Learning from *Novartis*: India in the quid pro quo world

The *Novartis* case shone a spotlight on India's unique patent system. **Deepa Kachroo Tiku** and **Taapsi Johri Singh** explore the questions and uncertainties raised by the controversial decision

The Supreme Court of India's recent decision concerning Novartis' anti-cancer drug Glivec is certainly the most crucial decision of 2013, with far-reaching implications on pharmaceutical businesses both in India and internationally. Much has already been said on this judgment, with polarised opinions split between the supporters of generic manufacturers and those of innovators. Despite all the commentary, there are still numerous unanswered questions as to the state of India's patent laws, and what patentees can do in this uncertain world.

One-minute read

The rejection of Novartis's patent for Glivec raises numerous questions about patentability in India. Major issues include whether incremental innovations will be protected and if so which kinds, how to deal with the tension between patent coverage and disclosure and how to demonstrate enhanced efficacy. The increased patent standards in India will also be a challenge for PCT filers, who will have to prepare additional data for Indian patents. Patent filers will likely respond by providing more in-vivo data during prosecution, which may prove to be expensive.

The *Novartis* case

The case concerned the patentability of Glivec (known as Gleevic in some countries). The main constituent of the drug is the β-crystalline form of imatinib mesylate. Imatinib itself is a derivative of N-phenyl-2- pyrimidineamine and was originally developed in the United States in the late 1990s. It is the subject matter of US patent 5,521,184, filed for N-phenyl-2-pyrimidine-amine derivatives and was believed to have valuable anti-tumour properties.

Further research led scientists to imatinib mesylate, specifically the β-crystalline polymorph, found to possess certain properties which made it more stable and suitable to be administered as an effective drug for treatment of chronic myeloid leukaemia. Novartis applied for patents for this form in various countries, including India. The patent was granted in nearly 40 countries, such as the US, China, Russia and Taiwan. However, the Indian application, filed in 1998, was rejected in 2006. Novartis challenged the rejection before various forums, and the dispute eventually reached the Supreme Court.

In its judgment, the Supreme Court expressly stated that incremental inventions can be protected under Indian law. However, genus-species type *Markush* claims were frowned upon. Moreover, the Court also held that section 3(d) is undoubtedly meant to deal with chemical substances and more particularly with pharmaceutical products. The Court, after winding discussions tracing the history of India's patent law, arrived at a final conclusion, holding that Novartis's drug is not eligible for patent protection.

However, has the Court been able to clarify and straighten out the law in India? Do inventors and innovator companies have clarity of what can and cannot be patented? These are some questions which linger on after the judgment. Public interest and access to medicines have been the impending concerns and the judgement does effectively address these concerns, but for the patentee, it has opened up a new set of challenges and questions which are yet to be resolved. In this discussion, we consider some of these challenges.

Will India protect incremental innovations in pharmaceuticals and chemicals?

On paper, yes. The Supreme Court does mention that section 3(d) is not to be looked at as a bar for all incremental innovation; however, the practical implications of the judgment may not always support this assertion. There is still doubt as to which incremental inventions will actually be protected, and if so, on what parameters.

For example, it is a well-known fact that although the active pharmaceutical ingredient (API) might be the same, various salt forms are in fact distinct chemical entities with their own chemical and biological profiles which may lead to differences in their clinical efficacy and safety. Pharmaceutically suitable salts are a result of extensive research and protected by patents in most jurisdictions of the world, so long as they are inventive. Uncertainty about patentability of such forms in India remains and is likely to be tested in future litigation.

The challenge of showing enhanced therapeutic efficacy

Most present-day inventions in the field of pharmaceuticals and chemicals are incre-

Finding a way forward

Section 3(d) is intended to prevent evergreening of medicines and is unique to Indian law. It is emerging as the most relevant provision for inventions pertaining to pharmaceuticals and chemicals. Therefore, in light of the Supreme Court's recent observations, patentees should be mindful of possible objections under section 3(d) and obviousness in applications covering pharmaceuticals or chemicals in India. The following suggestions may be kept in mind to tackle the section 3(d) obstacle:

