Patent threat in emerging economies shifts to biotech

Recently revamped rules for compulsory licenses—which allow national governments to revoke patents for use in urgent or emergency situations—have triggered a spate of challenges to pharma's intellectual property (IP) in emerging economies like those of India, Thailand and Brazil. Now those challenges are starting to extend to biotech patents.

The Indian Patent (Amendment) Act 2005 broadened the scope for compulsory licenses to include situations other than medical emergencies. Indian authorities can invoke compulsory licenses if a patented drug is unaffordable, unavailable in sufficient amounts, not manufactured in India by the patent holder or manufactured before 2005 by a generic company. Compulsory licenses can also be invoked to export drugs to countries with insufficient manufacturing capacity to address public health needs.

In India, Natco Pharma, of Hyderabad, India, recently pleaded for two compulsory licenses to produce cheap versions of drugs for export to Nepal. One of them is for a biotech drug: Tarceva (erlotinib), originally developed by Genentech, of S. San Francisco, California, and OSI Pharmaceuticals, of Melville, New York, and marketed in India by Roche; the other is for Sutent (sunitinib), the anti-cancer drug produced by New York-based Pfizer.

In March, Thailand's new government also issued compulsory licenses for a clutch of innovative medications, including three for cancer. And in South America, last May, the Brazilian government stated a national emergency to issue a compulsory license for patent-protected antiretroviral Sustiva (efavirenz) (**Box 1**).

The question is whether these instances will be taken as precedents spelling trouble for IP-reliant drug makers, particularly biotech firms, which are often valued on the basis of the strength of their patent portfolio.

In the Tarceva case, in which compulsory licenses were filed, the court has given only an 'interim' order and not the final ruling, meaning that so far there is "nothing yet for our generic firms to celebrate," says Gopinathan Nair, Mumbai-based patents consultant. And Dilip Shah, secretary-general of the Indian Pharmaceutical Alliance, does not believe Natco's precedent-setting filing for a compulsory license will create a chain reaction, either. "India refrained from giving CL [a compulsory license], even when bird flu created a potential emergency in 2006," he says. "Instead it placed an order for Tamiflu with Roche."

Prasanna Kumar Ghosh, former adviser to government on biotech, feels the attitude to compulsory licenses ought to remain that way. "CLs will turn the multinationals away," he cautions.

Tarceva is one of the first biotech drugs coming under patent pressure from compulsory licenses.

IN brief

New Alzheimer's endpoints?

The phase 2a success in Alzheimer's disease from Prana, of Melbourne, Australia, helped push its stock up 36% the day the news was made public, but the data could have a broader impact on the Alzheimer's disease field. Prana's drug, PBT2, a second-generation 8-OH quinoline, blocks the interaction between amyloid proteins and naturally occurring metal ions in the brain known to trigger beta-amyloid deposition. The data showed mild gains in tests of executive function and a marked reduction in a biomarker devised by the company to measure certain amyloid beta proteins (Abeta 42). But the gold standard measurement of efficacy for all approved Alzheimer's disease drugs is the ADAS-cog endpoint, which showed no benefit in the phase 2a trial. Clive Ballard, director of research at the Alzheimer's Society and professor of age-related diseases at King's College, London, says that the ADAS-cog test is "not very sensitive to treatment responses and changes occurring in early Alzheimer's disease." Elan of Dublin, Ireland, and Wyeth, of Madison, New Jersey, are also exploring alternative endpoints with bapineuzumab, a humanized monoclonal antibody that targets the beta-amyloid protein to dissolve the plaques associated with Alzheimer's disease. Bapineuzumab is the first antibody in phase 3 for Alzheimer's disease. The US Food and Drug Administration (FDA) in December gave the green light for the phase 3 trials based on results measured with the Neuropsychological Test Battery (NTB), a gauge of mental status that Elan devised, though both will be used.
—Susan Aldridge

GM grass trials blocked

A US court has blocked the resumption of open-air field trials involving genetically modified (GM) versions of creeping bentgrass and Kentucky Bluegrass. On March 17 the US Court of Appeals for the District of Columbia Circuit dismissed an appeal from Scotts Grass, of Marysville, Ohio, over testing the Roundup Ready grasses. The company appealed a 2007 ruling by a lower federal court, which found that officials of the US Department of Agriculture (USDA) had erred in approving plans for testing grass without first assessing environmental impacts. The GM grasses in field trials spread beyond the test fields to surrounding areas, including a protected 'National Grassland' area. Despite these findings, Scotts not only appealed the lower court ruling but also challenged the standing of one of the plaintiffs in that case, namely the Washington-based International Center for Technology Assessment (ICTA). "The court's ruling vindicates our challenge to USDA's inadequate review of these biotech grasses," says Joseph Mendelson, who is legal director of the Center for Food Safety in Washington, DC, a sister organization to ICTA, which initiated several lawsuits against the company and USDA (*Nat. Biotechnol.* **25**, 269, 2007).
—Jeffrey L Fox

In fact the Mumbai-based Organization of Pharmaceutical Producers of India (OPPI) that represents multinational (and some large Indian) companies views the compulsory license threat as a tempest in a teapot. "CLs in no way can be considered as an emerging trend for both pharmaceutical and biotech products," says OPPI director general, Tapan Ray.

