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Special report: Big Pharma's global guinea pigs

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By **Ben Hirschler**

LONDON (Reuters) - The Polish port city of Gdansk is famous for its shipyards. Hungary's fifth largest city, Pecs, is known for its ancient architecture and brewery. Neither is particularly renowned for medicine. Yet when AstraZeneca Plc tested its big new drug hope Brilinta on heart attack patients in a major clinical study, it was hospitals in these places that enrolled some of the highest number of patients anywhere in the world.

In fact, Poland and Hungary together accounted for 21 percent of all subjects studied in the pivotal 18,000-patient trial -- more than double the United States and Canada combined.

A few years ago that would have been unthinkable. Major drug companies, with an eye on the commercial promise of the world's largest and most profitable market, would have run half their tests on a major cardiovascular medicine like this in U.S. hospitals under the supervision of U.S. doctors.

Today, the clinical trials business has gone global as drugmakers seek cheaper venues for studies and cast their net further afield for big pools of "treatment-naive" patients who are not already taking other drugs that could make them unsuitable subjects for testing new ones. And it is not only the practicalities of running big clinical trials as efficiently and cheaply as possible that is driving the change. The drug industry is also paying a lot more attention these days to the promise of emerging markets, whose healthcare authorities, just like those in the United States and Western Europe, are keen to see cutting-edge science conducted in their backyards.

"The motivation to involve lots of patients is very high in Eastern European countries and also in Asia," says Dr. Ivan Horvath, head of interventional cardiology at the University of Pecs. "There are three factors driving this. Our patients get access to a new drug, which is free during the trial. It is also very important for scientific reasons. And we get paid."

The increasing reliance on clinical trials in Eastern Europe, Asia and Latin America raises serious questions. Is the quality of the data as reliable as that from a top U.S. medical center? Is it safe to extrapolate common clinical effects from studying patients with different lifestyles and genetic profiles? And are ethical standards in testing new drugs properly upheld in poorer countries? After all, there is an unhappy history of exploitation of the disadvantaged in trials, as highlighted by a shocking U.S. study in the 1940s which saw prisoners and the mentally ill deliberately infected with syphilis in Guatemala.

Given the sea change, it's perhaps no surprise that the rush to globalize clinical studies is starting to cause some headaches.

SOMEWHERE ELSE

In the United States, the widespread "off-shoring" of research was highlighted in a report last year by the inspector general of the Department of Health and Human Services, which revealed just how reliant the country has become on foreign testing. In 2008, a total of 78 percent of all subjects participating in trials to support drug applications submitted to the Food and Drug Administration (FDA) were enrolled at foreign sites -- and as more experimental medicines move through the pipeline the numbers are set to increase further.

In Europe, the picture is similar, with 61 percent of patients in pivotal trials submitted to the European Medicines Agency (EMA) between 2005 and 2009 coming from third countries. A further 11 percent of patients were enrolled in studies in Eastern European countries that are now members of the European Union. The number of Polish patients involved in such trials rose fivefold over the period, while Hungary was up 3-1/2 times.

"Today, wherever you stand in the world, the larger part of the data from clinical trials comes from somewhere else, so you have to have confidence in the framework in which those trials were done," says Fergus Sweeney, head of compliance and inspections at the London-based EMA, Europe's equivalent of the FDA.

Sweeney -- an Irish pharmacologist who has been working on inspections at the agency since 1999 and who chooses his words carefully -- spends an increasing amount of time grappling with the problem of foreign trials. But he admits the number of research sites actually inspected by EMA or FDA officials remains "tiny."

Drug companies are also finding that conducting clinical trials in dozens of countries at once is a tricky business and results can be unpredictable. Just ask AstraZeneca.

Its drug Brilinta -- a rival to Sanofi-Aventis SA and Bristol-Myers Squibb Co's \$9 billion-a-year seller Plavix, the world's second biggest-selling prescription medicine -- is potentially huge.

