5 and 6, but is weak for genotype 3, i.e. it is only 80% reactive. The next most important protein is the c100-3. However, it is only modestly reactive even against its own strain, i.e., genotype 1a, and it is extremely weak against genotype 3. The least important is 5-1-1. In this context it is completely non reactive against genotype 5 and has extremely low reactivity against genotype 3.
- 6.7. The problem I have as a medical virologist in setting up hepatitis C testing in Victoria is that **only approximately 45% of persons infected with hepatitis C are genotype 1a; 5-10% are genotype 1b; and 45% are genotype 3a.** There are two sources which support these statistics. One source is the data being generated at the moment from my own laboratory at Fairfield. This is not yet available in a published format. The other source has been published in a report prepared by the Hepatitis C Task Force of which I am the chairman, entitled "*Report On The Epidemiology, Natural History And Control Of Hepatitis C*" and tabled with the NH & MRC in November 1993. This report refers to studies from Western Australia which show that of the 23 Australians in one study, 13 of 23 (56%) were genotype 1, 3 of 23 (13%) were genotype 2; and 7 of 23 (31%) were genotype 3. The study conducted at Fairfield in Victoria showed that 45% were genotype 1a; 10% were 1b; and 45% were 3a. The significant point is that genotype 3 is an important strain in Australia.
- 6.8. The Hepatitis C Task Force recommendations contained in the November 1993 report focus on the laboratory diagnosis of hepatitis C, case definitions, epidemiology and control mechanisms of hepatitis C in Australia. The Hepatitis C Task Force, after receiving submissions and reviewing the literature, indicated that a number of important public health issues had come to light. The Hepatitis C Task Force found that Australian strains of hepatitis C are probably different from strains circulating in the northern hemisphere. Consequently, the first recommendation of the report was

- that Australian research laboratories "be encouraged to undertake full nucleotide sequence studies on Australian strains of hepatitis C virus". **The reason for this recommendation was that cases of post-transfusion hepatitis C were occurring in the community that were being missed by the existing, "second generation" screening tests.** The reason for this is still unknown today. The Ortho/Abbott second generation screening kits were introduced in Australia in May 1991. The Abbott "third generation" screening kits are presently being introduced in Australia.
- 6.9. **The concern of the Hepatitis C Task Force is the strong and unequivocal evidence indicating that, despite the use of second generation anti-HCV screening assays as supplied in Australia, there were antibody negative HCV infectious blood donors in Australia. So in the opinion of the Hepatitis C Task Force there is sufficient evidence to indicate that there are genotypes of hepatitis C in Australia which may not be detected by the current anti-HCV screening assays.**
- 6.10. In my view which is supported by the published literature, **the anti-HCV screening assay that is produced by Ortho or licensed by Chiron to Abbott Laboratories in Australia, is only 90% sensitive in relation to genotype 1a and probably much less so with respect to genotypes 3 or 5.** I have written a paper with Dr. A. Breshkin entitled "*Comparison of Three Second Generation Immunoassays for Detection of Hepatitis C Virus Antibody*" published in *Australian Journal of Medical Science*, Vol. 14, February 1993. The papers which support my view are as follows:-
Aach, R.D., et. al., 1991 *N. Engl. J Med.* 325 : 1325;
Alter, H. J., et. al., 1992 *N. Engl. J Med.* 327 : 1899;
Sugitani, M., et. al., 1992 *Lancet* 339; 1018 - 1019;
Wang, Y., et. al., 1994 *J. Hepatol* 21; 634-640.
- 6.11. **I am aware, from my position as chairman of the Hepatitis C Task Force, that the level of sensitivity referred to in paragraph 6.10 is not acceptable to blood banks in Australia.** What is acceptable is the benchmark set for HIV which is 99.4% sensitive and specific. **The current Chiron anti-HCV screening assay which is no more than 90% sensitive, is clearly unacceptable and must be improved upon.** Sensitivity is defined as the ability of a diagnostic test to actually find those who are truly infected to be positive, whereas specificity is to find those that are truly not infected to be negative, so when the test is evaluated for sensitivity one finds a high risk group that are likely to be infected. For specificity, one finds a low prevalence group.
- 6.12. **Apart from the differences in genotypes there are many factors that affect the performance of diagnostic kits.** When I first came into this field, in the mid 1970's, I spent six months collecting hepatitis A and hepatitis B specimens from patients and purifying local reagents so that the laboratory had local strains of hepatitis B as reference material. The laboratory also had reference material from the National Institutes of Health ("NIH") in the United States of America. The laboratory ran the NIH reference material and our own reference material in parallel. That is a very important function of a reference laboratory; by obtaining all its own local material the reference laboratory can produce its own diagnostic test.
- 6.16. Subsequently, the introduction of molecular biology in the production technology of diagnostic kits saw kit manufacturers mainly using *E.coli* and yeast systems to express HIV antigens. It was found that these antigens worked even better than the native antigens for HIV. These kits do not use native antigens, i.e. clinical material. They used fusion proteins. The *E.coli* produces a protein that is fused with HIV proteins. A protein is a three dimensional molecule, so that when a person becomes infected by a virus, a person's immune response is to the whole native antigen and antibodies are produced to the epitopes contained on the native antigen. With *E.coli*

or a yeast expressed protein, the fused protein that is produced is not necessarily conformational as it is in its native original form. A fusion protein is unlikely to retain the original native conformational epitope. As has been found with HIV this may not necessarily affect the performance of the screening assay/ diagnostic kit, since linear epitopes that are part of the fusion protein used in HIV kits are adequate in producing an antibody-antigen reaction. This is probably due to the form in which HIV epitopes exist *in vivo* (the natural setting).