Although it does consider national emergency reasonable grounds for a compulsory license, OPPI is opposed to granting them to extend commercial benefit to companies that manufacture copies of brand drugs. In the Natco case, Nepal has not given the generic version a nod, as it has not officially issued a notification to allow the generic drug version to be imported from India—a requirement under the Indian Patents Act for seeking compulsory licenses. "This has never happened in any country in the world and OPPI strongly believes that the situation will not be any different in India," says Ray.

This remains to be seen. "Although there hasn't been a biologics CL case as yet in India, it is certainly going to become prominent," says Shamnad Basheer, an associate at Oxford IP Research Center, UK. One driver for this is the Indian government's new 'biotechnology strategy', which is expected to facilitate the growth of biopharmaceutical companies that copy brand biologic drugs in a big way. Last May, Dr. Reddy's Laboratory in Hyderabad launched its second biosimilar drug Reditux, a copy of Roche's blockbuster Rituxan (rituximab), a monoclonal antibody used in the treatment of non-Hodgkin's lymphoma. Reddy's, which already sells Grafeel, a copy of Amgen's Neupogen (granulocyte-macrophage colony stimulating factor, which is used to boost white blood-cell production), announced in February it has eight more biologic copycats in its pipeline. "Assuming some of these are patented, Reddy's could try and avail itself of the Cipla ruling—whereby if the price is too high and it is not manufactured in India, this would be subjected to a CL," says Basheer.

Basheer warns, however, that growth of the sector will be unsustainable unless the Indian government moves to create a regulatory pathway for biogenerics; at the moment, there is a distinct lack of stringent regulations to address equivalence issues.

OPPI voices similar concerns. Because biologic drugs are difficult to replicate, the OPPI has suggested the authorities consider biosimilar drugs as new products and request all the necessary supportive data for their registration. The issue of biogenerics approval needs to be "urgently addressed," says Ray, a move expected to delay if not preempt compulsory licenses on biogenerics.

But Basheer argues that because drug prices are the key driver for compulsory licenses, the best way for big pharma and biotech to address this issue is by rethinking their model of pricing worldwide. He believes the increasing R&D collaboration between Indian generics and multinational companies may also reduce the incentives to apply for such licenses.

Another Catch-22 is that even if they do not like compulsory licenses, Western drug firms can't afford to stop marketing their products in India, says Mrinalini Kochupillai, a patents expert at Boston Law School. This is because "nonavailability in the local market is also one of the grounds for grant of CL," he says

One biologics sector, vaccines, has so far avoided compulsory licenses. There are several reasons they are not on the list of potential compulsory licenses, says Yennappu Madhavi, an expert on vaccine policy. Patents for the old vaccines in the immunization programs in most countries have expired, and, in fact, large pharma is not keen on producing them, she says.

But if a bird flu vaccine is produced, it ought to be available through compulsory licenses, says Cipla's chairman Yusuf Hamied. "In diseases like AIDS, tuberculosis, malaria or bird flu you cannot afford a monopoly." Hamied

SELECTED research collaborations

Partner 1	Partner 2	$ (millions)
Silence Therapeutics (London)	AstraZeneca (London)	*
CG Therapeutics (Seattle)	University of Washington at Seattle	*
Raven Biotechnologies (S. San Francisco, California)	Monogram Biosciences (S. San Francisco, California)	*

* Financial details not disclosed.

Box 1 Latin American countries and compulsory licenses

Brazil "complies strictly" with international rules, says Reinaldo Guimarães, Secretary of Science, Technology and Strategic Inputs of Brazil's Ministry of Health in Brasilia. The Brazilian government, he says, is committed to the agreement established by the World Trade Organization in 1995, including the Trade-Related Aspects of Intellectual Property Rights (TRIPS) Agreement for drug patent protection.

Guimarães says that Brazil's policies lean toward price capping through negotiations with pharmaceutical companies, but for a state that offers free prescriptions to the entire population, price hikes can lead to extreme situations. Last May, President Luiz Inácio Lula da Silva declared a national emergency and issued a compulsory license to acquire a low-cost version of the antiretroviral Sustiva (efavirenz), developed by Merck of Whitehouse Station, New Jersey. The drug substitution has helped about 80,000 people with AIDS. And in April, the country said that Foster City, California-based Gilead's HIV drug Viread (tenofovir disoproxil fumarate) was in "the public interest," suggesting Brazil might not grant a patent on the product and open the country to generic forms.