Yet while Brilinta has already been approved in more than 30 countries, including those in the European Union, it has been delayed in the United States -- the one market that will ultimately make or break it commercially. The reason? While the big trial known as PLATO found Brilinta was clearly superior to Plavix at preventing cardiovascular deaths globally, people in North America actually seemed to do worse on the new drug.



Why is unclear. One theory is that U.S. heart patients get given more aspirin alongside other medicines and this may somehow interfere with Brilinta's effectiveness. But it might just be play of chance, since the North American sub-group - which accounted for only 9.7 percent of patients -- was too small to draw any statistically sound conclusions.

Whatever the explanation, the discrepancy has left the new drug hanging in the balance. Some industry analysts think the FDA may demand further evidence before approving it in the United States, despite an advisory panel vote in its favor last year. These days the FDA has little appetite for sticking its neck out and officials will think long and hard before approving a drug that might not work for Americans. The watchdog has been slammed in recent years for failing to prevent a string of drug safety scandals, including heart problems linked to Merck & Co Inc's now withdrawn painkiller Vioxx and GlaxoSmithKline Plc's diabetes pill Avandia, as well as deaths from contaminated Chinese supplies of blood thinner heparin.

The U.S. agency is due to give its verdict on Brilinta by July 20 -- but the ripples from this study have already spread widely. According to an analysis of the situation by Dr. Magnus Ohman and Dr. Matthew Roe of Duke University Medical Center, the PLATO results "should serve as a warning to all stakeholders in global cardiovascular research that balanced enrollment around the world in pivotal trials should be the goal for any future drug development program."

AstraZeneca says it is confident in the conduct and results of the trial. Yet the study is now a red-hot topic for pharmaceutical investors and it has also got a lot of doctors talking.

THROWING IN THE TOWEL

April's annual meeting of the American College of Cardiology (ACC) in New Orleans was the usual frenetic mix of world-class science, networking and lobbying by the \$850 billion-a-year pharmaceutical industry, seeking to promote its wares to key opinion leaders. The commercial razzmatazz of the convention centre's giant trade stands, advertising big brand drugs and medical devices, painted a bright picture for medical science.

Under the surface, however, a growing number of doctors are worried about the tectonic changes in drug research. They resent the export of clinical trial work, which they blame not only on industry's endless pursuit of lower costs but also on the increasing red tape surrounding trial procedures at home.

"Many of my colleagues have just thrown in the towel and say 'I'm not going to do clinical research anymore'," says Dr. Michael Crawford, professor of medicine and chief of clinical cardiology at University of California-San Francisco, one of the top medical schools in the United States.

"It's pervasive. They've just quit clinical trial work. It's just too difficult and the expenses are so high you end up being in the red when you do a study."

That's in stark contrast to the experience of doctors in Hungary, many on a monthly salary of around 500 euros (\$740), for whom working on a clinical study can double their pay. For medics in places like India -- now also a major hotspot of clinical research -- the salary boost can be even greater.

But Crawford says he does not want data from these places. He wants to see how a new medicine performs in his own country.

"I don't have any way of assessing the quality of research in an Eastern European country. It may be wonderful, but I don't have any way of assessing that. I know if a study is conducted in the United States and Canada, it's done according to certain standards," he says.

Dr. David Holmes, president of the ACC and professor of medicine at the Mayo Clinic in Minnesota, is more circumspect but also believes the Brilinta case raises important issues: "We can't abrogate the responsibility of conducting clinical trials in the U.S. on people that live in the United States."

The EMA's Sweeney says there is no evidence that clinical trials conducted in developing economies are any worse than those done in the West. However, lack of evidence is not the same as positive proof and his team needs more resources to guarantee everything is squeaky clean on the front-line. Between 2005 and 2009, the European watchdog dealt with data linked to pivotal studies from 44,034 clinical trial sites, but it carried out only 44 good clinical practice inspections outside Europe and North America. The U.S. FDA, meanwhile, inspected 0.7 percent of foreign clinical trial sites in 2008, against 1.9 percent of domestic sites.