- 6.17. For hepatitis C, however, the same may not be true. **With hepatitis C it is now suspected, due to the fact that anti-HCV screening assays/diagnostic kits have not achieved sensitivity above 90% and the numbers of indeterminants that have been recorded, that many of the immune responses are conformation dependent.** In other words there are nuances of the three-dimensional folding which are critical to antibody detection. It is extremely difficult to reproduce the natural three dimensional folding of a protein containing an epitope in *E.coli* or yeast fusion protein systems. With such systems all that is produced is a linear epitope of one small fragment of the genome of a strain of HCV inserted in the *E.coli* or yeast expression protein. The difficulty with hepatitis C is that a person is not infected with *E.coli* containing clone 5.1.1 proteins, or c-100-3 proteins; that person is infected with the whole native hepatitis C virus of a particular genotype.
- 6.18. **There is also evidence emerging that some third generation kits such as the Abbott Laboratories anti-HCV diagnostic kits have no greater sensitivity than the second generation kits, even though the manufacturer has included longer fusion protein inserts (i.e., more genetic material) into the kits.**
- 7.1. ... With hepatitis C, as with HIV, all initial repeat reactors detected in the screening are tested in another test and a positive result must be obtained with the other tests before the result is classified as positive i.e., "antibody detected by EIA". Otherwise the result is classified as an indeterminant.
- 7.2. In my opinion it is a necessary policy for a reference laboratory like Fairfield to have more than one diagnostic kit available. **This is in the best interests of public health.** This is especially true for hepatitis C where, as discussed above, there are present in Australia at least three genotypes of HCV. Genotype differences are more likely to cause false negatives. This means that persons with HCV infection may be missed and infected blood may be transmitted to other persons.

In his second affidavit Dr. Locarnini answered a criticism suggesting that his complaints about the adequacy of the Chiron licensed HCV immunoassays were unfair since this test was better than no test as was the situation during the 1980's. Dr. Locarnini explained,

4. The question which Dr Beal poses is this: Is a test better than no test? In my opinion, this is not the right question. There is no doubt that, prior to the first generation anti-HCV test kits, the risk of being infected with PT-NANBV as a consequence of receiving a blood transfusion was much higher than today. However, in my opinion, there remains an unacceptable risk, even with the use of subsequent generation anti-HCV test kits, of hepatitis C being transmitted through blood transfusions i.e., false negatives. A more important issue for blood banks in Australia, however, is the number of blood donors permanently stood down by blood banks of blood donors as a consequence of indeterminate results or false positive results from the present anti-HCV test kits. Blood donors are a low risk group for HCV.
5. 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 "*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)

6. **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".**
7. 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.
8. 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.
9. What must be understood is that the test results from anti-HCV test kits need to be interpreted before a final conclusion can be reached as to whether a person does or does not truly have HCV. It is not simply a matter of testing a person's blood with a test kit. The background of that person is relevant. If that person comes from a high risk group, such as injecting drug users and a positive result is obtained, then one can conclude with a high degree of certainty that it is a true positive result, but if a person is from a low risk group, the same is not true.
10. A positive diagnosis drastically affects peoples lives. Once people are labelled HCV positive, their blood is lost to the community if they are a blood donor; they are referred to a liver clinic; their private lives are affected; their relationships are affected; their insurance policies are affected; their quality of life is affected. In the case of a false positive, this to me is unacceptable and a great deal of research must be undertaken to encourage improvement in the specificity of these tests.
11. When you contrast the developmental history of HIV tests with HCV tests the reasons for my concern are more readily apparent. With HIV the specificity and sensitivity was in the high 90s very quickly together with a confirmatory strategy that worked with the Western Blot. That has not happened with HCV, so clinical laboratories have had to struggle with the false positives issue.
12. **In my opinion the current anti-HCV tests are better than no test, but that is not the point. Once you have a test, the test needs to be highly sensitive and specific and the current tests are not as sensitive nor specific as they need to be.**
13. On 8 November 1995, at the 12th National Workshop on Retrovirus Testing my team at the Victorian Infectious Diseases Reference Laboratory presented a paper about the results of our research. What my colleagues and I did was to prepare a panel of 180 samples which were tested by the Roche PCR Amplicor as well as our in house PCR in order to determine the true HCV status of those serum samples. All samples were

repeatedly positive for HCV RNA in both assays. In other words they were all truly HCV positive. My colleagues and I then tested these samples against nine anti-HCV assays available in Australia in accordance with the manufacturers instructions. What was interesting was that none of the nine anti-HCV assays detected all 180 samples as reactive. One sample was non reactive in all nine anti-HCV assays. When we genotype tested this particular sample we found that the strain was HCV genotype 3A. Another sample was non-reactive in six of the assays and this sample was HCV genotype 1b. One of the assays gave non-reactive results for eight samples.

