its two sides together, Keranen says, but an unmapped offshoot might be more susceptible to rising water pressures. In the long term, a magnitude-6 earthquake near Oklahoma City is a plausible hazard, she says.

Regulators are starting to get involved. On 20 June, Oklahoma's governor approved a new rule that, beginning later this year, would require oil and gas operators to report injection volumes and pressures daily rather than monthly. In September 2013, the Oklahoma Corporation Commission (OCC) exercised its regulatory powers for the first time in an induced seismicity case: It ordered a well operator in Love County to dial back disposal volumes after the well was connected to a magnitude-3.4 quake. Regulators in other states, such as Ohio and Arkansas, have taken similar actions. Just last week in Colorado, regulators ordered a 20-day halt to operations at an injection well in Weld County after it was linked to a magnitude-3.4 earthquake. OCC says that it is evaluating the new study in *Science* and is in discussions with New Dominion about the four high-volume wells.

Several unresolved questions loom large for researchers. For starters, they have a hard time identifying a safe rate of wastewater disposal because so much depends on the local geology. "We don't have a magic number at this point. Some of this is trial and error and experiment," says OGS's Holland.

Nor does anyone know whether the extraordinary bursts of small earthquakes could signal bigger ones to come. As a rule of thumb, seismologists estimate that for every 1000 magnitude-4 earthquakes, there will be 100 magnitude-5 quakes, 10 magnitude-6 quakes, and so on. So far, the largest injection-linked earthquake to occur has been the 2011 magnitude 5.7 in Prague, Oklahoma, which knocked off spires at a university 25 kilometers away. Are worse ones looming? "That's the key question that no one has an answer to at this point," USGS's Ellsworth says.

Researchers hope that better earthquake monitoring—and better injection well reporting—will help them come up with answers. Holland says that by the end of the year, the state plans to boost its number of permanent seismic stations from 17 to 25—still far behind California's 2530 stations.

Meanwhile, in Jones, earthquake talk has become a staple at Shuff's Main Street Grill. Joe Dooling, who curates the town's historical museum and whose home's ceiling was cracked during one of the early earthquakes, jokingly says the mayor had better be working on his campaign promise. "Ray has been duly warned that if he doesn't stop the earthquakes, we're not going to elect him next time." ■

A 2013 Supreme Court decision that barred human gene patents is scrambling patenting policies.

INTELLECTUAL PROPERTY

Biotech feels a chill from changing U.S. patent rules

Supreme Court decisions hobble efforts to protect inventions involving natural products

By **Kelly Servick,** *in San Diego, California*

A year after the U.S. Supreme Court issued a landmark ruling that human genes cannot be patented, the biotech industry is struggling to adapt to a landscape in which inventions derived from nature are increasingly hard to patent. It is also pushing back against follow-on policies proposed by the U.S. Patent and Trademark Office (USPTO) to guide examiners deciding whether an invention is too close to a natural product to deserve patent protection. Those policies reach far beyond what the high court intended, biotech representatives say.

"Everything we took for granted a few years ago is now changing, and it's generating a bit of a scramble," says patent attorney Damian Kotsis of Harness Dickey in Troy, Michigan, one of more than 15,000 people who gathered here last week for the Biotechnology Industry Organization's (BIO's) International Convention.

At the meeting, attorneys and executives fretted over the fate of patent applications for inventions involving naturally occurring products—including chemical compounds, antibodies, seeds, and vaccines—and traded stories of recent, unexpected rejections by USPTO. Industry leaders warned that the uncertainty could chill efforts to commercialize scientific discoveries made at universities and companies. Some plan to appeal the rejections in federal court.

USPTO officials, meanwhile, implored attendees to send them suggestions on how to clarify and improve its new policies on patenting natural products, and even announced that they were extending the deadline for public comment by a month. "Each and every one of you in this room has a moral duty … to provide written comments to the PTO," patent lawyer and former USPTO Deputy Director Teresa Stanek Rea told one audience.

At the heart of the shake-up are two Supreme Court decisions: the ruling last year in *Association for Molecular Pathology* v. *Myriad Genetics Inc.* that human genes cannot be patented because they occur naturally (*Science*, 21 June 2013, p. 1387); and the 2012 *Mayo* v. *Prometheus* decision, which invalidated a patent on a method of measuring blood metabolites to determine drug doses because it relied on a "law of nature" (*Science*, 12 July 2013, p. 137).

Myriad and *Mayo* are already having a noticeable impact on patent decisions, according to a study released here. It examined about 1000 patent applications that included claims linked to natural products or laws of nature that USPTO reviewed between April 2011 and March 2014. Overall, examiners rejected about 40%; *Myriad* was the basis for rejecting about 23% of the applications, and *Mayo* about 35%, with some

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overlap, the authors concluded. That rejection rate would have been in the single digits just 5 years ago, asserted Hans Sauer, BIO's intellectual property counsel, at a press conference. (There are no historical numbers for comparison.) The study was conducted by the news service Bloomberg BNA and the law firm Robins, Kaplan, Miller & Ciseri in Minneapolis, Minnesota.