CHINA RISING

For now, the world's emerging economies still play second fiddle to the United States when it comes to testing drugs. Clinicaltrials.org, a website run by the U.S. National Institutes of Health, currently lists more than 106,000 trials around the world, of which just over 50 percent are in the United States. But the balance is shifting, particularly when it comes to the big late-stage trials that really matter in deciding whether a drug is approved for sale. U.S. centers account for only 43 percent of the nearly 19,000 trials in final Phase III testing.

As in so many other areas of life, the rising star is China, which already has a total of more than 2,700 clinical trials and is experiencing exponential growth.

Less than two hours by high-speed train from Shanghai, Dr. Zhang Chenyu's modern laboratory at Nanjing University's School of Biological Science shows how Chinese medical research has vaulted up the global league table. After nine years working as a research assistant professor at Harvard Medical School, Zhang returned to China in 2004, where he is dean of the Nanjing school, and these days he finds the world's top drugmakers beating a path to his door.

Zhang is a bit special because he and colleagues have discovered how certain molecules, or biomarkers, in blood can signal the presence of cancer as early as 33 months before conventional clinical diagnosis. As a result, his team is testing hundreds of U.S. blood samples in a lung cancer project with Johnson & Johnson, which is interested in developing a new diagnostic test using the biomarker. But Zhang is also convinced the wider Chinese research community has arrived firmly on the global clinical research scene, thanks to its relatively low cost base, its expertise, its modern facilities and -- crucially -- the huge potential market for Western medicine in the country.

China has already leapfrogged the likes of Germany and France to become the world's third largest market for pharmaceuticals, and by 2015 it is set to overtake Japan as the second-biggest, behind only the United States, according to pharmaceutical market information company IMS Health.

"Drug companies will surely vie for such a market," says Zhang. "Now, more Chinese can afford to buy Western-made drugs. So instead of performing a trial in China only after completing trials in Europe or the U.S., why not conduct them all at the same time?"

Independent expert Dr. Rory Collins, a professor of medicine at the University of Oxford and co-director of its Clinical Trial Service Unit, is a big fan of the power that Chinese clinical research can bring to medicine and is deeply impressed by how far the country has come in two decades.

"I remember 20 years ago giving lectures on randomized trials in China and the idea that you would randomly allocate people to get treatment, or not, was viewed as completely alien. The response was: 'We know which treatment works, we just ask the professor.' Today, China is a very organized place and all the structures are there," he says.

Indeed, the results of Chinese drug research are already bearing fruit -- and not just for patients in China.

Six years ago, Collins's Oxford team led a huge 46,000-patient study in China -- the biggest ever seen in the country -- to test the blood thinner Plavix and a beta-blocker in the emergency treatment of heart attacks. They found that adding Plavix to aspirin produced further benefit, while the beta-blocker metoprolol did not. That important discovery has since gone on to influence medical practice around the world.

"That study would never have been done if we couldn't have run this very streamlined trial in China at very low cost," says Collins, who is currently working on another pivotal heart drug study for Merck that contains no U.S. patients. "My preference would be not to do any trial in North America because it is so inefficient and so costly."

Western Europe may be a bit better but Collins and many other researchers are highly critical of the bureaucratic obstacles there as well, following the introduction of the European Union's 2004 clinical trials directive, which has led to a mountain of extra paperwork for each trial.

The aim of the EU directive is to harmonize standards and protect subjects.

AVOIDING EXPLOITATION

Everyone agrees that patients should not be exploited during the testing of drugs but trying to square the circle on ethics leads to fierce debate. Enrolling in a clinical trial can be a big health boost for many patients in poorer countries, who receive better-than-normal healthcare while being studied. But is it right to test an expensive new drug in a country where local people may never be able to afford it? And do patients always understand the risks associated with testing an unlicensed drug?

Caring for patients properly means drug companies "not just parachuting in, doing a study and leaving without recognition that these patients have really made a contribution, taken some risks and deserve to be respected and provided with certain broader aspects of care", FDA Commissioner Margaret Hamburg told the Reuters Health Summit in November.