14. **In my opinion, the sensitivity of these tests can be improved if the kit manufacturers would include reagents from genotypes other than from strains HCV 1a and 1b. In the Australian community HCV strains 1a, 1b, 3, 4 and 6 are present because of ethnic diversity of the population. In my opinion, the kit manufacturers need to develop and include better conformational antigens for all strains of HCV in their kits. Specificity is the real problem with HCV test kits and much more research is required before I am satisfied that anti-HCV test kits are sufficiently reliable in Australia.**
22. In a paper "Study on Reliability of Commercially Available Hepatitis C Virus Antibody Tests" Feucht et al published in the Journal of Clinical Microbiology, March 1995, p 620-624. The authors state, "*First generation HCV enzyme immunoassays (EIA) detected only antibodies against nonstructural region 4 (NS 4) with recombinant antigen c100-3. The tests of the second generation, the Abbott HCV 2.0, used additional antigens of the core region (c22-3), the NS 3 region (c33c), and (especially the Ortho RIBA 2.0) a part of the c100-3 (named 5-1-1) from the NS 4 region.*"
23. The Abbott HCV 2.0 assay is the assay marketed by Abbott Laboratories in Australia under licence from Ortho and Chiron. These assays included antigens of the core c22-3 region. Despite the inclusion of the c22-3 core antigen in the assay the authors reported, "*In daily diagnostic work, the commercially available Abbott second generation HCV EIA and the supplementary Ortho RIBA 2.0 often do not yield clear indications of whether an HCV infection exists.*"
24. The authors describe the study which they conducted and their results. They then concluded at page 623: "*One of the major problems in daily routine work is to decide whether a patient is HCV infected. In a number of cases, the commercial tests did not help us to decide whether an HCV infection existed...Until now, the absence of a "gold standard" for HCV antibody tests has made it difficult to compare the sensitivities and specificity's of diagnostic assays. **The lack of detectable specific antibodies against HCV does not exclude the possibility of an infection, especially during the acute phase of infection or of patients who are immunosuppressed because of transplantations, cancer, human immunodeficiency virus infection, or chronic hemodialysis, for example....A worldwide standard for HCV antibody testing should be established. Our results show that the commercially available HCV antibody tests need to be improved.***" I agree with this conclusion. In my opinion, the results of this research apply in Australia.
25. In a paper by Mayumi et al entitled "Hepatitis C virus antibodies among blood donors in Beijing" published in Journal of Hepatology, 1994; 21: 634 - 640 the authors describe a study that they conducted among blood donors in Beijing using the second generation EIA's. They stated in their paper that: "*Although EIA-1 has been useful for the diagnosis of acute and chronic hepatitis C and for excluding blood units contaminated with HCV, it is neither very sensitive nor specific. EIA-2 has overcome most of these shortcomings, but is still limited. In particular, the sensitivity of EIA-2 in detecting viremia is not satisfactory in the low-risk populations typified by blood donors. **Approximately 10% of post-transfusion non-A, non-B hepatitis cases***"

- cannot be prevented by screening blood units by EIA-2.** *These patterns require a more direct method to identify viremia, by detecting either viral RNA or viral proteins, like hepatitis B virus DNA or hepatitis B surface antigen used for the diagnosis of ongoing HBV infection."*
26. **After more than five years since Chiron/Ortho/Abbott first released their HCV EIA, the lack of a "gold standard" for HCV EIAs is a significant public health issue throughout the world.** This is in sharp contrast to my experience with the development of HIV tests. With HIV there were many more diagnostic manufacturers competing to make HIV tests. The dialogue between clinical laboratories and reference laboratories and diagnostic kit manufacturers was such that the sensitivity and specificity of HIV testing reached 99.9% very quickly. My experience with HCV has been to the contrary.
27. The only diagnostic kit manufacturer that has used antigens from a different strain of HCV is Murex Diagnostics. All other kits use antigens from HCV strain 1a. Murex uses HCV strain 1b. In Australia, we have a diverse ethnic population in which HCV strains 1, 3, and 6 exist. The only diagnostic kit manufacturer that has produced a serotyping assay is Murex Diagnostics.
28. **In my opinion, without competition amongst diagnostic manufacturers it is unlikely that this real public health issue will be addressed in Australia or in other parts of the world with different genotypes, for example, Egypt with genotype 4 or South Africa with genotype 5. There is a real need to encourage further research and development in the HCV diagnostics market both in Australia and the world.** The existence of the patent in suit and the manner in which Chiron has restricted licensing has had a detrimental effect on the development of more sensitive and specific HCV diagnostic assays.

Dr. Simmonds from the University of Edinburgh explained,

- 3.5 In about 1992 I began to realise that there was a significant problem in the nomenclature used to name different isolates of HCV. Different laboratories throughout the world used different classification systems to identify their isolates. This made a comparison of different HCV research results difficult. In collaboration with Dr. Michael Urdea of Chiron Corporation, we proposed a nomenclature that could be used to classify all HCV isolates. That nomenclature was subsequently published in 1994 in a letter to the editor of the Journal *Hepatology*. The letter was joint authored by 22 other leading researchers in the HCV field, which Dr. Urdea and I consulted [Simmonds. P., et al., (1994) "A proposed system for the nomenclature of Hepatitis C Viral Genotypes" *Hepatology*, 19 (1), 1321-1324].
- 3.6 Research effort for my HCV research group is now concentrated on the exploration of sequence variability of HCV and its effects on pathogenesis, diagnosis and treatment. The level of sequence variability in certain regions of the HCV genome is extremely high. All currently known variants can be classified into six major phylogenetic groups corresponding to genotypes 1 to 6 in the proposed nomenclature with subtypes within them.
- 3.7 The Department of Medical Microbiology at the University of Edinburgh where I work carries out a range of diagnostic tests on clinical specimens from the Royal Infirmary of Edinburgh, and elsewhere. My colleagues and I currently receive approximately 16,000 samples for HIV, HBV and HCV testing/year, 12,000 samples for virus culture and/or direct virus detection, and 5,000 samples for other virus serology. The laboratory in which I work is a regional reference center for chlamydia, hepatitis and HIV-1 testing and confirmation. Working in such a clinical laboratory has enabled me to gain research experience in all aspects of routine diagnostic virology, including cell culture and virus isolation, immunofluorescence,

