

fired its R&D head here for misrepresenting data in a preclinical study on an experimental drug for multiple sclerosis. The company halted phase I clinical trials of the drug and has asked *Nature Medicine* to retract a 2010 study. An internal audit leaked to *The New York Times* last week suggests that problems with research conducted by GSK's Shanghai center may have extended to other drugs. Then last month, media reports based on U.S. Food and Drug Administration (FDA) documents alleged that clinical trial data from China for the drug Eliquis, a blood thinner developed by Bristol-Myers Squibb and Pfizer, were marred by errors and fraud. The errors resulted in a 9-month delay for FDA approval, which was granted last December.

Observers say that the incidents could give ammunition to skeptics of China's R&D potential. "There are people in the U.K. and the U.S. who will say 'See? I told you,'" says the unnamed scientist. But China-based R&D is critical to big pharma's future business. Chronic diseases such as diabetes and hypertension are on the rise in China's large, rapidly aging, and increasingly affluent population. Drug companies emphasize diseases common in Asia in their China research operations: Novartis's Shanghai center focuses on hepatitis B and C, while AstraZeneca's Shanghai shop studies liver and gastric cancers. An army of efficient contract research organizations in China eases the path for drug development. Moreover, Chinese law demands

a presence: To register new drugs in China, companies must first conduct trials with local patients. The R&D operations are propelled by burgeoning revenue in China, which grew from \$4 billion in 2006 to \$10 billion in 2011 for the top 10 pharmaceutical multinationals, according to the consulting firm McKinsey.

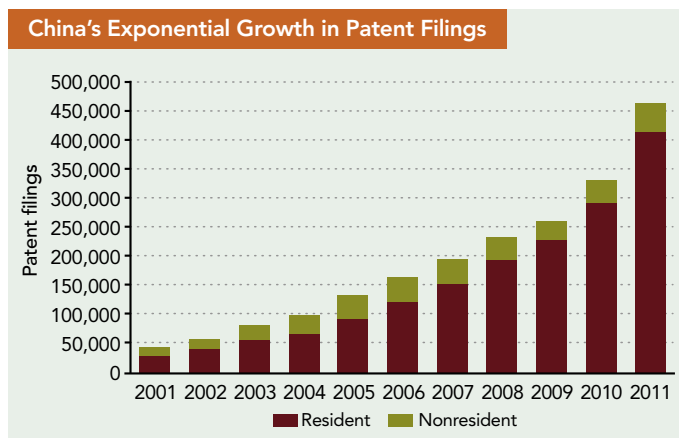
That growth may be about to flatten. As part of its healthcare reforms, the central government has mandated price cuts on hundreds of drugs, many produced by big pharma. And revised regulations now allow for compulsory licensing, which would allow domestic manufacturers to make generic versions of patented drugs on a case-by-case basis—a tactic the government has not yet invoked.

At the same time, the government has been aggressively promoting domestic drug R&D (*Science*, 3 July 2009, p. 21). The Major New Drug Innovation Program, launched in 2009 to boost drug development by establish-

ing innovation bases around China, enjoys more than \$1.5 billion in central government funding, along with \$3 billion from local governments and industry, according to Lux Research. And the government subsidizes patent fees for domestic companies, fueling a rapid increase in filings (see graph below). Multinationals "have to prepare for the prospect that one day they will compete with their Chinese counterparts as equals," Huang says.

Some of China's hopes for its domestic drug companies may be unrealistic. The central government has set a goal of developing 30 innovative drugs by 2015, and another 70 by 2020. "It's unlikely that we will see a great drug" by 2015, says Hu Zhuohan, president of the Research Institute for Liver Diseases here who has served on China's State Food and Drug Administration committees considering new drug applications. While the injection of cash should eventually yield results, Hu says, "what drugs come out is not directly correlated with how much money is put in."

Meanwhile big pharma, chastened by the corruption probes, is cleaning up its operations. Most clinical centers now scrupulously follow FDA Good Clinical Practices regulations, says Zhai, the Healthquest CEO: "The early days of making up data" are over, she insists. Zhai believes that the scandals have delivered a "wake-up call" to improve oversight and management in China. "In the long run," she says, "it's a good thing." —MARA HVISTENDAHL



Patent boom. Favorable policies have fueled a surge in resident patent filings, many by pharmaceutical or biotechnology firms.

SCIENTIFIC EXCHANGE

Marine Studies Show Potential for U.S.-Cuban Collaboration

CAYO COCO, CUBA—Dense mangroves eclipse the midday sun in this inlet off northern Cuba's La Redonda Lake, as a team of six ecologists steps off an idling speedboat. They are here to gather baseline data on the mangrove ecosystem and focus on a local mystery—the disappearance of the large-mouth black bass (*Micropterus salmoides*). Once prolific, it has been vanishing from this mangrove lake over the past few years. Elevated water temperature or other climatic factors are possible causes, but the team says nothing has been ruled out.

Adán Zúñiga Ríos, leader of the project, wonders whether something similar has happened in South Florida, more than 150

kilometers away, home to almost identical mangrove thickets. "Ecosystems know no country borders," says Ríos, director of the Center for Coastal Ecosystems Research (CIEC), based in this coastal town. Yet Zúñiga has been unable to work with U.S. scientists to gather parallel data in Florida.

