

Will All Tablets and Capsules Have On-Dose Physical Chemical Identifiers Soon?

As the global problem of counterfeit and diverted drugs continues to grow worldwide, will our medicine soon carry secure identifiers woven into the very fabric of the drug product? Advancing technology is finally allowing drug makers the ability to implement on-dose authentication.

Pharmaceutical product security has become a multi-layered problem. Security of solid oral dosage form drugs has become serious business for pharmaceutical brand owners over the last few decades. From concerns with tampering—like the Tylenol scares in the 1980s—to untold counterfeiting and diversion of gray market drugs, which occurs today, drug companies have deployed dozens of security technologies and hired global teams of personnel to manage this ever growing risk. Some of these deployed technologies have included color shifting inks, complex holograms, up-converting particles that change color when excited by lasers, covert near-infrared and ultra violet inks, and the list goes on. Additionally, major manufacturers employ teams of experts to evaluate new technologies, integrate them into packaging lines and execute the enforcement and detection of these measures in the supply chain. It can be daunting and frustrating work.

But many brand protection teams have experiences of deploying security technology on a package only to see a credible counterfeit on the market within months. This constant threat of technology compromises results in drug manufacturers using 'layered' technology elements. This way, if one feature is defeated, the others are still in place until a rotation of a new technology can be implemented. This constant replacement cycle wreaks havoc on packaging integration and re-training teams of people proper detection methodology in the field. And yet, even with this heavy investment in multiple, rotating technology solutions and vigilance by product security teams, there is a gaping hole

in the defenses. While these measure might be able to help the brand owners be more confident that the packaging in supply chain is harder to duplicate and fool distributors and consumers alike, there is still no guarantee that the drug product inside is authentic or has not been improperly diverted.

PRODUCT SECURITY IS CURRENTLY FOCUSED AT THE PACKAGING LEVEL

Packaging-level security is therefore limited in its ability to authenticate the actual product. This creates obvious challenges for brand owners and gaping opportunities for the criminals looking to take advantage. Mimicking legitimate packaging often requires only limited sophistication including high-quality printing and packaging equipment to replicate the look and feel of the authentic package; including in some cases the duplication of the security features. Graphical design and digital printing advances make this process far more feasible today than it was 20 years ago. Moreover, some fake drugs have been discovered because the printing on packaging was of higher quality than the authentic original. Many symbols like traditional bar codes and modern QR codes and 2D bar codes are used to comply with new "track and trace" requirements, but they do not provide product authentication assurance. And because these symbols are visible, they are easily copied. Since packaging-level security measures have been regularly defeated for decades, the pharmaceutical industry sought measures that can provide security at the product level: "on-dose authentication."

CHEMICAL ANALYSIS OF THE DOSAGE FORM HAS LIMITATIONS

When a questionable shipment or sample is discovered, manufacturers seek to chemically analyze suspect drug product directly to determine if it is fake—i.e., it contains little or no active pharmaceutical ingredient. The company needs to confirm a compromised product by retaining the suspicious product and performing a destructive chemical analysis in a centralized laboratory. Handheld detectors using technologies such as Raman spectroscopy have helped shorten some of the review time by allowing product security teams to do a quick, in-the-field chemical analysis scan to flag potentially fake product. However, to obtain a higher confidence level result, these flagged samples still usually need to be sent back to the labs for a more complete, albeit complicated and time-consuming, laboratory analysis. Further, at the end of this analytical process, often the best conclusion that can be reached is that the suspect drug contains the correct ingredients in the appropriate amounts and ratios, which suggests that it is probably the authentic product. While this may provide a high confidence level that the drug was most likely (or not) made by the manufacturer subject to specific formulation and standards, it provides no certainty or absolute custodial link to a manufactured provenance.

REGULATORY CLARITY PROVIDES A PATHWAY FOR THE CREATION OF HIGH-SECURITY PILLS

For the last few years, drug manufacturers have contemplated the ability to mark the solid dosage form product itself with an indelible, safe, and covert technology in order to obtain more precision in the authentication of its products. Manufacturers petitioned the FDA for regulatory clarity on this matter and in response, and the FDA released its final guidance to the industry in late 2011 regarding the use of Physical Chemical Identifiers (PCIDs) in Solid Oral Dosage Form (SODF) drug product for the purpose of anti-counterfeiting. In this guidance, the FDA was clear in its preference that these potential PCIDs be 'known' and well-studied excipients such as substances that are generally recognized as safe (GRAS) or ingredients that are listed in the FDA's Inactive Ingredients Guide (IIG) in minimal quantities for this purpose. Under these scenarios, the FDA points out, it is far more likely that only small changes to regulatory reporting will be required and the drug will not have to be submitted for re-approval.

Now that the FDA has provided a clear path for utilizing these PCIDs on or in SODF drug product, how come every manufacturer hasn't automatically deployed them in their most important products?

The answer is complex.

Adding new ingredients to an existing, successful drug product franchise can seem risky. The manufacturing operations team will want to know what changes are required to the manufacturing lines to incorporate the PCID. The formulation teams will want to understand what effect, if any, will the PCID have on the functionality and performance of an already approved, well performing, and pharmacologically effective drug? The marketing and finance teams will want to know what the return on investment will be for incorporating the PCID at the dosage level—how much will it cost, and what will the quantitative and

qualitative benefits be for the franchise? And the global security team will want to understand how secure the solution is, how easy it is to use, and how it can help them prevent unauthorized activities or figure out how the criminals are attacking their global supply chain.

