
Implementing On-Dose Authentication Technologies for Solid Dose Drug Products

A Colorcon Whitepaper
February 2021



Implementing On-Dose Anticounterfeiting Technologies for Solid Dose Drug Products

Globalization and outsourcing have resulted in complex supply chains for the manufacture of pharmaceutical and nutraceutical products. Over the past few years, manufacturers have devoted huge resources to meeting the legal requirements for serialization. Although this had yielded benefits in terms of track and trace, it has failed to halt the supply of counterfeit drugs.

The recent dramatic increase in online drug sales, driven by the COVID-19 pandemic, is making products more vulnerable to counterfeiting and diversion. This can result in significant loss of revenue and reputational damage for the brand owner, with health risks and loss of trust for the consumer. In 2018, the US Food and Drug Administration estimated that only 3 percent of online pharmacies complied with US pharmacy laws and practice standards; which means 97% are either illegal or not conforming to the regulations.¹ In 2020, the WHO identified the issue of counterfeit drugs as one of the urgent health challenges for the next decade, given that more than one in ten medicines in low- and middle-income countries are estimated to be substandard or falsified.²

There is a compelling need for the industry to further develop robust strategies to protect their supply chains from external threats. In addition to serialization and the use of security tags on the packaging, there is a recognition that further protection through 'on-dose authentication' can help mitigate this ongoing threat. With on-dose authentication, microtaggants are simply incorporated into the core ingredients or coatings of pharmaceutical and nutraceutical products, then the covert microtaggants detected using either field or lab-based equipment. Going a step further, some microtaggants can be verified using standard smartphones. This innovative technology will help to combat the threat posed by counterfeiting and product diversion and supports the detection, quality control, returns monitoring and product recall.

Types of illegal pharmaceutical medicines

There are many definitions of illegal pharmaceutical products. Three specific categories are defined by the Pharmaceutical Security Institute and align with categories used by many companies.

1. **Counterfeit:** Refers to products deliberately and fraudulently produced and/or mislabelled with respect to identity and/or source to make it appear to be a genuine product. Counterfeit medicines include **falsified medicines** which have less than or more than the required level of active pharmaceutical ingredient. They could also be products manufactured in unsanitary/unsafe conditions, or genuine products such as expired medicines put into counterfeit packaging.
2. **Illegal Diversion:** This usually involves genuine product which is approved and intended for sale in one country but illegally intercepted and sold in another country. It can also occur within the same country e.g. when medicines are sold at discount to a government group but find their way on to the retail market at higher price.
3. **Theft:** Illegal appropriation of medicines e.g. burglary or embezzlement. Theft can occur anywhere along supply chain.

The scale of the problem

For criminals, counterfeiting is low risk: high reward, with relatively lenient sentences and the potential to make millions of dollars in successful operations. The International Federation of Pharmaceutical Manufacturers and Associations reports that every medicine is potentially affected by counterfeiting, including life-saving medicines.³ Whether the drug is brand-name, generic, prescription, or over-the-counter (OTC), it is at risk; and while counterfeiters often target lifestyle drugs, life-saving medicines are the fastest-growing category of falsified medicines.

Despite the widespread introduction of serialization, the supply of counterfeit drugs is continuing to rise. The Pharmaceutical Security Institute (PSI) collects data on the incidence of counterfeiting, illegal diversion and theft incidents in the US.⁴ Their data shows that for the last five calendar years incidents increased by 69%, as seen in Figure 1, with the range of therapeutic categories targeted in 2019 shown in Figure 2; almost two thousand different medicines were involved in these incidents.

Figure 1: Counterfeit Incidents

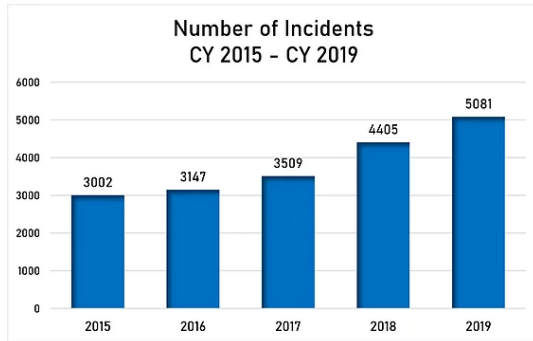
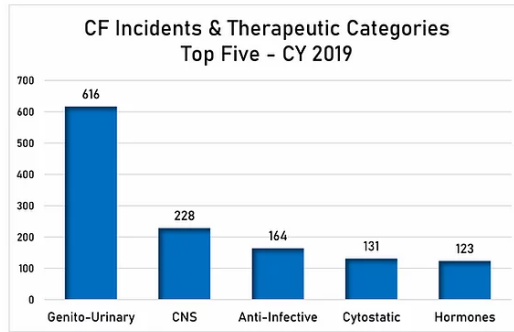


