Tablets & Capsules

Formulation Production Packaging

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Testing powder flow

On-dose authentication

anti-counterfeiting

On-dose authentication: Walking softly, prepared to stick

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While the exact size of the problem is unknown, counterfeit drug products harm patients and pharmaceutical manufacturers. This article discusses why on-dose authentication (ODA) is a superior anti-counterfeiting approach and how it can defray costs in other business areas.

Adulterated and unsafe drugs have threatened public safety since before President Theodore Roosevelt signed the Pure Food and Drug Act into law in 1906. Today, the distribution of counterfeit and/or uncontrolled medicines is an enormous problem, measured in the tens of billions of dollars [1]. The exact size of the problem is not known because of the illicit nature of the activity, but counterfeiting continues to attract sophisticated criminal organizations. Making fakes, after all, is a lucrative business for criminals. For drug manufacturers, however, counterfeiting—including adulteration and illegal diversion—reduces revenue, increases costs, exposes them to liability, and damages brand reputations. But most important, fake drug products put patients' lives at risk.

And counterfeiting is not the only risk to patient safety. With today's complex global supply chain, quality control can be a challenge. The recent federal investigation and attendant publicity involving GlaxoSmithKline (GSK) highlights this issue. In that case, which involved charges of mixing different drug products like diabetes medicine with antidepressants and of mixing tablets of different strengths in the same package, GSK pled guilty to felony distribution of adulterated drug products and paid penalties of $750 million [2]. ODA tools could have helped investigators and quality professionals quickly determine the provenance of the improperly packaged products and remedy the problems.

A virulent affliction

The demand for prescription drug products is strong, particularly for narcotic pain medication, life-saving pharmaceuticals, and so-called "lifestyle" drugs, such as those for treating erectile dysfunction. All of these drug products may cost patients a lot of money, depending on their health insurance plan, and many people thus seek less expensive options. For those without a valid prescription, internet pharmacies that peddle cheap, no-questions-asked drugs are alluring. They're usually also unreliable [3]. In less-developed countries, where supply chain security is weak, counterfeits may account for as much as 25 percent of the pharmaceuticals in the market [4]. Furthermore, price differences across geographic markets create arbitrage opportunities for people to exploit.

Plus, the laws against pharmaceutical counterfeiting and diversion carry relatively light criminal penalties. Therefore, distributing legitimate-looking erectile-dysfunction pills and anti-depressants entails minimal risk compared to other illicit activities, such as manufacturing methamphetamine or trafficking in cocaine or heroin. Pharmaceuticals are high-value items that are easy to transport, often simple to mimic in appearance and, until recently, impossible to trace at the dosage level.

The appeal of ODA

Pharmaceutical manufacturers have long battled the counterfeiting problem with a variety of measures: holograms, specialty inks, tamper-evident seals and, more recently, radio frequency identification tags. Again and again, counterfeiters have persisted in spoofing these package-level security measures.

Besides, there is no guarantee that authentic packaging contains authentic medicine. That's one of the biggest shortcomings of current e-pedigree and track-and-trace legislation: The focus is on the provenance of the package, which doesn't allow you to verify whether the medicine inside is legitimate or counterfeit.

Thus innovative brand owners are turning to ODA methods that mark or tag individual unit doses at the batch level, allowing you to distinguish between real and fake drug products. In addition to marking the individual tablet or capsule and bridging the gap in the pedigree chain, ODA offers brand owners the opportunity to extend this sophisticated tracking technology to other areas of their business. That's an important consideration because regulatory obligations, such as risk evaluation and mitigation strategies (REMS) and e-pedigree, require manufacturers to exercise more control over their supply chain. ODA can help do that as part of a multi-layered system that secures and tracks pharmaceuticals. That helps manufacturers protect the essence of their brand: the quality of the medicine itself.