Annelies den Boer of the Dutch non-profit Wemos Foundation, which has been following the globalization of clinical trials since 2006, worries a lot about just that sort of exploitation -- and worse.

She is concerned that the current benchmark guidelines on good clinical practice from the International Conference on Harmonisation (ICH) -- agreed by U.S., European and Japanese regulators and accepted by the drugs industry -- are unbalanced in emphasizing efficiency over ethics. And she fears that the out-sourcing of a growing volume of clinical work by pharmaceutical companies to specialist firms known as contract research organizations, or CROs, makes proper oversight increasingly difficult.

"People in many developing countries are often poor or illiterate, which makes them vulnerable," she says. "It's very difficult to check if companies do indeed abide by ICH because governments in countries where these trials take place do not exercise a lot of control. There's an entire chain -- vulnerable patients, doctors with conflicts of interests, CROs that are geared to doing trials extremely fast -- which is detrimental to ethical guidelines."

Given the numbers involved, it's no surprise that some subjects come out of the process disillusioned, as highlighted in testimonials gathered recently by den Boer's team.

Take Barbara, a 30-year-old Polish woman, who was initially thrilled when her eight-year-old son Marek was chosen to test a new drug for attention deficit hyperactivity disorder (ADHD). She received 200 zlotys (\$75) and, after about five weeks, the drug really seemed to work. Unfortunately, a short time later, the trial ended and the drug was withdrawn leaving Barbara both angry and deeply concerned about her son's future treatment.

"I can't believe I signed my son up for this trial without really understanding what I was agreeing to. I was blind. I realize now that people taking part in clinical trials should have the right to ask questions and be spoken to like human beings, not just guinea pigs," Barbara says.

Other subjects in Poland, Russia, China and India tell similar stories of the easy money that can be made from trials. But common complaints center on the lack of follow-up support and the impenetrability of jargon-filled contracts that can run to 50 or 60 pages.

Lifen, a 23-year-old graduate student living in Beijing, has taken part in five clinical trials to help pay for her studies. "The money is good, although recently I've noticed the payment rates have been going down. I think this is because there are more and more volunteers coming forward," she says.

Cases alleging serious side effects are rare, but not unknown. Pfizer Inc's 200-patient trial of the antibiotic Trovan during a 1996 meningitis outbreak in Kano, Nigeria, triggered a decade-long legal battle, after 11 children died and the company was accused of not obtaining adequate prior consent. It inspired John le Carre's novel "The Constant Gardener." Pfizer has always argued that meningitis and not its antibiotic led to the deaths. Still, two years ago the drugmaker reached a \$75 million settlement with Kano state government to compensate victims, and in February this year it settled all remaining lawsuits on undisclosed terms.

Other controversial cases in recent years have involved the testing of AIDS drugs in Africa, breast cancer and anti-psychosis drugs in India, and vaccines in Latin America.

History suggests we need to remain vigilant -- and it is not only commercial operations that can be culpable. Last October, U.S.

President Barack Obama personally apologized for an experiment conducted in the 1940s in which U.S. government researchers deliberately infected Guatemalan prison inmates, women and mental patients with syphilis.

ETHNIC DIFFERENCES

Today, the drugs industry insists, things are very different and its conscience is clear over the way modern clinical trials are conducted. The same strict standards apply to foreign trials as to those conducted domestically.

"We have exactly the same protocol and exactly the same standards for our trials around the world," says Roche Holding AG Chief Executive Severin Schwan, who is impressed by the modern hospitals he visits these days in places such as Brazil and China. "Some years ago quality might have been a real concern. Today the situation is different. This is a reason why more trials are being conducted in emerging markets."

The Swiss company, the world's largest maker of cancer drugs, is also doing more trials in these places because the healthcare authorities there want to see data collected from their own populations.

"I see this as an opportunity. A broader range of patients can take part in our trials and the patient population of our trials becomes ethnically more diverse ... If we do not include a certain portion of patients in our global trials, some countries might delay the approval of certain drugs," Schwan says.

