THERMO FISHER SCIENTIFIC

PASS OR FAIL Thermo's TruScan Raman device can identify drug substances through packaging.

FINDING FAKES

In the fight against **COUNTERFEIT DRUGS,** instrumentation companies are developing technology that is portable and easy to use

ANN M. THAYER, C&EN HOUSTON

IN MAY, THE Food & Drug Administration warned consumers about a counterfeit version of Adderall, an attention deficit hyperactivity disorder drug that's in short supply. The agency's laboratory tests revealed that tablets being sold on the Internet contained pain medications rather than the correct active pharmaceutical ingredients (APIs).

The bogus product was easy to spot. The drug had been packaged in blister packs, rather than the original manufacturer's bottles, and the label contained misspellings. The tablets were the wrong color and lacked the proper markings.

Not all counterfeit drug detection is this easy. Many counterfeiters are highly sophisticated, making it hard to uncover fakes by their packaging or appearance. To defend against these threats, pharmaceutical firms are creating harder-to-copy packaging and using identification technologies to track their products.

Despite advances by drug firms, counterfeiters find ingenious ways of getting around track-and-trace techniques, says Jerry Sellors, infrared product planning manager at the scientific instrument maker PerkinElmer. Although Sellors believes the approach will remain an essential defense, detection ultimately depends on deciphering the chemistry. "You need an analytical instrument to detect subtle differences between products," he says.

Differences between falsified and genuine drugs are often minor variations in formulation or in the amount of an API and its physical form. As the detective work becomes harder, "it is demanding more analytical horsepower," Sellors adds. Instrument suppliers must be able to provide lab-quality analysis in devices that work easily in the field.

Demand for such instruments is coming from pharma company security staff, health ministries, regulators, and law enforcement agents who want to quickly identify fake drugs before they move into commerce or patient's hands. Testing at transit, distribution, and sale locations requires devices that are portable, rugged, and reliable. Ease of use by nonexperts—which means no sample preparation, reagents, or consumables—is important. And nondestructive testing is desired to preserve evidence.

"The whole anticounterfeiting world has relied on taking samples from suspect pharmacies and bringing them back to a central lab for testing," says Maggie A. Pax, a senior director for portable analytical instruments at Thermo Fisher Scientific. "That's not very effective in actually shutting down counterfeit sales because of the time lag involved."

Rapid, field-based screening can help officials determine whether to detain or release products. "It's a net to catch bad materials and guide you on whether you need to do some more testing back in the lab," Pax says. "It reduces the workload because you are only sending a fraction of the samples back compared to what you would have been doing before."

Nigeria's National Agency for Food &

"There is a whole range of counterfeits out there. Some are very dangerous and some are only economically dangerous."

Drug Administration & Control has used Thermo's handheld TruScan RM instruments since January 2010. The Raman devices have aided the seizure of thousands of counterfeit medicines, mostly malaria drugs. Fake antimalarials with low API levels are believed to be a major factor in the growing drug resistance among disease-causing parasites.

Likewise, Bruker Optics has sold more than 360 of its MPA-brand Fourier transform infrared (FTIR) multipurpose analyzers to the Chinese State Food & Drug Administration for use in mobile labs, according to Bruker Applications Scientist Yan Wang. The MPAs replaced chromatography methods that are "time-consuming, labor-intensive, and not fast," he says, and that also consume samples and require solvents. Bruker provided China with hardware, methods, and support services worth more than $15 million.

Agilent Technologies has also helped equip China's van-based labs. Mobile labs can contain gas and liquid chromatography, mass spectrometry, and other analytical systems modified to work under field conditions, says John Seelenbinder, Agilent senior applications and product manager. For pharma applications, the company offers the 4500 portable FTIR spectrometer and handheld 4100 ExoScan FTIR device.

Similarly, PerkinElmer's Spectrum Two portable IR system is designed to handle "tough environments," Sellors explains. For example, it can operate in humid locations without air-conditioning. "Some of those tough environments are among our fastest-growing markets, where there is a growing interest in counterfeit detection," he says.

Counterfeit medicines are found worldwide, according to the World Health Organization, but they are most prevalent where law enforcement is the weakest. WHO's International Medical Products Anti-Counterfeiting Taskforce estimates that counterfeits make up about 10% of the global pharmaceutical market, up to 30% of drugs in some developing countries, and as much as 50% of medicines sold over the Internet.