- Include as much comparative efficacy data as possible in the specification, to prove unexpected properties and non-obviousness. This could include *in vitro* efficacy data, toxicity studies and safety data, which can be used to show health benefits;
- Provide *in-vivo* pharmacokinetic and pharmacodynamics data, such animal model data, showing higher therapeutic efficacy as compared to previously known treatment. In the absence of such data, the invention may be held as not being able to cross the barrier of section 3(d). Such data should ideally be generated before filing the application, but can even be generated after filing and should be submitted to the Patent Office as soon as it becomes available.
- In cases where the above data is not included in the description at the time of filing, supplement information by way of affidavits by technical experts at the earliest convenience.
- In claims directed at combination of known substances, comparative data showing enhanced efficacy of the combination when compared to individual components as well as the closest prior art should be provided. This might require generating data *de novo*, with the invention *vis-à-vis* the last known prior art to show enhanced efficacy.
- Wherever possible, avoid using the terms such as 'derivatives' in the description or in claims in case the claimed compounds are not mere derivatives of a known substance, as envisaged in the section 3(d) explanation.
- Illustrate embodiments using as many representative examples as possible to support what is being claimed. This is specifically relevant, for example, in cases where *Markush* compounds are claimed. *In vitro* efficacy data such as IC50 data for as many representative compounds should be included to support specific claims.

mental inventions, involving new forms of a known substance. According to the judgment, under section 3(d), the applicant will be required to show enhanced efficacy by comparing the new form with its immediate predecessor and support its assertions with empirical data *vis-à-vis* 'therapeutic' efficacy.

This is a unique requirement in India. An applicant will be required to include empirical and comparative data to show that the subsequent invention has enhanced therapeutic efficacy over the last known substance. This is certainly going to be an arduous task for several reasons. First, data will have to be generated *de novo*, further adding to the innovators cost, which will eventually have an impact on the market price of the drug offered to the consumer. Second, in most cases, data generation is not a straightforward process and in fact, *in vivo* therapeutic data is time intensive, cost entailing and involves sensitive experimentation. Finally, additional costs and the uncertainty of patent protection are likely to deter a company from investing in such further research, thereby impeding innovation.

How will patentees deal with the tension between disclosure and patent coverage?

The Court's conclusions on disclosure and patent coverage are probably the most damaging findings for innovation. This is because most newly invented compounds, such as the first form of imatinib, are not in their most-suitable pharmaceutical form when they are found. It takes years of research and analysis to reach the pharmaceutically acceptable form of the compound. Put another way, if compound X is invented and can have 100 forms, identifying the best form for administration as drug is a task which requires additional research. This further research has to be incentivised by way of patent protection, as was the intention behind the patent system.

Equating disclosure with coverage is also likely to cause confusion, especially when the two concepts are considered in separate domains of validity and infringement. The effect of this finding is yet to be seen, but is likely to cause much distress to patentees. What has also been ignored is that such disclosures in specifications provide the vital next steps for further research for new and better forms of treatment. The original invention may by itself not be in an administrable form and may require further research and investment, in order to provide an effective drug form. The Court's observation is likely to lead inventors not disclosing such possible next-steps and may therefore impede research.

What will be the scope and extent of therapeutic efficacy?

The Court's conclusions on therapeutic efficacy, specifically its excluding physicochemical properties from the same, may have unwelcome consequences. The aim, function or objective of an invention can include ease of administrability, ease of transportation, stability under different environmental conditions and palatability to name just a few. All of these attributes entail research and not incentivising such efforts does not appear justified. Similarly, an incremental innovation, resulting in pharmaceuticals with less toxicity and less side effects than its immediate predecessor would certainly be welcomed as a better drug. While factors such as improved physicochemical properties have been brushed aside by the Court, the question of whether or not reduced toxicity is a factor that could contribute in "enhanced efficacy", has been left open for discussion.

How can applicants deal with PCT filings?

The biggest challenge for patentees now will be to their national phase PCT applications in India synchronise with the latest requirements laid down by the Supreme Court. In general, the PCT International Applications are drafted in line with the universally accepted patent requirements. However, with India's specific requirements, which raise the bar for patentability of new drug forms, an applicant may find itself in troubled waters. Does this mean that data to support enhanced therapeutic efficacy will have to be incorporated in the application at the PCT stage itself? It is an extremely difficult question to deal with considering that even though the Court's requirement is that enhanced therapeutic efficacy has to be 'claimed', it is practically impossible for an inventor to have such empirical data available at the time of filing.

The use of additional technical affidavits containing evi-

Post-*Novartis*, IPAB decides on GSK's breast cancer drug patents

In a recent controversy, two patents for a breast cancer drug registered in the name of Glaxo Group were challenged before the Indian Intellectual Property Appellate Board (IPAB). In its orders, IPAB opined on the issue of Section 3(d), keeping in mind the Supreme Court's directions in *Novartis*.

Fresenius Kabi Oncology filed revocations against two patents registered by Glaxo. One of the two patents covered the basic pharmaceutical compound (lapatinib) and the other was for a salt form of the basic compound (ditosylate salt of lapatinib).