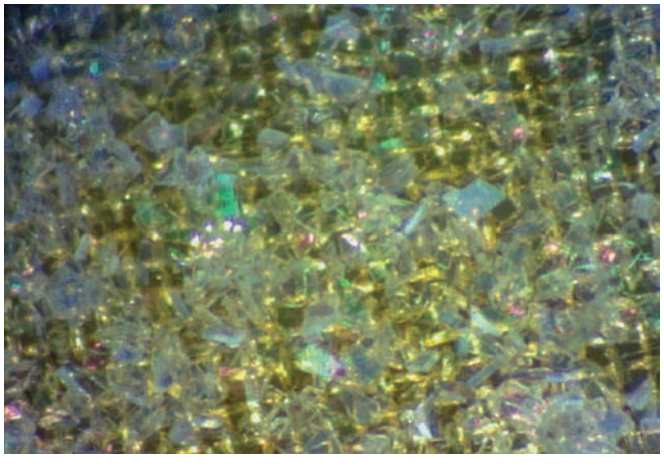
FDA support for innovation

A 2009 FDA draft Guidance provides a pathway for regulatory compliance when using an ODA system containing physical-chemical identifiers (PCIDs) at the dosage level [5]. The FDA has also noted its responsibility to "harness the latest advances in science and technology to improve the health and well-being of American consumers" [6]. That obligation includes "strengthen[ing] the safety and integrity of the global supply chain" for foods and drugs, one of the FDA's four strategic priorities.

Furthermore, the FDA emphasized one of its signature programs, the Analytical Tool Initiative, which focuses on identifying rapid analytical tools and putting them in the hands of field investigators and scientists. In fact, in 2010 the FDA trained field investigators how to use a counterfeit detection device and a toxic elements detection device to find and combat counterfeit drug products. As the FDA gains experience with these tracking and authenticating technologies, the agency, lawmakers, consumers, and other stakeholders will expect pharmaceutical manufacturers to make greater use of them. Additionally, the FDA will use its new technical expertise to promulgate other strategic priorities: stronger compliance and enforcement.

Assessing ODA systems

The FDA Guidance on PCIDs has also prompted brand owners to take a fresh look at innovative ODA



Micro-tags made of pure silica, a GRAS material. They can be encoded with one of as many as 1 trillion unique spectral signatures [9].

methods. Implementing a strategic ODA system requires planning, commitment, and a significant investment of time, money, and other resources. The ideal ODA system would address immediate needs and allow scale-up over the long term to justify the investment. To address immediate needs, look for an ODA system that demonstrates reliability, implements easily, and offers strong security. Fundamental questions include:

- Can the ODA system integrate easily into my existing manufacturing process and information technology framework?
- Does the ODA system allow automated authentication?
- How much training or expertise does the ODA system require?
- What kind of extraneous equipment is required to use the ODA system?
- To what extent does the ODA system rely on outside service providers?
- What regulatory hurdles might the ODA system impose that could delay or jeopardize drug product approvals?
- Do the security features of the ODA system truly defend against counterfeiters?

Furthermore, a robust ODA system should be equipped to evolve with the end-user's needs. Does it offer security features that can advance over time to meet an increasingly formidable and sophisticated enemy? Because the capabilities of counterfeiters will continue to progress, ODA defenses must as well. (Compare the security system of Blu-Ray DVDs, which allows manufacturers to renew and adjust security measures, to the one used with earlier DVDs. The early system had one security lock that, once broken, could not be repaired, and the secret key was thus available to everyone thereafter.)

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The ODA system should also scale up across the enterprise as a business tool in order to defray the cost of implementation and maintenance and to adapt to industry changes. The ODA system you select should offer a sound return on investment over the long term.

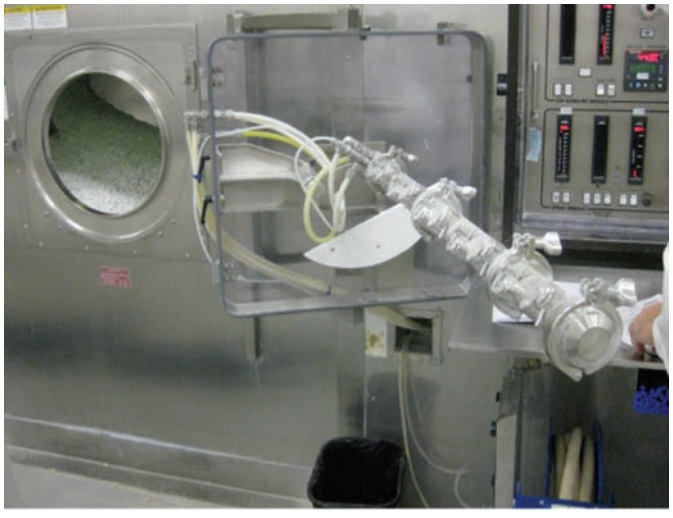
While you may implement an ODA system to address counterfeiting and secure your product, it should also serve a variety of departments and multiple applications, allowing you to cut costs or reduce risks. That alone could justify the cost of the entire ODA system. Examples include questionable product returns, mistakes in sample handling, REMS compliance, and clinical trials.