Figure 2: Targeted Therapeutic Categories



The rise of internet sales and impact of COVID-19

There is widespread agreement that the Internet has become the primary market for counterfeit pharmaceutical products. In 2015, WHO estimated that 50% of the drugs for sale on the internet were fake.⁶ The COVID-19 pandemic has led to a dramatic rise in online sales, and it is estimated that 1 in 4 US consumers now buy their medicines online. The FDA reports that only 3% of online pharmacies reviewed by the National Association of Boards of Pharmacy comply with US pharmacy laws and practice standards.¹ The remaining online pharmacies frequently operate without certification, prescribe drugs without adhering to legal guidelines, and may knowingly distribute counterfeit medicines.



A report from The Centre for Safe Internet Pharmacies claims that each month, 600 new illegal online pharmacies are launched, taking advantage of this ever-increasing online market. Growth is expected to continue as the detection and prosecution of the parent organizations is extremely difficult due to their large number and sophistication.

These well-organized counterfeiters are profiting from drug counterfeiting at the expense of patients and legitimate companies; with the pandemic an opportunity to expand their operations.

An analysis by *KrebsOnSecurity*⁷ shows the number of domain names being registered from the start of the pandemic in mid-January through to April 2020. The blue and red lines represent how many websites were being registered each day with either "Coronavirus" or "COVID" in their names. The high-risk score, represented by the red line, shows large increases in websites that are likely to be represented by scams. Legitimate organizations, shown by blue as low risk, tend to be a few weeks and thousands of daily registered domains behind the scammers.

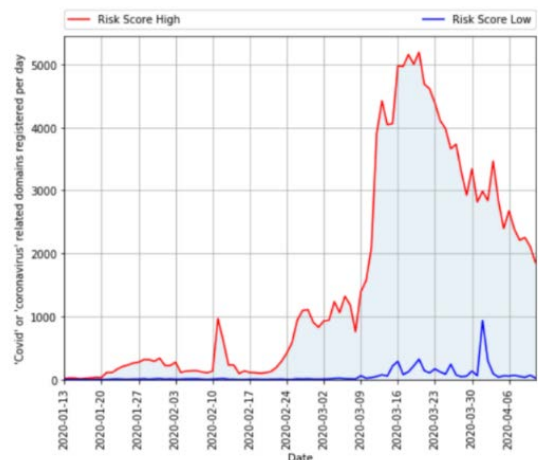


Figure 3: Total number of domain names registered per day that contain a COVID-19 related term

Industry and regulator response

Many countries have introduced serialization legislation; however, traceability and security measures focused at the packaging level are not enough to fully protect patients. Even if a secondary package appears authentic, it may be impossible to determine whether the medicine inside is real or fake, whether it has been diverted, or the packaging copied.

To better secure the supply chain and protect patients, on-dose authentication measures are needed. On-dose technologies provide a more robust and reliable means of deterring and identifying counterfeiting, verifying product identity, and ensuring product traceability. They may include overt tools like pigmented tablet coatings, which are difficult to replicate, and covert chemical or molecular markers added to the drug formulation and a combination of tablet coating and/or tagged ink on the primary packaging.

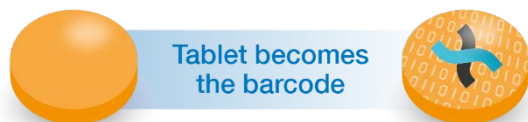
- **Overt technologies** are features that are visible to consumers and are incorporated into a product, such as a pill shape, color and identification marks or inks, and include the packaging.
- **Covert technologies**, such as microtaggants, are designed to be difficult to identify and require verification testing to authenticate the product. If the security features are not easily seen or detected, then it will be very difficult for a counterfeiting organization to find and defeat these measures.

The inclusion of microtaggants is gaining momentum following the publication in 2011 of the US Food and Drug Administration's guidance on the use of physical-chemical identifiers (PCIDs) in solid oral dosage forms (SODFs).⁸ The FDA issued two sets of relevant guidelines for pharmaceutical companies, considering the use of DNA- or silica molecular taggants; making it possible for drug manufacturers to incorporate PCIDs without having to repeat clinical trials. The document defines molecular microtaggants as a type of PCID and stated that when pharmaceutically inactive and incorporated into new or existing drugs, they can be treated as excipients. This allows for their incorporation into drugs already on the market, by simply including the incorporation of microtaggants as a Level 1 post-approval change reported in the Annual Report

On-dose authentication for smarter medicines

Colorcon, as the world leader in the development and supply of film coating systems and excipients, has developed a new, on-dose authentication solution, SoteriaRx™. This innovative platform leverages the best microtaggant technologies, for use on product and primary packaging, to meet the many security needs of the industry.