"If we were dealing with any other two countries," collaboration wouldn't be so difficult, he says. But this is Cuba, and for 51 years the U.S. economic embargo has made interactions cumbersome, if not impossible. But change may be coming. Early this year, Cuba eliminated the "white card," a type of exit visa required of anyone who wants to travel abroad. Other barriers

that keep professionals in both countries from visiting one another—especially doctors and scientists—might be relaxed soon, says Daniel Whittle, a conservationist and Cuba program director for the Environmental Defense Fund (EDF). Whittle says that he was encouraged by what he heard from U.S. and Cuban officials while hosting a workshop on fisheries in Cuba last month. Whittle says that no formal proposals are on the table, but both governments seem to be opening up to more "people-to-people" exchanges—not just ceremonial events in Havana.

The mangroves are just one area of potential cooperation; there's a huge environmental



Deep fieldwork. A research team gathers data on wildlife in a mangrove ecosystem near Cayo Coco on Cuba's north coast.

overlap between the two neighbors. “There is a lot we can learn from each other,” says Peter Agre, 2003 Nobel laureate in chemistry and former president of AAAS (*Science’s* publisher), who has traveled to Cuba three times in recent years to promote exchange.

There’s a lot the two countries could learn to avoid, too. “A shared environment means shared risks,” says Whittle, whose organization has worked with groups like CIEC since 2001 on marine conservation. Offshore oil exploration and commercial fishing are two current areas of risk. The Obama administration has taken small steps toward easing scientific exchanges in some areas, like oil. “It’s in our national interest to get this right,” Whittle says, although “we’re still a long way off.”

Ties between U.S. and Cuban scientists date back to the 19th century, but most exchanges ended in 1961, when the John F. Kennedy administration cut ties with Cuba and subsequently imposed an economic embargo after socialist leader Fidel Castro rose to power. Scientific exchange improved a bit in the 1970s when the Smithsonian Institution in Washington, D.C., signed an agreement to reestablish limited ties with the Cuban science academy. During the Clinton administration in the mid-1990s, scientists launched other collaborations, including an ongoing project led by the New York Botanical Garden to help Cuba identify vulnerable plant species.

But the barriers are still daunting. “The basic stuff is hard to get done,” says James A. Powell, founding director of the Sarasota, Florida-based Sea to Shore Alliance. His group was invited by the University of Havana’s Center for Marine Investigations (CIM) to participate in a study of manatees. Since 2003, Powell says, they have found movement between manatee populations in Cuba and Florida that was previously

unknown. Researchers rely on a massive photo database to track individual animals, identified by unique scars caused by being struck by boats. Powell recalls one manatee that he photographed himself in Florida in 1978; it was later sighted on a beach in Cuba, in 2007.

Powell says that researchers in Cuba have gathered DNA from carcasses and live animals suggesting that the predominant manatee in Florida may be “more closely related to the Antillean manatee found in Cuba than we thought before.” A key achievement, he says, has been establishing causes of death, including CIM work showing that many of Cuba’s manatees were drowning in fishing trawls. The government has taken steps to limit fishing in manatee areas, and the population may begin to recover. But without the embargo, Powell says, “we would be able to build on this strong foundation ... and develop a more comprehensive conservation program.”

The embargo guidelines set by the U.S. Treasury Department’s Office of Foreign Assets Control allow U.S. scientists to fund their own work in Cuba, but not to support work by Cubans. U.S. researchers may not donate equipment or purchase anything permanent in Cuba—be it a boat or office space. Powell says, “All my equipment—including binoculars—has to be registered and approved” by the U.S. government before being taken to Cuba.

The rules constrain activities, too, says Fernando Bretos, a Miami, Florida-based biologist with the Ocean Foundation who has studied sea turtles in Cuba since 1999. When Bretos wanted to track migration patterns, he waited months for authorization to take small satellite tags into Cuba. Bretos then learned that he couldn’t teach Cuban scientists how to affix the tags to animals without another license for “sharing of

information.” Dreading the paperwork and the likely 1-year wait, Bretos decided to put the tags on himself.

More than science could be at risk. Since 2011, Cuba has been opening up its economy, and experts worry that burgeoning commercial fishing, for example, could affect species that migrate to U.S. waters, such as grouper, snappers, and tarpon. Pollution and coastal development could also affect endangered animals shared by the Florida Keys—manatees, sharks, and sea turtles.

Cuba’s plans for its undersea oil reserves could pose a bigger threat. Little has been extracted so far—Cuba has just one working rig, off its central northern coast. But some think that the oil reserves could be vast, and just one blowout could be catastrophic. “*Deepwater Horizon* was a game changer,” says EDF’s Whittle, referring to the 2010 oil spill in the Gulf of Mexico. It forced everyone to recognize that the ocean is a shared ecosystem, and in 2012 the U.S. State Department and the Cuban Ministry of Foreign Affairs started discussions that could soon lead to an agreement outlining procedures and protocols in the event of a spill, Whittle says.

Scientists hope that the détente can be extended. In February, a group of U.S. scientists wrote to President Barack Obama noting that “the process for carrying out environmental projects with Cuba remains daunting.” They asked that he continue streamlining processes for securing equipment and travel licenses for work in Cuba, as well as ease regulations that limit the use of U.S. funding in Cuba. While there was no official response, several of the letter’s signatories met with White House and State Department staff members to discuss their recommendations, and they say there’s hope that President Obama’s second term will bring about further openings.

Cuba has its own constraints, scientists say: too much red tape and too little money. All projects must be vetted through government agencies, often waiting years to clear the bureaucratic labyrinth. Once a project is under way, there’s no guarantee of continuity.

Yet Cuban scientists can contribute knowledge and enthusiasm. On his visits to Cuba, Agre says that he was impressed by “so many bright-eyed young people passionate about wanting to do science.” He adds, “Politics is never an issue. ... We just start talking science and that’s it, connections are made.” He and others hope that can become the norm.

—JEAN FRIEDMAN-RUDOVSKY

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