The Pharmaceutical Security Institute, a nonprofit group set up by security directors from major pharma firms, collects data on counterfeiting, illegal diversion, and theft. It found 1,986 such incidents worldwide involving 532 different products in 2011. According to PSI, both branded and generic drugs are targets. Anti-infective, genitourinary, and cardiovascular drugs are the top categories.

If the counterfeiters "don't do a good job of matching the chemistry of the pill, we are going to find it."

Asia accounted for about 40% of reported incidents, followed by Latin America at about 16%, PSI reports. About half the total incidents involved customs seizures or police and health inspector raids, and about half were "commercial scale" involving more than 1,000 dosages.

PERKINELMER

MOBILE TEST PerkinElmer's compact Spectrum Two can analyze intact drug tablets and requires no sample preparation.

Falsified pharmaceuticals are designed to cash in on the name and market share of a premium brand but with none of the development costs. "There is a whole range of counterfeits out there," Seelenbinder points out. "Some are very dangerous, and some are only economically dangerous."

Nearly identical copies present the least danger from a public health perspective but can cause the greatest financial harm. Illegal generic versions launched before a patent expires or genuine drugs that have been stolen and repackaged sometimes fall into this category. If the workmanship is top-notch, these products are the hardest to uncover. They are also the most expensive to make.

FOR BIGGER PROFITS, counterfeiters want products that cost little to create, including those that have no API or the wrong API. Some contain random, even toxic, fillers and impurities. Although such pills are designed to look the part, they won't provide the desired therapeutic effect and, in the worst case, can cause serious harm.

Other times, counterfeiters want to delay detection and have repeat business. To do so, they incorporate enough of the correct API to pass simple wet-chemistry tests or so a patient experiences some of the taste, side effects, or sensation of the real drug. Other cheap APIs may be substituted to fool patients by producing similar effects.

Fortunately, the more dangerous counterfeits containing no, wrong, or inadequate APIs can be uncovered with the right analytical equipment. If the counterfeiters "don't do a good job of matching the chemistry of the pill, we are going to find it," Seelenbinder says.

To do the detective work, mid-IR, near-IR, and Raman spectroscopy have emerged as popular approaches. These methods are simple, fast, and selective, and they can analyze solids with no or limited sample preparation. Features in the spectra of drug samples act as identifying fingerprints.

"You can select an absorption band corresponding to the absorption of the API, or you can select other regions corresponding to other materials like the coatings and capsules," Bruker's Wang explains. The company's MPA near-IR system is modular and can analyze liquids, solids, powders, and tablets. An automated sample wheel holds 30 intact pills.

IR and Raman spectroscopy are widely used across the pharma industry supply chain, explains Curtis Marcott, a consultant with Athens, Ga.-based Light Light Solutions. Raman devices are often used to inspect incoming raw materials in a manufacturing plant; IR methods are common in process and quality control.

Most analytical instrument makers now offer portable or handheld spectroscopic devices, often battery operated, for materials detection applications. Although the techniques may differ in sensitivity and complexity, they all typically collect and process information in less than a minute, even in a few seconds. Users are generally guided by on-screen instructions.

Data collection and analysis software may be onboard a device or accessed wirelessly. Although the number crunching is in the background for the user, the raw data generally are available for further analysis, review, and storage, suppliers say. This traceability is important for law enforcement or regulatory compliance purposes.

AGILENT

SELF-CONTAINED Agilent's 4500 infrared spectrometer comes in a portable case.

Most devices are designed to give unambiguous pass/fail responses after comparing sample data with reference information on known or genuine materials. "You don't get data at the end; you get an answer," Seelenbinder says.

Chemical and physical differences in fake products will generate spectra distinguishable from those of authentic ones. A material is deemed counterfeit if there isn't a statistically acceptable correlation with data for the genuine product. Although this approach confirms whether a product is counterfeit, determining why it failed or what exactly it is can require further testing.

Straight out of the box, some analytical systems contain reference data, but they may need to be educated about specific target products or materials. These added spectra will be composite pictures of existing drug products. "Many times pharmaceutical companies don't want to reveal their exact formulation," Seelenbinder says, so the drug firms generate their own libraries.