Microtaggants are covert, uniquely encoded materials that are virtually impossible to replicate or reverse engineer. When their presence is detected in a sample then authenticity is directly confirmed.



The microtaggants can be added to the film coating applied to tablets, incorporated into inks used to print on tablets or capsules, and onto primary packaging to protect parenteral products. Crucially this requires no additional manufacturing equipment or processes.

Colorcon currently offers two different types of microtaggants, one produced from non-biologic DNA and the other from silica: both well understood and inert materials. These tags, used in minute quantities, are invisible to the naked eye yet easily detected using field instruments. In simple terms, the microtagged coated tablet or printed dosage form becomes the lock and the corresponding detection method (which is unique for each taggant) is the key, which is securely held.

The taggants are customer-specific and may be used on multiple drug products, or each drug product can be uniquely tagged. As the product is being used as an anti-counterfeiting measure, there is no special branding to advertise this unique feature. Many companies, especially those utilizing contract manufacturing services, may find it beneficial to maintain anonymity regarding the use of authentication measures.

DNA microtags

DNA is robust and easy to detect; due to its structure, it's possible to have different versions of the DNA sequence to make it a product, company, or region specific. These codes can then be detected using appropriate reagents; so, the DNA taggant with a unique code becomes the lock and the corresponding reagent the key.

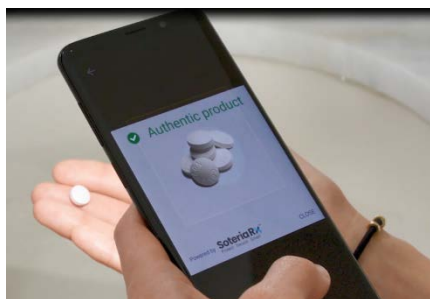
No new investment is needed to incorporate the microtaggants, they are simply added to the tablet using an Opadry film coating system or via an ink applied to the capsule or primary package printing process. Although the DNA is added in parts per billion, every tablet is positively identifiable through the DNA molecules. The technology can create countless unique taggants, distinguishable by data such as company, product or manufacturing site.

Compatibility of the microtaggants with the other formulation components and the impact of the coating cycle when the DNA is exposed to heat and pressure has been investigated. Colorcon can provide experimental data that confirms that the standard coating process doesn't damage or change the microtaggants and detectability, and the integrity of the DNA remains consistent throughout the shelf-life of the product. Also, Colorcon has developed know-how around application and cleaning procedures to ensure that no residues of DNA tags are left which could contaminate the next product in the manufacturing lines.

Detection of the DNA microtaggants is done using a polymerase chain reaction (PCR) test and a single molecule is all that is needed to identify the taggant. There can be no doubt about the identity of a tablet – a positive signal can only be obtained in presence of the DNA tag and the corresponding reagent.

Silica microtags

The silica tagging technology is based on spectrally encoded microtaggants, which are detected by the way they reflect light. Like DNA, the microtaggants are incorporated into the film coating or printing ink and applied during the manufacturing process; they can be customized with unique information for product verification and traceability. Silica is already used in the majority of tablet and capsule formulations and is proven to be safe.



Proof of concept shows that silica microtaggants can be identified using both a mobile lab-based reader or a smartphone app. The smartphone app enables wide use from local regional offices to agents within the supply chain, enforcement agencies and ultimately at the patient level.

Choosing the best solution

Pharmaceutical companies are accountable for making sure their medicine is safe. Manufacturers increasingly recognize they can no longer rely solely on secondary packaging security features to ensure the authenticity of the product and are turning to on-dose authentication solutions that offer more security.

It is important to evaluate how effective and reliable the on-dose authentication process will be from implementation through to scalability and the benefits gained to implement this advanced technology.

With no change to the coating process, the additional cost per tablet is negligible, making the inclusion of microtaggants a practical and cost-effective solution.

Security

Colorcon has developed processes to ensure security during shipment of the taggants as well as shipment of the tagged Opadry; the reagent for DNA tag detection and supporting codes for silica taggants are never shipped or stored together. It is virtually impossible to detect the taggants in the Opadry, or successfully reverse engineer the codes or algorithms within the taggants.

Product stability

Some of the questions raised by pharmaceutical manufacturers are: will the use of microtags affect how we apply the coating; will it affect the stability of the product, and will it affect the disintegration or dissolution? The clear answer to these questions is no. The quantity of taggants added to the film coatings is negligible. Colorcon has completed extensive validation work and has found that there is no evidence of degradation or impurities.

