GILLES SABRIÉ FOR *NATURE*

THE SECRET WAR AGAINST COUNTERFEIT SCIENCE

CHINA HAS A LUCRATIVE MARKET FOR FAKE RESEARCH REAGENTS. NOW SOME SCIENTISTS ARE FIGHTING BACK.

BY DAVID CYRANOSKI

In 2013, Huang Song walked into a printing shop in northwestern Beijing and stumbled upon evidence of a brazen and widespread criminal enterprise. Huang was just 15 kilometres from Beijing's National Institute of Biological Sciences, where he does synthetic-biology research. Scouting out a small desktop machine to produce the hundreds of labels needed for his experiments, he asked if a certain model could print on heat-resistant paper. The shop owner proudly pulled out some samples he had made for customers using the same machine.

Huang was shocked to see names such as Abcam and Cell Signaling Technology on labels that looked exactly like those on vials of expensive antibodies produced by the Western companies. Although the writing meant nothing to the friendly shop owner, for Huang it directly corroborated what he and a number of his colleagues had long suspected: many of the antibodies sold by Chinese distributors were not what they were supposed to be. Counterfeiters were getting fake and diluted research reagents on to the market, and this shop in Zhongguancun, Beijing's premier technology park, was one of the places they were buying machines to make their labels. "I had a suspicion. That confirmed it," Huang says.

China is famous for knock-off DVDs, Louis Vuitton bags and Rolex watches. But counterfeit reagents aren't on sale in busy public markets. They are sold through sophisticated websites, mixed in with legitimate supplies, and sourced and sold using a network of unwitting partners, such as the Zhongguancun shopkeeper. Even university cleaning staff have been implicated in the hidden process that creates counterfeit laboratory products, including basic chemistry reagents, serum for cell culture and standard laboratory test kits. Although it's

Huang Song has taken steps to stem the purchase of counterfeit reagents at the National Institute of Biological Sciences in Beijing.

difficult to quantify the effects of this illegal trade, Chinese scientists and some in Europe and North America say that fake products have led them astray, wasting time and materials.

Some in China fear that the problem could undermine the country's efforts to become a world leader in science. Options for combating the counterfeiters are limited. Reagent companies whose brands are tarnished — and the scientists taken in by fakes — shy away from legal action, partly because of embarrassment and partly because they have little faith that law-enforcement agencies can make much of a dent in the trade. "You cannot stop them from trying. The profit margin is just too high," says Huang.

Scientists and suppliers are now devising strategies that could help change the equation. Major reagent manufacturers have launched educational campaigns. Scientists are sharing their tales of frustration, along with tips for avoiding fraudulent supplies. And Huang has helped to establish a partly government-owned reagent-importing enterprise that takes advantage of new customs and quarantine procedures — something that could help shrink the market for fakes. But these measures won't help everyone. Researchers at universities and institutes outside hubs such as Beijing and Shanghai are especially at risk. "I know a lot of labs who still buy and use fake imported chemical reagents," says Can Xie, a biophysicist at Peking University in Beijing. "I feel sorry for them."

SUPPLY CHAIN

China is an attractive target for this specialized form of counterfeiting. Investment in research has expanded rapidly — the biomedical-science budget for the National Natural Science Foundation of China has quadrupled over the past decade. And the sheer size of the country means that foreign companies, unable to keep up with demand and loath to navigate China's tricky distribution system, have become dependent on local distributors. "The country poses many distribution challenges and shipping is logistically difficult," says Jay Dong, global vice-president and Asia Pacific general manager for Cell Signaling Technology, an antibody manufacturer based in Danvers, Massachusetts.

So local companies often carry out the much-needed role of distribution. Some are authorized by the manufacturers. Many are not, however, and it is often difficult for scientists to tell the difference, says Jack Leng, chief executive of Shanghai Universal Biotech, one of the largest distributors of antibodies in China. Disreputable merchants can take advantage of the inflated prices and long waits created by China's laborious customs and quality-control measures. They offer low prices and fast service for what appear to be the same products, sometimes claiming that the goods have been smuggled into the country. "We do notice counterfeiting in China more than other countries," Dong says.

Xie, who worked in the United States as a postdoc, says that it took him a few years after his return to China in 2009 to realize that some chemical reagents he was buying were sub par. Distributors, he says, claimed to represent foreign companies with premium products, but were actually selling cheap, domestically produced versions. He cannot say conclusively that impure, low-quality reagents were to blame for failed experiments, but he adds that "mysterious, insoluble stuff" he found in some solutions should have been a warning sign. He now buys only from well-known companies with branch offices in China.