Instrument makers also build libraries as a service to end users, says Michael Lands, vice president for marketing and sales at ASD. The Boulder, Colo.-based company offers a portable visible/near-IR spectrometer called the LabSpec 4. In late 2011, FDA and the U.K.'s Medicines & Healthcare Products Regulatory Agency bought LabSpec systems for counterfeit drug analysis.

Raman and IR techniques differ but are complementary in what they can analyze, Marcott says. Generally, Raman methods are good at chemically detecting APIs, whereas IR analysis picks up both the API and the inactive ingredients, known as excipients, he says. IR spectroscopy is a broadband technique; Raman methods use a single-frequency laser to which something in the sample must respond. Other sampling modes and configurations will also extend what any one spectroscopy can do.

For example, Raman methods tend to give well-resolved surface signals, and in specific detection modes, they can provide information about sample interiors or even package contents. Like Raman methods, mid-IR spectroscopy has good specificity, but it is more of a surface technique. Near-IR spectroscopy is useful for probing in bulk or solid samples but generates more complex and somewhat harder to interpret spectra.

"Pills are relatively homogeneous, and looking at the surface or one face will generally give you a good view of the entire pill," Lands says. "In most pharmaceuticals, the active ingredient is a very small percentage of the whole pill," he points out, but it is still detectable.

A DIFFERENT PROBLEM may be finding subtle differences in colorants or excipients in counterfeits. "The active ingredient may be the correct type at the correct dose, but the binders and excipients are done cheaply," he says. "Most of the time near-IR does a very good job at differentiating and isolating all the components."

The detection technique choice "depends on what question you are trying to answer," Thermo's Pax says. "Raman is

qualitative, whereas near-IR can be quantitative and also look at other properties of a material." What one is trying to determine—whether a product has the right ingredients, adequate amounts, or is in the proper form—will dictate which technology is best suited, she adds.

In addition to the Raman-based TruScan, Thermo offers a handheld near-IR instrument called the MicroPhazir. The company acquired the technologies through the 2010 purchases of Ahura Scientific and Polychromix. Competing handheld Raman instruments for material identification are made by Intevac's DeltaNu division, Cobalt Light Systems, and Rigaku, which acquired BaySpec in late 2011.

"The ideal technology tends to depend on the sample itself," PerkinElmer's Sellors says. "IR can discriminate fine differences between similar formulations from different manufacturing plants. Quite often we see that the difference between a genuine and counterfeit product is a subtle change in the ratio of the various ingredients."

To distinguish these subtleties, the instrument may have to be set up with an exhaustive reference model. "You have to build a model that encompasses all of what we call the 'spectroscopic space' that good samples will occupy, and that means teaching the system with all the spectra of genuine material," Sellors says. For drug manufacturers, this process involves looking at product samples from different plants or suppliers.

Although the approach requires work up front and involves more data, "you have the ability to measure small differences and statistically say if the chemistry is identical to a group of manufacturing samples," Seelenbinder says. Having a complete database might also prevent calling a genuine drug counterfeit just because it originates from a different plant.

REMOTE TESTING

Minilabs Offer An Affordable Chemistry-Based Approach

Portable and handheld analytical devices for counterfeit drug detection can cost anywhere from $10,000 to $50,000. To make testing accessible in developing countries where counterfeiting is widespread, the Global Pharma Health Fund has provided the wet-chemistry-based GPHF-Minilab since 1998. GPHF has been funded exclusively by Germany's Merck for the past five years. International organizations participate in programs to use and distribute the Minilabs.

Housed in two suitcases, the $4,700 Minilab contains lab ware and reagents to run about 1,000 thin-layer chromatography (TLC) tests and at least 3,000 dye tests. Drug identity and quality can be verified, and counterfeits detected, through the kit's simple physical and chemical tests, along with available reference standards for comparison. Methods include visual inspection of dosage forms and packaging, disintegration testing to confirm formulations, color reactions to identify a drug's presence, and TLC to check drug content and potency.

The self-contained lab doesn't require special storage and can work outdoors in tropical climates. Reference standards have a shelf life of about two years, and reagents can last for at least five. Manuals provided in different languages "read more like a cooking recipe than an instruction booklet," GPHF states, and are "written in a nonscientific format and rich in illustrations." Training is also available.