That ethnic issue is important. As drug treatments become more targeted, scientists are unraveling how small genetic variations may make one medicine suitable for a particular group of people. AstraZeneca's lung cancer drug Iressa, for example, failed to help Western patients overall in tests but proved much more effective in Asians -- a discovery that has shed valuable new light on ways of tackling the disease worldwide.

"We are starting to understand ethnic differences through the responses seen in global trials. If each of us were an island unto himself, there would be no way we could make this comparison," says Dr. David Kerr, president of the European Society for Medical Oncology. "By cherishing our genetic diversity we can identify biomarkers like the one for Iressa. That is really exciting."

For drug companies looking to globalize their vast portfolio of clinical trials it all boils down to two over-riding factors -- time and money. And in this business, where the clock is always ticking down to the next drug patent expiry, time also means money because shaving six months off drug development timelines can spell hundreds of millions of dollars of extra sales.

So it is perhaps surprising that many in the industry are still struggling to work out just how much cheaper it really is to do clinical research in faraway places.

Back in 2008, former GlaxoSmithKline Plc Chief Executive Jean-Pierre Garnier gave a startling estimate of savings in an article for the Harvard Business Review, when he said a midsize company with 60,000 patients in clinical trials could save \$600 million a year by switching 50 percent of its trials to low-cost places such as India and Latin America. A top-rate academic medical center in India would charge just \$1,500 to \$2,000 per patient case report, while a second-rate U.S. center would bill \$20,000, he said.

In practice, things are a bit different, according to Kenneth Getz, senior research fellow at the Tufts Center for the Study of Drug Development in Boston. He believes off-shoring clinical research is not quite the bargain many drugmakers had thought. Getz reckons the per patient cost of running a trial in India and China is probably about half what it would be in Western Europe or the United States -- a big margin, of course, but considerably less than Garnier had suggested. And then there is the considerable extra cost of managing multiple studies across myriad sites.

"The economics are not nearly as attractive as once thought," Getz says. "Clearly, companies want to test their drugs in markets where they hope to commercialize a new treatment, so that is a driver for deciding where to conduct clinical studies. But given the increased operating costs and the inefficiencies, which can sometimes result in delays in some parts of the world, I think companies will begin to rethink just how many countries they wish to use."

FAIR PAY OR BRIBE

Reputational issues, too, may weigh on gung-ho Western drugmakers -- not only because of the rising public profile of the issue but also as a result of some new legal questions. In the United States, the Justice Department has mounted an investigation under the Foreign Corrupt Practices Act to see if drugmakers are offering overseas bribes, and clinical trials are firmly in the spotlight. That's because doctors in many countries are government employees and therefore any payments to them deemed above fair market value might be viewed as bribes. Britain, too, is introducing a strict new Bribery Act in July that also covers such overseas payments.

"Companies have to be aware that there is a legal power here and there is the possibility of prosecution," says Lincoln Tsang, a partner at the London offices of law firm Arnold & Porter LLP. "It adds a level of uncertainty and companies will have to do more due diligence to ensure that any new clinical trial site will really add value to the existing network."

In the offices of the European Medicines Agency in London and the FDA in Washington, plans are afoot to ramp up inspections of foreign clinical trial sites to check protocols are being followed and there is no risk of dodgy data that could skew approval decisions in the West and jeopardize patient safety. Getz expects both agencies to audit many more sites this year and next to address these concerns.

Yet the action will only scratch the surface and the small teams on tap at the EMA and FDA will be able to check only a fraction of the tens of thousands of trials conducted outside their own territories.

Back in Hungary, Dr. Horvath is very confident about the way clinical trials have been conducted over the years at his hospital and has the raw data going back decades to prove it. "Obviously you need to follow good clinical practice and stick by all the ethical criteria," he says.

But he is still waiting for the first knock on the door from the FDA. (Additional reporting by Ransdell Pierson in New York, Ee Lyn Tan in Hong Kong and Katie Reid in Zurich; Editing by Jim Impoco and Claudia Parsons)

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