Securing product. Product security teams can use handheld readers to immediately authenticate or confirm as frauds products in the field. On-the-spot detection allows brand owners to identify leaks in their global supply chain.

Returns monitoring. Spot-checks of returned product can determine whether the tablets in the returned containers correspond to the merchandise documentation. Any discrepancy would allow you to reject a return and withhold refunds until the documentation is corrected. Returns are not a small problem. According to the Healthcare Distribution Management Association, as much as 2 percent of products are returned to U.S. pharmaceutical manufacturers for refunds [7]. For blockbuster products, refund errors could total tens of millions of dollars.

Quality control and sample handling. When workers take samples during manufacturing, on-dose taggants or markers indicate the lot from which the samples came. Quality incidents can be investigated more effectively.

REMS compliance. The FDA's focus on REMS obliges manufacturers to demonstrate control over the use and distribution of their products [8]. That can be a costly exercise, but penalties for products that don't comply with REMS begin at $250,000 for the first offense. An ODA system might be especially valuable in cases where



Micro-tags can be applied during standard coating operations.

the FDA mandates controlled distribution of a product. In fact, there's a debate right now about whether the FDA should impose greater control over Schedule II narcotics. But even products requiring basic REMS may benefit from an ODA system because it would demonstrate brand owners' concern for patients' well-being and offer a powerful management tool for compliance and planning.

Clinical trials. In blinded clinical trials in which the placebo and comparator appear identical to the investigative product, a covert ODA system provides dosage-level tracking of the many small batches used in a trial. A clinical research organization can use an automated ODA system to check and reconfirm the provenance of products in a blister pack without revealing the information to blinded patients or administrators. The importance of this dosage-level authentication increases as brand owners outsource and offshore clinical trials.

Types of ODA systems

The key is finding an ODA system that can support all these functions. There are several approaches on the market, including ones that use

- Botanical DNA, which can hold vast amounts of information as a forensic marker;
- Small fluctuations in the amount or ratio of key ingredients to differentiate between products or lots;
- Taggants of GRAS materials that bear symbols visible only through a microscope;
- Nano-size lithography or etching of the surfaces of tablets or capsules that is identified and interpreted by special equipment at authentication centers;
- Forensic markers at the core of a drug product that are recovered upon dissolution to confirm authenticity; and
- Unique flavorings and/or pearlescent or other specialized coatings that are difficult to mimic.

The technology that my company offers uses micro-tags of inert, edible, pure silica, a GRAS ingredient that has been used in foods and drug products for decades [9]. The micro-tags (photos page 29) are encoded with one of as many as 1 trillion unique spectral signatures. That allows great flexibility in on-dose and on-package labeling. The micro-tag can reveal lot number, authorized country of sale, customer name, shipment data, and dosage strength, as well as other information. It's also possible to link the labels of the micro-tags with an enterprise resource planning system to connect the dosage information with data related to the bottle, pack, carton, case, or crate.

The micro-tags can be applied in a standard pan coating operation (photos page 30) to cover a single tablet with multiple covert and secure spectral "bar codes." The brand owner can then implement this ODA system throughout the company, as described above. The micro-tags are analyzed by readers on a bench top, in the field, or at the manufacturing site. The randomized features of the micro-tags allow you to add even stronger security measures over time.

Conclusion

When evaluating ODA systems, investigate how they protect your brand, but also how they improve your business. FDA Commissioner Margaret Hamburg paraphrased Theodore Roosevelt in discussing the counterfeit problem: "In a moment of decision, the best thing you can do is the right thing. The worst thing you can do is nothing."

That describes today's reality. Companies that do nothing stand to lose the most. In the face of evolving challenges and new opportunities, opt for action and examine how implementing an effective ODA system can provide immediate and sustained benefits. *T&C*

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Counterfeits . . .

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Criminal
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All these terms describe counterfeit and diverted medications. ***On-going*** is also apt, because the criminal organizations that manufacture and purvey fake medicines show no signs of stopping.

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Join Marv Shepherd, Ph.D., as he scrutinizes the latest trends in spoofing medicines and enumerates the costs of fighting them. Shepherd is the director of the Center for Pharmacoeconomic Studies at the University of Texas's College of Pharmacy. He is also the President of the Partnership for Safe Medicine, an organization dedicated to combating counterfeit drugs.

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