- electron microscopy, ELISA and other serological techniques, and result interpretation.
- 5.2 The greatest sequence variability amongst all HCV genotypes arises in the envelope region. In that region there is only about one-half predicted amino acid sequence identity between the different genotypes. The core and 5' non-coding region (5' NCR) are the most highly conserved. Elsewhere, sequence variability is approximately evenly distributed throughout the remaining viral genes. Antibodies elicited by infection with one HCV genotype as the extent of variation observed could possibly fail to neutralise other HCV genotypes. The extent of variation observed within HCV is comparable to that between serotypes of other RNA viruses. HCV differs from most RNA viruses in its ability to establish chronic infection and progressive disease in a large proportion of those exposed to it. The mechanism for this remains uncertain.
- 5.3 Some genotypes of HCV (types 1a, 2a, 2b) show a broad worldwide distribution. Others such as type 5a and type 6a are only found in specific geographical regions. Understanding the current distribution of HCV requires knowledge of routes of transmission, historical data on the prevalence and risk groups for HCV, and the time of the divergence of the major genotypes and sub-types. We know very little about any of these factors. It is difficult to draw conclusions from existing information. The problem is compounded by the scarcity of information concerning genotype distribution in many geographical regions such as Africa.
- 5.4 In the United States of America there is predominantly HCV type 1a and 1b. In Europe (including the United Kingdom) there is predominantly HCV types 1a, 1b, 2 and 3. In the Middle East there is predominantly types 3 and 4. Individuals from countries like Pakistan, India and Bangladesh are most frequently infected with and other subtypes of type 3a. Type 4 is frequent in central Africa, type 5 is frequent in South Africa and type 6 is frequent in South East Asia (including Vietnam). In Australia there are basically 3 HCV types, type 1, type 2, and type 3. I believe type 5 and 6 have also been reported in Australia. There are no strict geographical boundaries limiting the various HCV types.
- 6.1 Different immunological screening assays use antigenic material from different sources. The Murex HCV assays uses antigenic material derived from a human donor in the UK and is of HCV genotype now known as type 1b. In the United Kingdom genotype 1b is one of the most prevalent genotypes. That is the sequence that Murex first isolated and that Murex antigens are based on. **The Chiron based assays use antigenic material derived from a chimpanzee in the USA and is of HCV genotype type 1a, which is the most predominant type in the USA.**
- 6.2 Part of the research we have conducted on the distribution of HCV throughout the world has focused on determining the efficiency of the early immunoassay kits. We found that antigens that were used in first generation immunoassay kits exhibited variable degrees of efficiency in identifying HCV, depending on the genotypes present. In a scientific paper written by my colleagues and I entitled: "Mapping of Serotype-Specific, Immunodominant Epitopes in the NS-4 Region of Hepatitis C Virus (HCV): Use of Type Specific Peptides to Serologically Differentiate Infections with HCV Types 1, 2 and 3". Simmonds P., *et al.*, Journal of Clinical Microbiology (1993), 31(6), 1493-1503 we observed "... *the consensus subtype 1a sequence of the first antigenic region (residues 1691 to 1708) differed from subtype 2b at 9 of the 18 amino acid residues and from type 3 by 6 residues. In the second antigenic region (1710 to 1728), sequences of types 1a, 2b and 3 differed from each other by 7 to 12 of 19 residues. This specific difference in antigenicity between peptides corresponding to the two regions is consistent with the absence of serological reactivity of most sera from HCV type 2- and 3- infected individuals to the recombinant protein 5-1-1*

(8,33), which extends from residues 1694 to 1736 and therefore includes part of the first antigenic region and all of the second (2). **Similar type-specific reactivity has been also observed with the longer c100-3 protein, which includes all of these residues, those upstream in NS-3 and those downstream towards the end of NS-4...**”
(Emphasis added)

6.3 **Thus by using polypeptides derived from clone 5-1-1 and c100-3 sequence information, disclosed in the Chiron patent specification, in an immunoassay kit we failed to identify many type 2 and 3 infected individuals.**

6.4 My colleagues and I found that a large proportion of infected individuals were missed by the early assays (based on the Chiron’s sequence data) because they contained antibodies generated against HCV genotypes other than type 1. If you incubate a type 2 serum against type 1 peptides containing 5-1-1 epitopes, recognition of the serum is generally very weak or may not be observed at all.

6.5 Subsequent research conducted by my colleagues and I examined the variability of nucleotides and amino acids in the NS-4 protein around the 5-1-1 region in six different genotypes of HCV. Amongst the findings made in those studies we showed substantial amino acid variability between the six HCV types in the NS-4 protein region. From this information we prepared a phylogenetic analysis of a 342 nucleotide region of NS-4 which summarised the degree of variability observed within the 6 HCV genotypes. The results of this research, including our phylogenetic analysis, were published in a paper entitled “Use of NS-4 peptides to identify type-specific antibody to hepatitis C virus genotypes 1, 2, 3, 4, 5 and 6”. Bhattacharjee V., *et al.*, (1995) Journal of General Virology, 76, 1737-1748. This research showed that substantial amino acid diversity exists between the HCV genotypes in the region corresponding to clone 5-1-1 (amino acids 1694 to 1736).

6.6 The phylogenetic differences observed in the NS-4 region of the isolates examined in Bhattacharjee V. *et al.*, (*supra*) are, in fact, mirrored in other subgenomic regions of the subgenomic structure of different HCV genotypes. NS4, NS5, E1 all produce the same phylogenetic tree. This observation reflects the degree of nucleotide variation that exists between the different genotypes of HCV.

6.7 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.

6.8 In essence these observations were the stimulus for some of my current research. That is to develop immunoassays that are sensitive to all HCV genotypes and immunoassays that are capable of distinguishing between the various HCV genotypes.