It is worth noting that even though the use of taggants is not a safety issue, manufacturers must notify the regulator that a product has been tagged as part of their annual disclosure in the DMF (Drug Master File). Colorcon is in discussions with the FDA and would be happy to discuss specific issues in more detail with manufacturers' regulatory departments.

SoteriaRx™ On-dose Authentication



Colorcon, as the world leader in the development and supply of film coating systems and excipients, offers different technologies depending on client needs, helping to protect patients and brands. Colorcon has the exclusive worldwide rights to molecular taggants from Applied DNA® and TruTag® silica technology for on-dosage use and now markets these under the SoteriaRx solution platform.

Following extensive R&D by Colorcon scientists and our technology partners, we're now confident to bring these unique technologies to market. We aim to deliver proven solutions that effectively meet market needs, and we always thoroughly assess our new technologies before implementation. We're continuing with extended stability and proof of concept studies to ensure these solutions are reliable in-use.

Colorcon is now working with leading pharmaceutical companies to help them consider how SoteriaRx integrates with their current product security strategies, understanding their current challenges and needs, and developing an optimal solution. It's up to brand owners, product security and quality team members to determine the most appropriate solution for their product, and Colorcon is ready and able to work together with these cross-functional teams to support the impact of these new technologies for the benefit of patients across the world.

References:

1. *FDA Online Survey*, available at <https://www.fda.gov/drugs/besaferx-your-source-online-pharmacy-information/media>, accessed January 2021
2. *WHO Substandard and Falsified Medical Products*, available at https://www.who.int/health-topics/substandard-and-falsified-medical-products#tab=tab_1, accessed January 2021
3. *Falsified Medicine, a Collective Fight*, available at International Federation of Pharmaceutical Manufacturers and Association (IFPMA), <https://www.ifpma.org/topics/falsified-medicines/>, accessed December 2020
4. Gaurvika M. L. Nayyar et al; Am. J. Trop. Med. Hyg., 100(5), 2019, pp. 1058–1065, *Falsified and Substandard Drugs: Stopping the Pandemic*, available at <https://www.ajtmh.org/content/journals/10.4269/ajtmh.18-0981>, accessed January 2021
5. Incident Trends, available at The Pharmaceutical Security Institute <https://www.psi-inc.org/incident-trends>, accessed December 2020
6. *Rise In Online Pharmacies Sees Counterfeit Drugs Go Global*, Fiona Clark, available at WORLD REPORT, vol 386, issue10001, P1327-1328, Oct 03,2015 [https://www.thelancet.com/journals/lancet/article/PIIS0140-6736\(15\)00394-3/fulltext](https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(15)00394-3/fulltext), accessed December 2020
7. Sipping from the Coronavirus Domain Firehose, available at KrebsonSecurity <https://krebsonsecurity.com/2020/04/sipping-from-the-coronavirus-domain-firehose/>, accessed May 2020
8. Guidance for Industry Incorporation of PhysicalChemical Identifiers into Solid Oral Dosage Form Drug Products for Anticounterfeiting, Oct 2011. Available at <https://www.fda.gov/downloads/drugs/guidances/ucm171575.pdf>, accessed April 2020

The information contained herein, to the best of Colorcon, Inc.'s knowledge is true and accurate. Any recommendations or suggestions of Colorcon, Inc. with regard to the products provided by Colorcon, Inc. are made without warranty, either implied or expressed, because of the variations in methods, conditions and equipment which may be used in commercially processing the products, and no such warranties are made for the suitability of the products for any applications that you may have disclosed. Colorcon, Inc. shall not be liable for loss of profit or for incidental, special or consequential loss or damages.

Colorcon, Inc. makes no warranty, either expressed or implied, that the use of the products provided by Colorcon, Inc., will not infringe any trademark, trade name, copyright, patent or other rights held by any third person or entity when used in the customer's application.

For more information, contact your Colorcon representative or call:

North America	Europe/Middle East/Africa	Asia Pacific	Latin America
+1-215-699-7733	+44-(0)-1322-293000	+65-6438-0318	+54-11-4552-1565

You can also visit our website at www.colorcon.com



© BPSI Holdings LLC, 2021.

The information contained in this document is proprietary to Colorcon and may not be used or disseminated inappropriately.

All trademarks, except where noted, are property of BPSI Holdings, LLC.

Authentication Technologies 2021_Whitepaper-V12021

This document is valid at the time of distribution. Distributed 07-Dec-2021 (UTC)