Indian patent decision highlights the bond between politics and patent law

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In a major ruling the Indian Supreme Court has rejected Novartis' appeal to gain patent protection for a novel beta crystalline form of its anti-cancer drug Glivec. The decision shines a fascinating light on the current principles of Indian patent law and their origins. It also illustrates the difficulties faced when trying to balance incentives for research with access to the commercial products of that research.

We examine the background of the case and grapple with the issues pitting patent versus patient in India and the developing world.

Development of the drug

Imatinib is the active ingredient in the anti-cancer drug Glivec. It consists of a derivative of N-phenyl-2-pyrimidineamine and was found to inhibit certain protein kinases, especially one called BCR-ABL. Research had shown that the presence of this protein kinase in the body caused chronic myeloid leukaemia (CML) as a result of continuous stimulation of cell-growth pathways and transformation of normal cells into ones that proliferate without restraint.

After an extensive screening programme, the inventors found that that imatinib killed cultured cells that required BCR-ABL activity to survive, but did not affect a cell line that depended on a different protein kinase, v-SRC. This was the holy grail: a compound that selectively blocked the disease causing protein kinase, but had no effect on other protein kinases thus avoiding wide ranging toxic side-effects.

As well as its use in treating CML through the inhibition of BCR-ABL, later research found that imatinib inhibited two further protein kinases which cause other diseases. Following further human trials, the drug was found to be effective in treating patients with gastrointestinal stromal tumor (GIST) and hypereosinophilic syndrome (HES). In a 2009 estimate, 120000 CML patients and 28000 GIST patients were being treated with Glivec worldwide.[1] The researchers who developed imatinib were awarded the Lasker Clinical Medical Research Award in 2009 and the Japan Prize in 2012 for their work.

The imatinib patent

In 1994, patent applications were filed in over 30 countries worldwide (including New Zealand) but no application was filed in India. At the time, India only afforded patent protection to new chemical processes rather than new products. The patent specifications discussed the therapeutic benefits of the compound and contained claims covering a number of compounds that were believed to be effective inhibitors of BCR-ABL. One claim specifically covered the compound imatinib in free base form, i.e., the pure basic form of the amine, as opposed to its salt form, plus *pharmaceutically acceptable salts* of imatinib. Of 37 examples given in the patent specification, one related to the compound imatinib, but none specifically described how to prepare the mesylate salt of imatinib (which eventually became the major component of Glivec).

It may seem excessive to claim a large number of compounds when only one, i.e., imatinib, is eventually used. However, it should be considered that a patent application has to be filed before any human trials (and likely any animal trials) have been carried out to avoid compromising the novelty of the invention. There is a high rate of attrition for even the most promising lead compounds from the lab owing to the pharmacological and physicochemical constraints on new drugs.

Of all the salts of imatinib tested, imatinib mesylate (marketed under the name Glivec or Gleevec) was found to have appropriate properties for human administration and showed considerable promise in drug trials. In one study of the drug in more than 1000 chronic-phase patients it so outperformed the control interferon-based therapy that the researchers closed the trial and switched almost everyone to Glivec. Five years after diagnosis, overall survival of patients treated with Glivec was 89 percent compared with 60% for interferon-treated patients.[1] The patent on imatinib is due to expire in the USA on 4 January 2015 and expired in New Zealand on 31 March 2013.

The *beta* patent

In 1998, Novartis filed a further patent application to cover a new form of imatinib mesylate – the beta crystalline form of the compound. This form was found to have the following enhanced properties over the non-crystalline form:

i. more beneficial flow properties,
ii. better thermodynamic stability, and
iii. lower hygroscopicity.

According to the beta patent specification, these properties provided advantages for *processing and storing* the drug, i.e., more efficient production techniques and longer shelf life, when compared to the non-crystalline form. The beta patent has been granted in about 40 countries with the New Zealand patent due to expire in July 2018.

The Indian Supreme Court decision

In a refreshing departure from the typically staid, formulaic legal decisions, the Supreme Court's decision is not limited to consideration of solely legal matters. Reference is made to the moral and political background of the current law and the Court unashamedly refers in the introduction to a consideration of the need to strike a balance between promoting scientific research and development, and keeping private monopoly to a minimum.

The decision revolved around a challenge of the *beta* patent

application by both generic pharma firm Natco Pharma and the charity Cancer Patients Aid Association. The application was rejected by the Supreme Court on the basis that it was unpatentable under section 3(d) of a 2005 amendment of the Indian Patents Act. Section 3(d) reads:

> *The mere discovery of a new form of a known substance which does not result in the enhancement of the known efficacy of that substance… [is not an invention within the meaning of the Act]*

A further explanation of this section states:

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

The main question considered by the Court was therefore whether the advantageous properties of the beta crystalline form of imatinib mesylate were considered an *enhancement of the known efficacy* when compared to the *known substance*.