6.9 My colleagues and I started this research by examining the extent to which antigenic variation between genotypes affects the sensitivity of two 3rd generation enzyme immunoassays (Ortho EIA 3.0 and Murex VK48). We investigated the influence of viraemia status, HCV genotype and host factors such as age, gender and risk group upon antibody levels in a consecutive series of 117 anti-HCV positive volunteer blood donors. The results are discussed in a paper entitled “Influence of Viraemia and Genotype upon Serological Reactivity in Screening Assays for Antibody to Hepatitis C Virus” Dhaliwal S.K. *et al.*, Journal of Medical Virology (1996) 48,184-190. Our results showed lower serological reactivity to the type 1a (Ortho EIA 3.0) or 1b (Murex VK48) antigens used in the immunoassay kits with samples from donors infected with non-type 1 genotypes. In particular we observed the following “*By multivariate analysis no evidence was found for any significant effect of age, risk*

group or gender upon antibody reactivity, while the genotype differences were shown to be independent of the differences in antibody level between PCR-positive and negative samples (see above). The magnitude of the difference in levels provides an estimate of the relative amounts of genotype-specific and cross reactive antibody to the core, NS-3, NS-4 and NS-5 antigens. For **example the 4-4.5 fold difference between type 1 with types 2 and 3 infected donors could be interpreted as indicating that a major proportion of antigenic determinants in the EIA's are genotype-specific. This conclusion is consistent with the finding of type-specific epitopes in core, NS-4 and NS-5 regions** (Machida et al., 1992; Simmonds et al., 1993, Tanaka et al., 1994; Bhattacharjee et al., 1995; Zhang et al., 1995)" (Emphasis added).

- 6.10 **This research provides grounds for concern that antigenic variability of HCV impairs the performance of current assays. It also shows that antigenic variability is a problem, dictated by genotype and phenotype (i.e. nucleotide and amino acid) differences amongst HCV's.**
- 6.11 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.**

Dr. Nicholas Crofts then of the Macfarlane Burnet Centre for Medical Research in Melbourne explained,

21. During discussions I had with Dr John Barbara, Head of the North London Blood Transfusion Service, Dr Phillip Mortimer, Director of Virology at the Central Public Health Laboratories and Professor Richard Tedder I was told that in **the UK, the Health Department made a decision, that was a carefully discussed and calculated decision, not to use the first generation HCV assays when they were first released by Ortho in 1990. The UK blood banks did not start screening for HCV until the second generation assays were introduced, some eighteen months later. This meant that during that period there were a number of people that were potentially infected with HCV as a result of receiving blood transfusions.** The justification for this decision was based on the concern of the UK blood banks that too many blood donors would be lost from the already over stretched blood supply. **They recognised that the first generation tests would produce too many false positives and that would place enormous pressures on the UK blood supply to keep up with demand for blood.** There was also concern about the potential misunderstanding that could occur in explaining to HCV positive blood donors that they may not in fact be truly HCV positive. The social consequences of positive results that could not be confirmed also influenced their decision.
22. The reality is that most blood banks around the world have less blood on hand than is actually needed at any point in time. Blood banks cultivate donors who regularly donate blood for many years. These donors are a very valuable resource. The UK blood banks realised in 1990 that once a positive HCV assay result was obtained (irrespective of the fact that the first generation HCV assay lacked specificity), those donors would be lost forever as it was not be possible to determine which donors were truly false positives.

23. The statistical reality is demonstrated by this example. If I take a high risk person such as a drug user and test for HCV with an assay that is 99% specific and a positive result is obtained then I would believe that positive result. If I apply that same assay to a low risk person such as a blood donor and the result is positive the chance that the result is a true positive is in the order of 1 in 10 to 1 in 100.
24. The Australian blood banks, however, did not hesitate in 1990 to introduce HCV screening because of the potential for litigation. Most Australian blood banks at that time were being sued with respect to HIV transmissions in the 1980's.
25. Nevertheless, the Australian blood banks cannot afford to lose regular blood donors unnecessarily. The Melbourne Blood Bank has blood reserves of one day. It obviously very important to remove real HCV positive donors from the blood supply but the cost of achieving this is that for every real positive blood donor that is removed at least nine blood donors are removed that are not HCV positive.
26. The numbers are small but because the margins in blood bank reserves are also small it is imperative that these numbers be further reduced. The only feasible way that this can be achieved is through the implementation of the standard adopted for HIV testing with respect to HCV. One of the significant deficiencies in HCV testing in Australia at the moment is that all of the anti-HCV assays except for assays manufactured by and supplied by Murex use exactly the same genotype (1a) proteins. **I have been informed by my colleagues that these assays are manufactured or supplied by Chiron licencees. Murex uses proteins from strain 1b. However, we also need in Australia, HCV assays that use proteins from other strains such as genotypes 2, 3 and 6 because we have a very diverse ethnic population base. HCV 1 and 3 are the most prevalent. HCV 6 is mostly in the Asian community. No firm conclusions can yet be reached but there is no doubt in my mind that much more research is needed to be done about the genetic diversity of HCV and how this impacts on the specificity and sensitivity of current HCV testing. There are still many unknowns about HCV; much more than with HIV.**
27. Despite recent reports that attempt to show that HCV assays in Australia are 100% specific and sensitive, in my opinion it is impossible to achieve this result. The HIV assays are the most specific and sensitive assays in the world today. There is no doubt that the HCV assay manufacturers should work to achieve the same levels, but the answer to the problems that I have already discussed are in the standards that have adopted for positive HIV results from low risk populations that is, it is necessary to have a confirmatory assay or assays.
28. Sensitivity is not solely characteristic of the assay because the same assay will work differently with different sera because of cross reactivity with contaminants in the sera. Accordingly it would be undesirable to use only one type of assay.
29. Then there is the effect of different antibody window periods. Between the time a person is infected and the time that detectable antibodies are produced to infection there is a window when these types of assays cannot be used to detect infection.
30. The only way to overcome the problems of detection during window periods is to use an antigen test i.e., a test that detects antigen and not antibodies to the antigen. Ideally this is what we should be testing for with HCV. However, to produce an antigen test assay manufacturers must be able to grow the virus in commercial quantities *in vitro*. This is not yet possible with HCV.
31. It is important to note that even with HIV assays that have achieved a sensitivity of 99%, a positive blood screening result is not the only test that is conducted on positive blood samples. Once the blood bank has a positive HIV result from a donor, that sample is subjected to further tests to confirm the initial blood screening test

result, such as a Western Blot HIV test. The same needs to apply with respect to HCV.

