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EDITORIAL

Science and Law: The Gleevec Case

Laws passed by the Legislature in a democracy are always subject to judicial interpretation. In India, with very few exceptions, laws are framed by the executive, debated, refined, amended and enacted by Parliament and interpreted and enforced by the judiciary. Litigation is a popular pastime in democracies and lawyers abound. Lawyers, by definition, can provide the most compelling arguments to support completely opposing points of view. Courtroom dramas can provide riveting theater, both in real life and on the screen. Spencer Tracy's performance as Clarence Darrow in *Inherit the Wind*, the 1960 movie version of the 1925 Scopes 'monkey' trial, drew public attention to Darwin's ideas on evolution and highlighted the infirmities of the arguments for creationism. A vast majority of people (I am amongst them) view lawyers from a great distance, often bemused by the ability of practitioners of the legal profession to deal easily with contradictions and ambiguities, without the slightest sign of discomfort. It is the ability to be able to speak on all sides of a debate that sets lawyers apart. Unsurprisingly, lawyers swell the ranks of politicians in democracies. Laws can be hard to frame. When confounded by the intricacies of law, ordinary people are sometimes driven to exclaim, as Mr Bumble famously did in *Oliver Twist*: 'The law is an ass'. Eminent lawyers can transform into learned judges, often compelled to use their erudition to weigh both sides of a complex argument in order to deliver a final judgement. The pronouncements of lower courts can always be challenged, with many long running cases eventually reaching the court of last resort – the Supreme Court. In the last few weeks, the highest court in the land has been frequently in the news, delivering final verdicts on appeals against death penalties, imposing punishments in cases that have run for the better part of two decades and in admonishing the Italian ambassador, in a case that undoubtedly illustrates the complexity of situations, in which the writ of national and international laws are debated. In a recent brief, but pointed, commentary an eminent jurist, a former judge of the Supreme Court, V. R. Krishna Iyer noted: 'The Supreme Court is final not because it is infallible but it is infallible because it is final' (*The Hindu*, 13 April 2013). The processes of law, especially when criminal acts are to be judged, always attract the attention of the popular press. Civil cases are considerably less newsworthy. A recent exception, the battle waged by Novartis to obtain a patent for its anti-cancer drug *Gleevec* (*Glivec*) in India, prompted me to draw attention to the law and science in this column. The judgement delivered on 1 April 2013, by a two-judge bench, dismissed Novartis' claims, opening the door to manufacture of generics, which dramatically lower costs of patient care.

The reactions to the Gleevec judgement have been predictable. Patient groups, generic manufacturers and the vast majority of observers concerned about the unaffordability of many drugs, protected by patent regimes, have welcomed the judgement. Novartis has, of course, raised the spectre that the ruling might stifle innovation in India; a view that has been forcefully countered by many knowledgeable commentators. Multinational pharmaceutical companies have long projected astronomical costs for the drug discovery and development process, arguing that patent regimes and monopoly pricing allow companies to recoup the immense costs of the long drawn out research, development and regulatory clearance process. How are blockbuster drugs discovered nowadays, when the pipeline of potential new molecular entities is running dry? In reflecting on this question, the story behind Gleevec is worth revisiting. In 2009, the Lasker Award for Clinical Medical Research went to three researchers: Brian Druker of the Oregon Health and Science University, Nicholas Lydon who did his award winning work at Novartis and Charles Sawyers of the Memorial Sloan-Kettering Cancer Center. In introducing the work of the prize winners Joseph Goldstein, the chair of the Lasker Awards Jury, made this assessment: 'Gleevec has unquestionably transformed the treatment of CML (chronic myeloid leukemia) in much the same way that insulin transformed the treatment of people with Type I diabetes' (*Nature Medicine*, 2009, **15**, iii). In the complex and difficult area of cancer research, successes in developing specifically targeted chemotherapeutics are extremely rare. CML, which is a significant contributor to adult leukemias, is one of the first cancers to have a clear genetic link established. The identification of a gene linked to disease led to the identification of a gene product, a protein tyrosine kinase, whose enzymatic activity contributes critically to the process of cell proliferation. Brian Druker had by 1990 both the background in oncology and the expertise on tyrosine kinases to move towards testing the