The $3,200 TLC portion works for 58 drug compounds, and the $1,500 dye test part covers 32. The compounds were selected "on the basis of prevailing prescription practices, public health interest, and existing counterfeit case reports," according to GPHF. Its list includes antimicrobials, anthelmintics, antiretrovirals, antimalarials, and antituberculosis drugs.

Variations in legitimate manufacturing, however, are generally quite small because of tight controls and careful monitoring. Pharmaceutical manufacturers are in the business of making highly reproducible products and usually validate them spectroscopically to meet regulatory requirements.

"Even a very good counterfeit manufacturer is going to have a hard time matching the precision that a name-brand pharmaceutical company can get across its plants," Seelenbinder says. Spectroscopy provides "great insight on not only the product fingerprint but also the process fingerprint," he adds.

Counterfeiters may inadvertently introduce impurities and variations during manufacturing and storage that can reveal them as the source. Spectra of counterfeits can be included in reference libraries to look for repeat offenders.

Consistent characteristics—such as crystal form, shape, size, and dispersal—are not easily duplicated by counterfeiters. "Particle size and distribution can be highly specific about a product's origin," explains Tom Tague, senior FTIR applications manager at Bruker Optics.

To capture the most sophisticated counterfeits, authorities need to look at the whole construction of the tablet instead of just the chemical composition. For this they often turn to IR imaging or microscopy, which provides spatial information on the contents of a solid sample rather than a single conventional spectrum.

By collecting thousands of spectra across a tablet, imaging will show the distribution of an API and the excipients. Information from any one pixel, or point in the sample, in the IR image still describes the chemical composition there.

In April, Bruker launched an FTIR microscope called the Lumos. Smaller than traditional IR imaging instruments, it is a self-contained device that can work in a mobile lab, Tague says. With automated sample positioning and scanning, the microscope is designed to be operated by nonexperts.

Besides seeing within a pill, many Raman and some near-IR devices can work through packaging, such as clear plastic bags holding raw materials or drug blister packs. In the mid-IR spectrum, signals from these plastics often interfere with those from the API. Although problematic, the information can be important, Sellors points out.

"In a number of our studies, when we have looked at differences between a genuine and counterfeit product, the telltale signals are actually in the fake packaging," he says. Specifically, changes in printing inks and polymer laminates may help identify out-of-date or stolen products that have been repackaged, he adds.

In addition to wanting to preserve drug packets, counterfeit drug inspectors would like to avoid opening shipping containers because they risk destroying valuable shipments of genuine products. Fortunately, radio-frequency (RF) radiation and response can travel through layers of wood, plastic, glass, and cardboard, explains Jamie Barras, a research fellow at King's College London.

A CONSORTIUM led by King's College is using this property in developing a portable quadruple resonance (QR) device. The RF method targets APIs, of which about 80% have the needed quadrupolar nuclei. Called Conphirmer, for counterfeit pharmaceuticals interception using radio-frequency methods in real time, the three-year project has $3.2 million in European Union funding.

Although a QR spectrum is simple, other parameters measured simultaneously can help identify an API. "It's also quantitative; you get a bigger response the more material is present," Barras adds. One year in, the partners have compiled a list of commonly counterfeited medicines crossing EU borders and are generating reference databases.

The QR method works only on crystalline materials, but its signals are sensitive to chemical structure, crystal form, impurities, and formulation and storage conditions. "We can tell how much of the active ingredient is there and if it is there in the form it should be, consistent with the manufacturing process," Barras says.

The King's College group and coworkers at Sweden's Lund University have created a similar QR device to scan small drug packages. In 2010, the project won a $737,000 grant from the Wellcome Trust, a U.K. charity interested in improving health care in developing nations. The Italian instrument company Stelar has built a briefcase-sized prototype and will help produce the Conphirmer system.

In counterfeit drug detection, needs vary greatly by user, product type, location, and resources. How a particular technique meets those needs will depend on the product of interest and the analytical challenge at hand. Finding answers can require trying a variety of approaches, Marcott, the consultant, says. "There isn't a magic bullet that will solve the problem." ■