Huang, who is deputy director of administration at his institute, witnessed a colleague facing similar frustrations in 2012, when, for six months after publishing a paper, he found that he couldn't repeat the results of some experiments. The researcher went through all the normal troubleshooting steps and asked colleagues for help. Finally, he discovered that a reagent used to introduce DNA into cells was hampering his replication efforts. Huang now attributes the problems to a counterfeit. "The last thing you think about is the reagent," he says. "This is the kind of stress you cannot put a price on."

Counterfeit antibodies are a particularly widespread source of frustration. Antibodies are crucial in a variety of biological experiments, offering the ability to label and track proteins in a range of living systems. But even untainted ones present some difficulties: there can be natural variation from batch to batch, and they may target unanticipated proteins.

These layers of uncertainty make fakes hard to ferret out. "When you look at a negative result it could be many reasons," says Zhu Weimin, senior vice-president of antibody technology for Abcam, which is headquartered in Cambridge, UK, but has a regional base in Shanghai. "The problem is serious."

The effects of this confusion and uncertainty are not limited to China. In 2012, for example, researchers in London and Białystok, Poland, reported using an antibody-based kit, called an ELISA, to detect a certain protein in the blood of people with chronic kidney disease[1]. But when kidney-disease specialist Herbert Lin of Massachusetts General Hospital in Boston purchased the same kit — branded as a product of USCN Life Science in Wuhan, China — and subjected it to rigorous testing, he found that it targeted another protein altogether[2]. The authors of the original study agreed it was now clear that the antibody was targeting the wrong protein[2]. "The fact that we did not receive replies from the manufacturers in relation to a couple of e-mails about their assay should perhaps have alerted us that something was not quite right," they wrote.

Cancer researcher Ioannis Prassas of Mount Sinai hospital in Toronto, Canada, had a similar experience with USCN-branded ELISA kits. Prassas says his team spent two years and some US$500,000 trying to identify the problem[3].

Chris Sun, who heads technology development at Cloud-Clone Corporation, the company in Wuhan that sells USCN products, says the company investigated the kit purchased by Prassas, but never identified the problem. It partially reimbursed Prassas. Sun denies that the company intentionally sold bad antibodies. "We have thousands of antibodies that we produce ourselves. We have no reason to use fake antibodies when we have the real ones," she says, adding that they have no record of a complaint about the kit Lin found problems with.

Most of USCN's kits are sold through distributors, Sun adds, and the company has sometimes found counterfeits posing as USCN products.

Estimating the scale of the issue is difficult, although some companies are trying. Late last year, Abcam tallied up roughly a year's worth of concerns that it had received from scientists in China about the authenticity of Abcam-labelled products. After checking barcodes, lot numbers and purchase times, the company determined that counterfeit products were to blame for 42% of the hundreds of cases raised.

SECRET INGREDIENTS

What scientists are getting in the vials can vary. Sometimes, cheap, common antibodies are relabelled and sold as expensive, rare ones, says Jade Zhang, general manager of Abcam's Shanghai branch. The counterfeiters will try to find an antibody of similar molecular weight so that scientists who do a quick test to verify the reagents won't be alarmed. But in experiments, the antibodies will miss their targets.

More common than antibody substitution is dilution. Counterfeiters buy authentic products from Chinese distributors or from overseas, then dilute one packet to make five, says Leng. "Customers get much weaker versions. Sometimes they can use them, sometimes not."

The counterfeiters "work hard to replicate our packaging, creating tubes and labels that resemble our own so closely that it can be difficult to tell the difference", says Dong. "The counterfeiting problem seems to come from a small but active segment in the market."

And many of the players don't realize they are involved. The Zhongguancun shop owner had no idea he was mixed up in illegal activity. "They are all part of a chain, but they are not evil," Huang says.

In 2015, Huang noticed a cleaner in his lab plucking empty bottles out of the rubbish and setting them aside. Confused, he asked why. "I warned her that she shouldn't drink from them," he says. She told Huang that someone was coming to buy them for 40 yuan (about US$5) a piece. It was another 'a-ha' moment.

The bottles had originally contained fetal bovine serum (FBS), a

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At a printer shop similar to this one in Zhongguancun, China, a researcher found evidence of the counterfeit-reagents trade.

ubiquitous cell-culture product derived from blood harvested at slaughterhouses. But a ban on imports of beef products from the United States, Australia and New Zealand, because of infectious diseases, had put a stranglehold on the supply of high-quality FBS.