32. In Australia today there are at least 100,000 people infected with HCV. Those infected people can live for another twenty or thirty years and not all of them will die of liver failure, but the same sort of numbers will die from HCV as will die from HIV infection. The period of illness with HCV is much longer and some people will need very expensive medical treatment, such as a liver transplant to keep them alive. The impact on the community in terms of social and economic cost is, in my opinion, at least equal to HIV and yet we know much less about HCV than what was known about HIV for the corresponding period. There are many reasons for this including the level of government intervention and the political priority given to HIV as compared to HCV, but in my opinion, there has been a significantly lower level of cooperation with HCV assay manufacturers than there was with HIV in all respects. The consequences of this are now being understood. While with HIV the increase in infections has fallen with HCV it is still rising. At the present moment in Australia that is rising at a level of 8,000 to 10,000 people per year. When you extrapolate this into social and economic cost terms, the cost is very significant.
33. In my opinion it is against the best interests of the Australian community that only one type of anti-HCV assay be permitted to be manufactured and supplied using the same antigen produced in the same way. We need many different HCV tests made in different ways for the reason that I have given.
39. Dealing with the HCV epidemic requires the coordination of many fields in disease control at both a political and medical level. It also requires that we learn from our experience with HIV. **In my opinion, the HCV diagnostic process will be considerably harmed if the only anti-HCV assays available to Australian laboratories are those which use the same antigens. It is absolutely essential that confirmatory assays be available to Australian laboratories.**

In a US House of Representatives Committee Report entitled *Hepatitis C: Silent Epidemic, Mute Public Health Response* dated October 15, 1998 at page 11 the Committee reported,

“The sensitivity of the first generation test was 84-89 percent, while the sensitivity of the second generation test was 93-95 percent. The specificity of the first generation test was 22 percent, while the specificity of the second generation test was 30%.”

This evidence demonstrates that despite the grant of a patent to Chiron and the introduction of Chiron licensed HCV immunoassays in 1990 there were serious concerns about the performance of these assays in accurately identifying HCV infected blood donors.

One problem with the 624,105 patent is that any use of HCV polypeptides in any diagnostic assay or therapeutic treatment comes within the scope of the patents monopoly. Despite there being a clear health need for HCV diagnostics that were different in manufacture and composition to the HCV immunoassays sold in Australia under license from Chiron, that need was not met.

In his evidence, Professor Baruch S. Blumberg who was awarded the Nobel Prize for Physiology or Medicine in recognition his research concerning mechanisms involved in the origin and spread of infectious diseases and, specifically, for the discovery of the hepatitis B virus and for the development of methods for detection of HBV and the vaccine for HBV. He testified,

“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.”

Question 5: Are there any overwhelming arguments for consideration of *pre-grant* conditions for patents as a complement or alternative to an experimental use exemption under Australian law?

Yes. The answer to question 4 is an example of the need for pre-grant conditions. Given the restrictions which arts. 28, 30 and 31 TRIPS impose on WTO members on their ability to permit the use of an invention beyond the exclusive rights of a patentee, there is an overwhelming need for pre-grant conditions to be applied to patent applications that concern inventions which may have adverse consequences on human or animal health or the diagnosis or treatment of the causes of human and animal illnesses, disorders or diseases.

Art. 27.2 TRIPS permits WTO members, at their option, to exclude from patentability “*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*”. Although this exclusion to patentability exists, its effectiveness is questionable. Many WTO members do not have any specific exclusions to patentability in their patent laws and even those that do, such as the UK, the exclusion is rarely applied.

Australia has only two specific exclusion, i.e., s.18(2) and (3). Otherwise, the only other exclusion is implied in the language of s.6 of the Statute of Monopolies. The effectiveness of this implied exclusion is questionable given the Full Federal Court decision in *Bristol-Myers Squibb Co. v F. H. Faulding & Co. Ltd.*¹. Finkelstein J. explained,

¹ *Bristol-Myers Squibb Co. v F H Faulding & Co. Ltd.* (2000) 170 ALR 439.

“The debate concerning the ethics of medical patents continues. One aspect of this debate remains substantially unresolved so far as the courts are concerned: whether it is possible to obtain a patent for medical treatment or a surgical procedure. *The answer to this question cannot depend upon the resolution of moral or ethical issues.* Judges should not be called upon to resolve moral questions and, speaking generally, legal principles are not to be ascertained by reference to standards of ethics or morality..”²

It seems that an available option flowing from art. 27.2 TRIPS is to impose conditions on the grant of patents in order to protect *ordre public or morality, including to protect human, animal or plant life or health or to avoid serious prejudice to the environment* and for the reason given by Finkelstein J, it maybe appropriate for such conditions to be imposed prior to grant by an administrative agency.