NEW ON-DOSE TECHNOLOGIES OFFER VIABLE SOLUTIONS

Thus, the challenge for on-dose authentication solutions providers is to satisfy and work with multi-disciplinary group of experts spread across a complex, global organization. Frankly, technologies that can satisfactorily address the foregoing question have not been readily available until recently.

Early pioneering technologies in the on-dose authentication space included GRAS beads printed with symbology and read under magnification; reagent kits using an immunoassay that turned the drug sample a certain color when secondary chemicals are introduced; nanolithography inscriptions interpreted by ultra-high powered microscopes; and spectrally coded GRAS silica particles that are machine readable in the field.

KEY CONSIDERATIONS FOR SELECTING AN EFFECTIVE ON-DOSE SOLUTION

Each of the aforementioned technologies provides some level of certainty that the dosage form under scrutiny has provenance traceable to a particular manufacturer. These and other new technologies indicate that there are a number of options for security-minded brand owners when implementing on-dose authentication. Some of the first questions that drug makers will want addressed is the ease and cost of employing the security measure with an existing product manufacturing, packaging and supply chain process. Will new equipment be required? Does the operational process need to be changed? Will substantial training have to be provided to current operations teams? An effective on-dose solution should be able to address these initial concerns satisfactorily and not create a significant burden on a franchise that is successful enough to be subject to attacks by counterfeiters and diverters.

Additionally, the drug maker will want to understand how effective the authentication solution will be, and what benefits will be gained as a trade-off for the time and resources required for investing in an advanced technology. On-dose authentication solutions with more sophisticated features will allow manufacturers to implement them for long periods of time and will not be susceptible to defeat within months like current packaging measures.

The first key feature to consider is whether the technology is covert. If the security features are not easily seen or detected, even by using a powerful microscope, then it will be very difficult for a counterfeiting organization to find and defeat these measures. The criminals will look for easier products to attack. Second, if an authentication solution is machine readable, it will provide faster analytical results and can likely be used in high-volume situations, offering for greater speed and efficiency. Also, the technology would be less vulnerable to the effects of human error in analysis and judgment. Third, an authentication system that can differentiate drug product at the batch level offers powerful product identification options. A brand owner would be able



production plants, dosages, and manufacturing lots can provide great flexibility in on-dose and on-package labeling. The micro-tag can reveal specific information the user selects, including authorized country of sale, customer name, shipment data, and dosage strength, as well as other information. It is 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 chosen method for application to SODF product is via the standard pan coating operation that already exists and has now been proven in trial manufacturing runs with multiple brand owners across the world.

to do more than just simply figure out if a product is real or fake. Rather, they would be able to distinguish between expired and unexpired product, because it could trace that particular product's point of manufacture. If specific batches were manufactured for a target geographic territory, the manufacturer could then identify if the product has been improperly diverted from a lower price-point territory to a higher price-point territory, thus protecting its profit margin. And in cases where a product has suffered a quality incident, knowing the batch the product came from and thereby enabling a manufacturer to quickly bound the scope of a potential recall and provide specific forensic information to determine if there is a quality problem in a particular part of its global supply chain. Further, the drug maker can tie the product intelligence found "on-dose" with the product information coded on the packaging, thereby providing a digital lock between the product and its packaging.

Further, in the long-term, with machine readability and batch serialization, drug manufacturers would be able to digitize these batches of high-volume, high-value SODF drugs and analyze the data as the product flow around the world through its global supply chain, supporting the growth and development of the Internet of Things.

A SIMPLE, YET ROBUST ON-DOSE SECURITY AND INFORMATION TOOL

TruTag Technologies, a provider of product authentication and brand protection solutions for several industries, works with PCID implementation, and has developed an on-dose solution featuring microscopic particles (tags) of inert, edible, pure silica (SiO₂), a GRAS ingredient that has been used in foods and drug products for decades.

These micro-tags are encoded with a unique spectral signature that is available from a vast library of codes. This unique ability to identify products at the batch level to differentiate between

With multiple covert and secure spectral "bar codes," the brand owners can apply tags to a product once, then implement this PCID system throughout the company for use in fighting counterfeits, detecting diverted product, monitoring the authenticity of returned products, managing product sample quality assurance during manufacturing (prior to packaging), and scoping and forensically investigating potential quality or recall incidents. The micro-tags are analyzed by proprietary readers on a bench top, in the field, or at the manufacturing site. The randomized features of the micro-tags allow even stronger security measures to be added over time.

ON-DOSE AUTHENTICATION HAS ARRIVED AND DRUG SAFETY AND SECURITY WILL INCREASE

While it is certain that PCIDs with substantive information and security capabilities will soon be on board a growing number of solid oral dosage forms, it may take a few years for PCID markers to become pervasive and widely deployed, including on lower cost, higher volume OTC products. However, the presence of these important markers will offer the ability for the ultimate audit, the final assurance, and will render special laboratory tests unnecessary in the long run. We are headed for a world where all solid oral dosage forms will carry an on-board PCID that will forever change the landscape of how drugs are protected and identified in the field. **CP**

References

1. "Guidance for Industry: Incorporation of Physical-Chemical Identifiers into Solid Oral Dosage Form Drug Product for Anticounterfeiting," Food and Drug Administration, Center for Drug Evaluation and Research (October 2011).



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