The IPAB's revocations were based on obviousness, insufficiency, non-disclosure and non-patentability under Section 3(d) of the Indian Patents Act. The IPAB heard both parties and passed two orders whereby one patent was upheld (for lapatinib) and the other, pertaining to the salt form, was revoked.

Regarding the basic patent, the IPAB noted that in a revocation petition, the burden to show non-patentability under Section 3(d) is on the applicant, who must plead and prove his assertions. In the present case, as no proof was brought forward and other issues weighed in favour of Glaxo, the basic patent was upheld, much to the relief of the patentee.

On the other hand, IPAB revoked the patent covering the salt form on the ground that even though it was thermodynamically stable and less hygroscopic, these qualities do not result in increased therapeutic efficacy of the salt form when compared to the basic compound. This finding was in line with the Supreme Court's ruling in *Novartis*.

dence of enhanced therapeutic efficacy will be key for patentees. The current practice at the Indian Patent Office is to allow additional data in the form of technical affidavits to support the assertions made by the applicants and to overcome objections on lack of inventive step or section 3(d). This is well justified and fair since the applicant is given a chance to prove that even in the absence of such data available at the time of filing, the claimed invention is in line with the *Novartis* decision and satisfies the raised bar of patentability. On a practical level, we believe that the Indian Patent Office will continue allowing data even after filing of an application, so long as it is presented as part of the evidence deposed by a technical expert.

Will the phrase 'known efficacy' emerge as a problem?

Section 3(d) requires establishment of enhanced efficacy *vis-à-vis* the 'known efficacy' of the known substance. In terms of drug regulatory requirements, efficacy refers to the determination of whether a drug demonstrates any health benefits over a placebo or other intervention when tested in an ideal situation, such as a tightly controlled clinical trial. The Madras High Court has in the past defined efficacy as "the ability of a drug to produce a desired therapeutic effect". However, neither of the two definitions requires any comparative study with the last known or predecessor drug. While placebo studies are usually done for purpose of drug approvals, the requirements set by the Supreme Court takes it up another notch. Now, efficacy under section 3(d) has to be tested *vis-à-vis* the last known substance and not a placebo and the data generated has to be connected or shown to have resulted in some health benefit.

In the *Novartis* case, it was argued that since there was no 'known efficacy' of imatinib or its mesylate form, the efficacy of the β-crystalline form of imatinib mesylate could not have been compared with it. And since imatinib, as per Novartis was the 'known substance', they could only have shown bioavailability studies.

Generic un-enabled disclosures in a patent application may later become subject matter of further patent applications in view of new results emerging from ongoing research. In such cases, does the un-enabled but disclosed compound qualify as the last 'known substance with known efficacy'? It cannot be. In the real world, data generation or experimentation will probably be done only for the product which is most likely to be commercialised. The requirements put forward by the Supreme Court would require *de novo* generation of comparative data which poses a huge challenge for the applicants.

There could also be some instances where the known efficacy of the known substance is not available. For example, in a pending case, the specification provides data with regard to enhanced bioavailability of the claimed new form when compared to the 'known' bioavailability of the last known-predecessor substance. An increase in bioavailability by about 54% has been shown. It is argued that since the known efficacy data is not available, data of 'known bioavailability' versus bioavailability of new form is furnished. However, following the Supreme Court judgment, an increase in bioavailability should then be shown to have resulted in some health benefit, for instance less toxicity etc. Generation of such data at this stage is certainly not a practical option.

A pragmatic view would be to look at comparisons between bioavailability rather than look for comparative therapeutic efficacy. Will the Patent Office bind itself to the narrower Supreme Court view or will it look at the case with fresh perspectives? Since no two cases are identical, a wiser approach by the Patent Office would be to base its analysis on the facts and merits of each case rather than mechanically applying the Supreme Court's findings. More so, since the Supreme Court, while assuring that incremental inventions shall remain patentable, also noted that the ruling is case-specific and the assessment could vary on a case-to-case basis.

A quid pro quo world

Every country has the sovereign right to protect its national interest over others; however, prudence lies in adopting policies, laws and precedents that are conducive to future growth and development and consistent with international obligations. In the ironic quid pro quo world of patents, where innovation is increasingly being questioned at multiple levels, one can only hope that genuine efforts get acknowledged and are given due recognition. Patent incentives have to work in unison with the various government mechanisms for price control and regulation, wherever necessary. The innovators, on the other hand, need to be more sensitive to pricing issues which prejudice the general masses against the patented technology.

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