In this regard IP Australia would be an obvious candidate, however, it maybe appropriate to establish a separate agency that is independent of IP Australia to make an assessment of the subject patent application so as to determine the appropriate conditions of grant. Such an agency could be made up of both legal and technical experts that can inquire into the patent application and its impact without the constraints of the rules of evidence that apply in judicial proceedings. Moreover, the creation of an independent body to IP Australia will create a check to the power of IP Australia and will install some balance between these two organisations. This check and balance is important so as to avoid the possibility of an abuse of power.

Question 6: Does fair dealing (or fair use) in copyright law hold any lessons for "experimental use" in Australian patent law? For example, could any of the provisions for fair dealing/use be translated into an experimental use provision in patent law? Or do differences in the nature and application of copyright and patent rights limit the analogies between the two systems?

The exemption of specific uses as infringements of copyright under the general heading of 'fair dealing' are attractive to some who are searching for a solution to the restrictions on research created by the exclusive right to 'use' a patented invention. The problem with this solution is that it is incompatible with patent law. The reason for the incompatibility stems from the detail that separates the work of an inventor from the work of an author or artist and the end result of that work.

When a detailed comparison of their work is undertaken it becomes clear that 'fair dealing' is not a solution, rather, it so fundamentally impacts upon the exclusive rights of a patentee that such an exemption would violate art. 30 TRIPS which permits exceptions only if "*such exceptions do not unreasonably conflict with a normal exploitation of the patent and do not unreasonably prejudice the legitimate interests of the patent owner*". This is the case despite art. 13 TRIPS which provides that copyright exceptions are confined to "*certain special cases which do not conflict with a normal exploitation of the work and do not unreasonably prejudice the legitimate interests of the right holder.*"

The solution implied in question 6 is only appropriate if the 'legitimate interests of the patent holder' are identical with the 'legitimate interests of the right holder' and unfortunately this is not the case.

True it is that both patent owners and right holders possess certain exclusive rights to exploit their invention or creation, but that is where the similarities begin and end. Beyond this superficial connection, their legitimate interests diverge and this divergence stems from a

2 Ibid, 472 para 100

number of factors that include the very nature of the work that leads to an invention on the one hand and a copyrightable work on the other. The divergence stems from the following:

First, the terms of exclusivity are very different, as a comparison between art. 12 and art. 33 TRIPS shows.

Secondly, the nature of the exclusive rights are very different, as a comparison between arts. 9-11 and art. 28 TRIPS shows.

Thirdly, copyright is created by an author or an artist through the original *expression* of their ideas and talents in a specific medium, whereas a patentable invention is created through the *creation* of a new and useful thing that is novel, inventive and industrially applicable. While it is true that both the process of expression and creation have the 'idea' as their genesis, what results in a patentable invention compared to a copyrightable work is the end result. The end result differs because a copyrightable work is the medium which captures the original expression of an idea, whereas a patentable invention is a new and useful creation.

The totality of this divergence makes an analogy between copyright and patents meaningless.

Question 7: Do basic, applied or hybrid research have different needs with respect to the patent system? If so, how can the patent system accommodate these differences?

Research and experimentation have taken place for hundreds of years along side the patent systems that have evolved into what is today summarised in TRIPS. The pharmaceutical industry is a perfect example. The problem that the modern patent system has created with respect to research is not due to the sudden realisation that there is a difference between basic, applied or hybrid research, rather it is due to the grant of exclusive rights with respect to things that are not or should not be inventions. The desire by the biotechnology industry to seek intellectual property protection for DNA sequences is a perfect example. Art. 5.2 of the European Biotechnology Directive³ of 1998 states,

An element isolated from the human body or otherwise produced by means of a technical process, including the sequence or partial sequence of a gene, may constitute a patentable invention, *even if the structure of that element is identical to that of a natural element.*

The Directive is a direct result of a decade of lobbying by the biotechnology industry in Europe. The effect of this Directive has been to lower the patentability threshold to include within patentable subject matter the materials of basic research. This is the real problem. Once a patentee has ownership of the basic material upon which any research or experimentation is to be conducted and that may lead to an improved or alternative application of that material, a research bottleneck is created.

A patent over an isolated human gene or an isolated viral genome that is causative of human illness means that anyone that wishes to use that gene or genome or any part of it to make an improvement to a specific application, such as a better diagnostic test or the development of a vaccine, must have the permission of the patent owner. The owner has the absolute and unfettered right to object

The grant of patents over genes or genomes is simply inappropriate within the patent system, but in the absence of any practical alternative, the biotechnology industry has sought to exploit the patent system. The end result is a debate over whether experimental use exemptions can overcome the resulting research bottleneck, but the real solution is in the

3 Directive 98/44/EC of the European Parliament and of the Council of 6 July 1998 on the *Legal Protection of Biotechnological Inventions*. Official Journal L 213, 30/07/1998 P. 0013 – 0021.

creation of a new *sui generis* intellectual property right that specifically deals with the identification and industrial application of genetic information and materials.