idea that specific inhibitors may pave the way to viable therapeutics. Druker, an academic researcher, turned to Lydon at Novartis for potential inhibitors, developing a screen that yielded CGP57148B (or STI571), which was eventually named Gleevec or Imatinib Mesylate. Druker moved from the laboratory to the clinic in a relatively short period, especially as there were CML patients with 'no treatment options remaining' (Druker, B. J., *Nature Medicine*, 2009, **15**, xv). Lydon had by the mid-1980s, working at Ciba-Geigy (later Novartis), reached a conclusion, that many workers in the field endorsed, which pointed to the protein kinases as promising pharmacological targets. The Druker–Lydon partnership opened the doors to 'screening the Ciba-Geigy compound collection', a key step on the road to drug discovery. 'The challenges and excitement of medicinal chemistry', which Lydon refers to in his Lasker Award commentary are not often appreciated in academia in India, but are an integral part of the research that eventually leads to pharmaceuticals. As in most targeted approaches, ensuring selectivity was critical. In Lydon's words: 'On the basis of biochemical profiling data… Juerg Zimmerman made the key observation that substitutions of a methyl group at the 6-position of the anilino phenyl ring abrogate PKC inhibition but enhance ABL and PDGFR inhibition' (Lydon, N., *Nature Medicine*, 2009, **15**, xix). For readers mystified by a multitude of abbreviations, I might add a word of comfort, that Lydon merely refers to the targets that must be hit, while others must be unharmed. Collateral damage can lead to unacceptable toxicity and side effects if drugs attack biochemical pathways indiscriminately. It is the 'Zimmermann patent' which is referred to in the Supreme Court judgement. Gleevec or imatinib's discovery in the mid-1990s was based on the fact that CMLs origins are traced to a gene product – a tyrosine kinase – whose inhibition should yield a satisfactory therapeutic conclusion. A cautionary note is introduced by the third 2009 Lasker Award winner, Charles Sawyers, who describes the growing understanding of drug resistance and emphasizes the shifting view of cancer drug research: 'Although the success of imatinib was not a revolution in the Copernican sense, it spawned a transformation in cancer research that has fueled an urgency to characterize cancer genomes comprehensively and discover the driver mutation in all cancers' (Sawyers, C. L., *Nature Medicine*, 2009, **15**, xxiv). A retrospective view of the 'crusade against cancer', 40 years after its launch, notes that 'even the most successful targeted therapies lose potency with time'; for Gleevec a median time to resistance of 5 years (17% of patients) is a quoted statistic. The pitfalls of predicting the progress of cancer research are highlighted by James Watson's optimistic view in 1998 that antiangiogenesis drugs would 'cure cancer in two years'. Nearly a dozen years later, in 2009, Watson is reported to have suggested a move away from cancer genetics to 'understanding the chemical reactions within cancer cells' – old fashioned cellular metabolism (Kaiser, J., *Science*, 2011, **331**, 1542). Classical biochemists, long swept away by the surging tides of molecular biology and genetics, may appreciate the tinge of irony.

The Supreme Court judgement on the Gleevec case is remarkable in its sweep of chemistry and law. The question before the court was whether a new physical form of Gleevec, 'the beta crystalline form of Imatinib Mesylate' could be granted a patent in India under the TRIPS Agreement and the multiple Patents Amendment Acts enacted in subsequent years by Parliament, to meet India's obligations under international agreements and to 'adequately protect national and public interest'. The Zimmermann Patent granted in the US in May 1996 was for Imatinib Mesylate and Novartis sought protection under a new patent regime in India for its apparently novel 'beta form'. Was this an invention, new and distinct from the original substance or was this an attempt to extend the life of an unenforceable patent by 'evergreening' – a common subterfuge in the unending drive to maintain a monopoly. The Supreme Court judgement contains pages of chemical procedures, and discussions of chemistry which make interesting reading for anyone with a rudimentary knowledge of the subject. New forms of old molecules, polymorphs and formulations disguised in clever ways are often claimed to have greater stability and better bioavailability. 'Incremental innovation' is a powerful strategy in extending monopolies and in breaching patent protection. It is the courts that must eventually pronounce judgement. The marshalling of arguments to reach the conclusion, that 'Imatinib Mesylate is fully a part of the Zimmerman patent' and does not constitute a new invention in any form, requires a fusion of chemistry and the intellectual property protection laws as they stand today. The learned judges cite the scientific literature extensively, quoting from papers by the Novartis group in *Cancer Research* (1996) and *Nature Medicine* (1996). The judgement provides a fascinating glimpse of a complex debate at the confluence of chemistry and law.

Are there lessons to be learnt? A point that clearly emerges is that the many amendments to the Patent laws enacted by Parliament have indeed been valuable in protecting public interest. The judges note that the 'Court was urged to strike a balance between the need to promote research and development in science and technology and to keep private monopoly (called an "aberration" under our Constitutional scheme) at the minimum'. Gleevec's origins can be traced to excellent basic science in cellular biology and its development to the great strengths in medicinal chemistry within a pharmaceutical research laboratory. Future innovation in India in this area depends critically on our ability to recognize that such collaborations are central to drug discovery. There is also little doubt that science and law will intersect with greater frequency in the future.

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