The price for reserves of serum from banned locations has doubled over the past few years, to about 10,000 yuan per bottle. Low-quality FBS from other sources costs about one-quarter as much as the banned imports, but it is a poor substitute. Thermo Fisher Scientific of Waltham, Massachusetts, which makes one of the most popular brands of serum, noticed the problem and created labels and bottles that are difficult to duplicate. That's where the cleaner's 'recycling' efforts came in. Counterfeiters can simply refill the bottles with low-quality FBS and charge premium prices.

It's hard to know how widespread the problem is, but Huang offers a back-of-the-envelope estimate: given the number of bottles consumed and discarded by major labs, the potential market for FBS counterfeiters in Beijing alone could be tens of millions of yuan per year.

Counterfeiters are slippery, moving targets. In most cases, distributors will return payment or replace goods if a customer complains. That means there is no way for researchers to make a legal claim about their lost time and resources, which are the real cost. "Police will only look at direct loss — which is nothing," says Leng.

Companies lose revenue and may suffer dilution of their brand, but they also have little recourse. Abcam confronted some of the unauthorized distributors that were supplying apparent counterfeits of its products. The distributors said that they did not know where the antibodies had come from or how the problem occurred. Lawyers have advised against pursuing legal action, which would be costly and probably not get far. "If we shut one down, another would just pop up," says Zhang. Leng agrees. He says the counterfeit companies, usually one or two people, "register a new company every year, then do the same business again".

And some scientists, although angry, don't want to make a fuss, which would draw attention to the fact that they had been using counterfeits, says Zhang. The admission might raise questions about their previous research results.

DISINCENTIVE PLAN

Huang himself doesn't want to follow up with the cleaners, printers and others who are cogs in the counterfeiting machine, because they are just trying to earn a living. "If the printer makes 1,000 copies of a label, what's wrong with that? The people who sterilize the bottles — they are probably doing a really good job," he says.

But scientists can take action in other ways. Huang centralized ordering for his institute's most common reagents, so that for the majority of purchases he can ensure scientists are not being duped. And he set up a system that requires researchers to return an old FBS bottle before they can get a new one; the used bottles are destroyed.

Others told *Nature* that after having been burnt, they pay higher prices to avoid third-party distributors. Luo Wei, a chemist at the Shenzhen Academy of Metrology and Quality Inspection, a third-party testing company, says that a starch-catalysing enzyme he bought had a suspicious smell and packaging. Its label said it came from Sigma-Aldrich of St Louis, Missouri, and the batch number and related information matched details of products on the company's website. But Sigma confirmed that the white bottle it came in was not something it used for that product. It was counterfeit.

Some reagent companies have also developed programmes to fight counterfeiters. Abcam, Cell Signaling Technology and Universal Bio have been teaching current and prospective customers how to spot fakes through seminars and online manuals. They've also opened complaint lines for those who suspect forgery. "The choice was to take legal action or educate our customers. We chose the latter," says Zhang.

Scientists can work together to spread awareness. Online chat rooms are full of advice, often based on experience, about how to avoid counterfeits. Some include blacklists of companies that have been found to deliver bad products.

But for the many scientists in China outside major research hubs, there are fewer choices of distributor, and the word may not be reaching them, says Zhang. They may also have less funding, so price becomes a factor. They are more likely to be persuaded by claims that they are buying smuggled, high-quality goods at a low price. "We think most customers do not know they've been given a counterfeit," says Zhang.

Huang says the ultimate solution is to destroy the profitability of the enterprise. He helped to establish iBio, a 60% state-owned company that opened in December 2015 and brings customs and quarantine inspection under one roof, right on his institute's campus. Huang, who doesn't profit from the business, says most reagents are now available within ten days, compared with the month or more it might have taken before. Similar companies have been established in Shanghai and Suzhou.

The speed puts Chinese scientists on an even footing internationally. "For each experiment there are one or two reagents that are a bottleneck," Huang says. If Chinese scientists need months to get something that others get in days, "there's no way Chinese science can compete with the outside world", he says.

It was that logic that in 2012 helped convince government officials to amend regulations, enabling expedited imports of biological reagents. But change has taken time.

Huang is grateful for these improvements because they promise to make Chinese science more competitive. An added benefit might be the direct impacts on counterfeiters. "If you get rid of the customs burden, you destroy their profit margin," Huang says. That's better than tracking down culprits, to his mind. "If you cut out the source, you don't have to go after them," he says. ■

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