Novartis argued that the *known substance* was imatinib in free base form because this was what was specifically disclosed in the imatinib patent. However, the Court ruled that the salt imatinib mesylate was the *known substance*. This was on the basis of it being specifically mentioned in a January 1996 *Cancer Research* article[2] and assertions in an April 1998 Investigational New Drug Application[3] stating that the imatinib patent covered imatinib mesylate.

Internationally recognised definitions of *efficacy*[4,5] were considered by the Court and it was determined that efficacy meant therapeutic efficacy. Such efficacy was adjudged to be *known* from the extensive drug trials carried out. Therefore it fell to Novartis to establish that the *therapeutic efficacy* of the beta crystalline form of imatinib mesylate was enhanced when compared to the non-crystalline form.

While it was accepted by the Court that the enhanced properties of the *beta* form (better flow properties, better thermodynamic stability and lower hygroscopicity) may be beneficial for processing and storing the substance, these physical properties did not qualify as properties that indicated enhanced *therapeutic efficacy*.

Origins of the Indian position

Indian patent law clearly sets out (in section 3(d)) the position that new forms of known substances are unpatentable and this decision merely reinforces that position. Therefore the result of the case should be no surprise and similar decisions are to be expected in the future.

The text of the decision[6] itself provides a fascinating insight into the history and evolution of patent law in India. The latest step in this evolution occurred in 2005. Before this, India only allowed patents on new manufacturing processes; new chemical compounds were unpatentable. This led to the development of a strong generics sector which focused on circumventing Indian process patents filed from overseas to produce compounds with demonstrated therapeutic efficacy for supply to the Indian and developing world markets.

In 2005, to comply with obligations under the WTO TRIPS Agreement, India changed its patent law to allow patents to be granted for new chemical compounds. Members of the Indian Parliament expressed their concerns at the time the new law was being considered that it would unreasonably limit availability of medicines to the Indian population or to other developing countries owing to their inability to pay for patented medicines. To address these concerns, the 2005 law excluded from patentability new forms of known substances which do not result in the enhancement of the known efficacy of that substance.

The Indian position on patentability of new forms of known substances is at odds with every other major patent system which allows patents to be granted for non-obvious advancements in the form of known compounds. The policy rationale of most jurisdictions to allow such patents is that they encourage further development of known compounds to produce better methods of production and administration as well as safer and more convenient drugs.

The irony of the Indian position is that if it were widely adopted, research into novel forms would likely be curtailed owing to lack of commercial incentives, and the development of better drug forms would be limited. Even if such development were to be carried out, with no possibility of an exclusive market position, any advances would probably be kept as trade secrets rather than being disclosed as the patent process requires. Without the dissemination of knowledge, further innovation would likely be retarded and the knowledge concentrated in the hands of a few big players.

The role of the generics producers

India has made a name for itself as a large scale manufacturer of pharmaceuticals for export to other countries, both developing and developed. The generics industry has been assisted by the laws applied by the Indian Patent Office and Courts which are generally more favourable to the industry than in other major markets. One factor whom drives the government to support the industry is no doubt a desire to deliver affordable healthcare to India's 1.24 billion people, a third of which fall below the international poverty threshold of US$1.25 per day.[7] In 2006 a generic version of Glivec was available in India for $200 per month compared to a reported $2600[8] in some countries where Glivec was covered by a patent. This disparity has led to an understandable desire to limit patent monopolies on pharmaceuticals.

Exports of Indian generic drugs are relied on by countless developing countries. The international humanitarian organisation Médicins Sans Frontières (MSF) even heralded the Supreme Court decision as a 'major victory' for patient access to affordable medicines. However, generics from India are not only important to developing countries; they are also a major source of cut-price, high-grade pharmaceuticals for developed countries to access once a patent on the original drug has expired.

However, in the case of Glivec, freedom to manufacture a generic version of Glivec was never at stake as no patent was ever granted for the non-crystalline form in India. Even if the *beta* patent had been granted, this would only provide a monopoly for the beta crystalline form of the compound. A drug containing the free base form of imatinib or the non-crystalline form of imatinib mesylate would not infringe as long as there was no use of the beta form.