In Mexico, the country's spending on antiretrovirals has almost doubled in a year, but compulsory licenses have not been invoked. That does not preclude their future application "if necessary," says Ector Ramirez Barba, president of the Health Commission's Lower House. However, the Mexican Congress has already rejected two bills requesting "biosimilar drugs" for treating critical health problems like diabetes, though a couple of regulations have been passed by Congress. The first one, passed in November, sanctioned the Mexican endorsement to the Protocol for Amending the TRIPS Agreement. In March, the legislators passed a law that, for the first time, defines and makes a distinction between chemical drugs and their generic versions, and between biotech drugs and biosimilars.

Argentina hasn't made use of compulsory licenses either. Sonia Tarragona, an official from the Argentine Ministry of Health, says they would most likely be used in a sanitary emergency, but there has been no cause "to employ any type of licenses yet." The Argentine government hasn't shaped any policy toward the import or export of compulsorily licensed products, nor has it been discussed.

Verónica Guerrero Mothelet *San Miguel Chapultepec, Mexico*

argues in such cases of communicable diseases, generic makers should be allowed to produce copies of patented drugs and vaccines on payment of a royalty. If India did not grant compulsory licenses, Hamied says, Cipla would set up factories in the least developed countries where product patents will not apply until 2016. "We have already set up a factory in Uganda and we are starting one in Morocco," he says.

Industry watchers say Cipla's model is bold, but doubt whether opening up markets for generic drugs in the least developed nations makes economic sense. "The total pharmaceutical market of Africa is less than $2 billion," says Chandra Mohan Gulalthi, editor of *Monthly Index of Medical Specialties*. Although it may be easy to set up a bicycle factory in the least developed countries, he notes, pharmaceutical manufacturing requires trained scientists. "Where will Cipla get the trained manpower for its facilities in the least developed countries?"

Killugudi Jayaranam *Bangalore*

Details
The companies will work on delivering siRNA molecules. Both Silence and AstraZeneca will be allowed to commercialize any delivery systems developed. Silence offers the functional systemic delivery of siRNA *in vivo* using its proprietary AtuPLEX technology, though both parties will contribute expertise. The deal is independent of the parties' three-year collaboration signed in July 2007.
CG Therapeutics offers CG201, a vaccine designed to produce antibodies aimed at neutralizing hCG (human chorionic gonadotropin), a hormone associated with tumor cell growth. The two will work to develop human monoclonal antibodies against hCG that can be used with CG's CG201 vaccine.
Raven entered an agreement for Monogram to evaluate selected Raven monoclonal antibodies for use with Monogram's VeraTag technology in diagnosing cancer.

IN brief

Bush pushes plant energy

US President George W. Bush early in March renewed his pledge to increase energy security through a variety of reforms, which include bolstering corn-based and cellulosic-derived ethanol for renewable energy. Bush pointed out that the Department of Energy (DOE) invested a total of nearly $1 billion since fiscal year (FY) 2001 into technologies for producing cellulosic ethanol from sources such as wood chips and switch grass. The FY 2009 budget proposal calls for an increase of nearly $27 million, or 13%, for supporting biomass and biorefinery R&D. But Carol Werner of the Washington-based Environmental and Energy Study Institute (EESI) notes that "funding priorities reflected in the President's FY 2009 budget appear to conflict with the goals of expanding renewable energy development and making the economy more energy efficient." The FY 2009 budget request for DOE programs supporting renewables is $1.26 billion—a mere 5% of the total DOE budget. This figure is "essentially flat" compared to the FY 2008 budget request and 27% below FY 2008 appropriations. To complicate matters further, a debate is raging among climate-change experts as to whether moving to greater reliance on renewable ethanol will lead to changes in agricultural land use that could exacerbate global-warming trends. More immediately, the rush to make ethanol from corn is driving up food prices.
—Jeffrey L Fox

Changes for ESAs

Recommendations March 13 by the US Food and Drug Administration (FDA)'s Oncology Drug Advisory Committee for three erythropoiesis-stimulating agents (ESAs) included suggestions of a black box warning on the products for an association with increased tumor growth and shortened survival time. And the panel voted against using ESAs in patients with metastatic breast cancer, as well as cancer of the head and neck and in patients likely to be cured by treatment. Two of the three ESAs at issue—Epogen (epoetin alfa) and Aranesp (darbepoetin alfa)—are produced by Thousand Oaks, California-based Amgen, while the third, Procrit (epoetin alfa), is sold by Johnson & Johnson of New Brunswick, New Jersey. Still, Amgen's shares traded up by nearly 5% when the news broke, mainly because of what the panel didn't recommend: dropping use in chemotherapy-induced anemia. Should the FDA adopt these recommendations, Mark Schoenebaum, a biotech analyst at Bear Stearns of New York, sees a 40% drop in cancer sales for Amgen's Aranesp, which racked up total sales of $3.6 billion last year. Last month, Amgen was hurt by a black box warning on Enbrel (etanercept), for rheumatoid arthritis and psoriasis. The FDA said the label should carry a warning about the risks of infection, including tuberculosis. Enbrel, which inhibits tumor necrosis factor, a protein involved in inflammation, earned Amgen $3.2 billion in sales last year.
—B J Spalding