The numbers suggest USPTO is extending the decisions far beyond diagnostics and DNA, attorneys say. Harness Dickey's Kotsis, for example, says a client recently tried to patent a plant extract with therapeutic properties; it was different from anything in nature, Kotsis argued, because the inventor had altered the relative concentrations of key compounds to enhance its effect. Nope, decided USPTO, too close to nature.

In March, USPTO released draft guidance designed to help its examiners decide such questions, setting out 12 factors for them to weigh. For example, if an examiner deems a product "markedly different in structure" from anything in nature, that counts in its favor. But if it has a "high level of generality," it gets dinged.

The draft has drawn extensive criticism. "I don't think I've ever seen anything as complicated as this," says Kevin Bastian, a patent attorney at Kilpatrick Townsend & Stockton in San Francisco, California. "I just can't believe that this will be the standard."

USPTO officials appear eager to fine-tune the draft guidance, but patent experts fear the Supreme Court decisions have made it hard to draw clear lines. "The *Myriad* decision is hopelessly contradictory and completely incoherent," says Dan Burk, a law professor at the University of California, Irvine. "We know you can't patent genetic sequences," he adds, but "we don't really know why."

For now, Kostis says, applicants will have to get creative to reduce the chance of rejection. Rather than claim protection for a plant extract itself, for instance, an inventor could instead patent the steps for using it to treat patients. Other biotech attorneys may try to narrow their patent claims. But there's a downside to that strategy, they note: Narrower patents can be harder to protect from infringement, making them less attractive to investors. Others plan to wait out the storm, predicting USPTO will ultimately rethink its guidance and ease the way for new patents.

USPTO has extended the deadline for public comment to 31 July, with no schedule for issuing final language. Regardless of the outcome, however, Stanek Rea warned a crowd of riled-up attorneys that, in the world of biopatents, "the easy days are gone." ■

RUSSIA

Plan to grade institutes rattles Russian academy

Researchers fear reforms mark path to institute closures

By **Vladimir Pokrovsky**

To researchers at the beleaguered Russian Academy of Sciences (RAS), the omens are dark. Last month, the government body that took over management of RAS property and finances in January published a road map for reform. Among the measures it calls for is a formal assessment of the research effectiveness of RAS institutes. Scientists have concluded that the only reason to grade institutes is to decide which ones to close down.

"Such suspicions have existed from the very beginning of this period of RAS reform," says physicist Andrey Tsaturyan of Moscow State University's Institute of Mechanics and co-chair of the Council of the Researchers Society, an organization of RAS scientists. The timing of the road map is especially alarming, he adds, given that a yearlong moratorium on any changes to the staff and property of RAS, set by President Vladimir Putin (*Science*, 6 December 2013, p. 1157), will soon come to an end. Meanwhile, a draft of a law setting an age cap for institute directors threatens to leave many centers leaderless and vulnerable.

Few dispute that RAS, which runs the country's major research institutes and flourished during the Soviet era, needs reform, but many academy scientists are wary of the government's approach. Under the road map, which appeared last month on the website of the Federal Agency for Scientific Organisations (FASO), the next 6 months will be spent devising criteria for the assessment, which will begin on 1 January 2015. Other measures will follow, including developing competitive funding schemes, upgrading equipment, raising publication activity, boosting researchers' qualifications, and transferring staff employment terms to a contract system.

The road map also proposes raising RAS researchers' salaries to twice the average in the region in which they work. Researchers, who are often poorly paid, welcome the increase but wonder where the money will come from. The one cost-saving measure in the road map is a reduction in the proportion of technical and support staff from 50% to 41%. That worries biologist Viktor Krivokhatskiy of the RAS Zoological Institute in St. Petersburg, who says that "cuts in technical personnel would worsen the already miserable state of equipment and collections in Russia."

Researchers are also skeptical about FASO's intention to develop new criteria for assessing institutes. "There is no point in inventing new criteria of effectiveness and denying the only effective ones that are used in the world, relating to publications and research results," says Vasily Afonyushkin, a biologist at the Novosibirsk RAS Experimental Veterinary Institute.

Although the FASO road map doesn't mention closing down institutes, some are concerned that the same result will be achieved through stealth. In early June, the Russian Cabinet sent a draft law to the Duma setting an upper age limit of 65 years for institute directors and their deputies. According to RAS trade unions, half of RAS's 800 institute directors would have to stand down.

Such a measure will "behead the majority of such institutions and probably ruin them," says academician Michael Ugrumov of the RAS Institute of Normal Physiology in Moscow. Because of the severe brain drain that afflicted Russia during the economic turmoil of the 1990s, there is a shortage of senior scientific managers with the skills to take over so many directorships, he contends. "I'm not saying the laboratory heads scenario is inevitable, but I see certain signals and believe that we have to prevent such a disaster." ■

Vladimir Pokrovsky is a writer in Moscow.

New problem for older directors

65

Proposed age cap for directors of RAS's institutes

50

Percentage of directors older than that age cap, according to RAS trade unions