So why did the parties challenging the *beta* patent go to so much trouble and expense if there was never an issue of being able to make a therapeutically effective form of the drug? This question becomes even more pertinent when one considers that the non-crystalline form exhibits identical therapeutic efficacy so there would be no advantage in terms of improved patient outcome.

One reason may have been to simply uphold the principle that new forms of a known compound are unpatentable. While this would be laudable, a more likely reason is the potential commercial benefits to be had for the generics industry if they can exploit the best process to produce the drug with best storage characteristics. The lower labour costs in India and the minimal research and development costs would provide the generics producer with a competitive edge over the patent holder that would likely secure the entire Indian market for generic Glivec as well as servicing other countries where no patent exists. It would also place them in prime position to compete once the beta form of the drug went off-patent in developed countries. As such, there were clearly commercial reasons for the generics producers to mount a challenge to the grant of the patent.

A two-tier patent system

The decision examines the general principles that govern the global patent system and appears to arrive at the conclusion that what is best for the developed world is not necessarily best for the health and economy of India (and, by extension, the developing world). Essentially it affirms India's right to enact and apply patent laws in its national interest, as long as they comply with obligations under international trade agreements.

Effective enforcement of IP rights in the developed world is generally accepted to successfully result in promotion and dissemination of technology. However, this model breaks down when applied to countries with small or non-existent innovation ecosystems which also lack the funds to pay for patented products.

So should patent systems be allowed to vary depending on the industrial maturity of the country? If a country is less developed, poorer and has less capability to innovate, should higher thresholds of patentability should apply? While answers to these questions depend on your perspective, what is clear is that seeking to impose developed world IP laws on the developing world is unlikely to assist innovation or patients. These countries and the majority of their citizens simply cannot afford to pay developed world prices for patented medicines. In addition, pharma companies are often loath to cut prices for the legitimate concern that these products could find their way back to developed world markets as parallel imports.

While it may seem unfair that there could be a two-tier global IP system in which some countries enforce while others ignore IP rights, the economic reality is that without this enforcement, new drugs would not be developed, and if enforcement was ubiquitous, life-saving medicines would be inaccessible to millions more people in developing countries. The trick therefore is balancing the scales to encourage both development and access.

A two-tier system already exists to some degree but is manifested more by some countries lacking effective enforcement prospects or suitable disincentives for infringement. Effective enforcement of existing rights is certainly an issue in India and China and adds to the difficulties which multi-nationals have in doing business in these countries.

Global reactions

The US industry trade group Pharmaceutical Research and Manufacturers of America (PhRMA) said the decision reflected a deteriorating environment for innovation in India, "Protecting intellectual property is fundamental to the discovery of new medicines. To solve the real health challenges of India's patients, it is critically important that India promote a policy environment that supports continued research and development of new medicines". Novartis called the decision "a setback for patients that will hinder medical progress for diseases without effective treatment options [and] discourage future innovation in India".

So will this decision be a turning point for investment by the traditional pharma firms in India? Unlikely. Despite assertions that the decision will discourage innovation and investment, it would be a brave CEO to pass up the opportunity to gain a monopoly on their product in India; in doing so they would effectively cede control of manufacturing and distribution of the drug for a large part of the global market.

However, potential ramifications of the decision for India may materialise through other channels. The US Information Technology and Innovation Foundation (ITIF) – a US think tank – referred to the decision when lobbying the US Congress to increase trade tariffs on Indian imports. The ITIF said a response was needed to India "enacting regulations that harm American industry and jobs".

Patent versus patient

This decision by the Indian Supreme Court clearly reinforces the fact that Indian patent law has a threshold for patentability of chemistry-related inventions higher than most developed nations. However, the decision's significance should not be overstated; it only relates to the patentability of new forms of known compounds and does not prevent the protection of new chemical compounds (or even more highly efficacious forms of known compounds). It at least provides clarity on what is allowable in India.

Weighing intellectual property rights against access to medicines is a difficult balancing act with legitimate concerns by parties on both sides of the debate. However, tipping the scales too far in favour of one or the other will lead to either innovation or patients suffering.

If you have any queries regarding intellectual property related matters (including patents, trademarks, copyright or licensing), please contact: *tim.stirrup@baldwins.com* or Patent Proze, Baldwins Intellectual Property, PO Box 5999, Wellesley Street, Auckland.

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3. IND# 55666
4. IUPAC describes efficacy as "the property that enables drugs to produce responses". When comparing the efficacy of two substances, efficacy describes "the relative intensity with which agonists vary in the response they produce even when they occupy the same number of receptors" - IUPAC Glossary of Terms used in Medicinal Chemistry, 1998 in CPAA Vol. 9, p. 7.
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