Prior to the *Directive* being passed by the European Parliament commentators in the field of intellectual property in Europe were advocating an alternative to the *Directive*. Professor Margaret Llewelyn from the University of Sheffield wrote, “[i]f the existing European patent system is providing an obstacle to the working of the E.U., and the decision to introduce the Patent Directive would appear to signal that this is the case, then the implementation of a more appropriate system of protection should be paramount.”⁴

More recently, in response to the continuing debate in the United States about the patenting of DNA, Professor Rebecca Eisenberg from the University of Michigan argued that the patent system was created for ‘a bricks and mortar world’ that has inherent and logical limitations to the seemingly unlimited expansion of patentable subject matter. She suggested that “[a]t some point, we may need intellectual property rights that permit the creators of information products to capture the value of the information itself in order to motivate socially valuable investments. But if we have arrived at that point, then we need to look beyond the patent system for a suitable model.”⁵

My suggestion is for the creation of a genetic sequence right or GSR. A GSR is a non-exclusive right to the gene or genome first identified by the discoverer to have a specific function or that is shown to be the cause human illness or disease. The GSR once registered is freely available subject to the registration of any proposed use by an individual or entity with the central registry and to the payment of a set and scaled royalty by the user to the GSR holder. The set and scaled royalty varies depending on the type of use. Experimental use can be rated at the lowest end of the scale and commercial application at the highest end. Moreover, a GSR does not give the GSR holder any right to a patentable invention that is created through the use of the genetic sequence. For example, the development of a vaccine that prevents infection of hepatitis C can be the subject of a patent and the GSR holder has no rights to that invention. The GSR holder will simply receive a set royalty based upon the use. Of course, it follows that with the creation of a GSR, isolated genes and genomes would be specifically excluded as patentable subject matter.

Question 8: Is there any evidence for a "patent thicket" or "tragedy of the anti-commons" problem in research and development? If so, what are the issues/effects?

Yes, see answer to questions 4 and 7.

Question 9: Does biotechnology, and genetic technology in particular, have special issues that warrant special treatment under patent law with respect to experimental use?

Yes, see answer to questions 4 and 7 above.

Question 10. What is the justification for an experimental use exemption?

4 Margaret Llewelyn, *The Protection Of Biotechnological Inventions: An Alternative Approach* 1997 19(3) EIPR 115 at 127.

5 Rebecca S. Eisenberg, *Re-Examining The Role Of Patents In Appropriating The Value Of DNA Sequences* 49 Emory L.J. 783.

To remove research bottlenecks created by patent owners exclusive right over the 'use' of an invention.

Question 11: Is a criterion based upon whether the experimentation is *on the invention itself* as opposed to experimenting *with* an invention for *its intended purpose (use)* a useful criterion for determining "experimental use" in Australian patent law?

No it is not. The ability of the patent owner to control the exploitation of an invention stems from the scope of the monopoly defined by the claims. The ultimate use of the invention as described in a patent specification is irrelevant if the scope of the monopoly is directed to a material or to information that can have a multitude of uses or applications. For example, AU patent 624,105 (HCV patent) granted to Chiron Corporation in 1992 provides a monopoly over any use of any HCV protein that is constituted by 10 or more amino acids. Even though there is no specific claim to a vaccine for this disease, the use of any HCV protein in a vaccine would infringe the patent. The patent makes it clear that HCV proteins can have a multitude of uses including in the development of a vaccine.

In these circumstances the proposed distinction is useless.

There are many AU patents that are similar in scope to 624,105. Other examples include the patent over the isolated BRCA 1 and 2 human genes for breast and ovarian cancer granted to Myriad Genetics, Inc. and the patent over the isolated human gene for Erythropoietin granted to Kirin-Amgen, Inc.

Question 12 : If so, is it sufficient by itself?

Question 13. Should an experimental use exemption cover only the situation where experimentation is the *sole* purpose of the use of the invention?

The problem will always be with the what activity constitutes the *sole* purpose and what happens if the experimentation steps over the line. Such a limitation renders the exemption virtually useless.

Question 14: If not, what are alternatives or supplementary criteria for an experimental use exemption?

The solution is not to grant patents over the basic materials on which research is to be conducted. The events which have given cause to this Inquiry is not the result of problems with pharmaceuticals. For decades new medicines and treatments have been developed without any serious research bottlenecks being created with respect to pharmaceuticals. As explained in the answer to question 7, the problems stem from biotechnology and the grant of patents over isolated genes and genomes (see art 5.2 European Biotechnology Directive).

Question 15: Are improved licensing practices by research organisations a whole or partial alternative to an experimental use exemption in Australia?

The research bottleneck will not be solved by improving the licensing practices of research organisations, given that it is the patent owners that control the use of an invention. An alternative is to improve the licensing practices of the patent owners. A more extensive use of compulsory licensing may be one solution, but given the history of compulsory licensing in Australia, it is unlikely that this is a practical alternative.

Question 16: If so, how could licensing practices be improved to provide better outcomes for researchers?

No answer.

Question 17: In what fields are patent pools a realistic whole or partial alternative to an experimental use exemption in Australia?

No answer.

Question 18: Are the potential benefits of patent pools likely to outweigh their potential disadvantages?

No answer.

Question 19: Is compulsory licensing a realistic whole or partial alternative to an experimental use exemption in Australia?

Not under the present patent legislation.

Question 20: For this to happen, do Australia's compulsory licensing provisions need to be changed? If so, how?

Yes. My suggestion is that the ACCC be given the specific function and power under amending legislation to the Trade Practices Act to seek compulsory licensing of any technology that is the subject of a patent that can be shown to be useful to the diagnosis or treatment of human illness or disease irrespective of whether the patentee is working the technology in Australia or elsewhere.

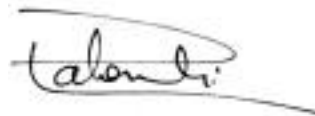
Question 21: Are open source principles a realistic whole or partial alternative to an experimental use exemption in Australia?

It is a partial alternative, however, it does not deal with compensating the organisation that makes the 'breakthrough'. The GSR right discussed briefly in answer to question 7 is a better alternative because it provides access for any research but gives a fair level of compensation to the GSR holder.

Question 22: Are the potential benefits of open source likely to outweigh their potential disadvantages?

No answer.

Submitted to ACIP on April 29, 2004.

A handwritten signature in black ink, appearing to read 'Palombi', with a long horizontal stroke extending to the right.

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