Counterfeit drugs: why on-dose authentication offers the most viable solution

Leading excipient and film coating manufacturer Colorcon has developed a solution to help in the fight against fake drugs through the inclusion of taggants embedded onto individual pills … and the use of smart readers to track and verify branded/authentic products

The issue of counterfeit drugs is moving higher up the pharmaceutical agenda owing to COVID-19; the ongoing pandemic is massively increasing the rate of online drug sales through illegal websites. In the UK, for example, the problem will only get worse now we've left the EU and the Falsified Medicines Directive ceases to apply. *Manufacturing Chemist*'s Dr Kevin Robinson caught up with Colorcon's Chief Scientific Officer, Dr Ali Rajabi-Siahboomi, and Global Product Authentication Lead, Gary Pond, to discuss the latest developments.

KSR: Wasn't the serialisation and widespread implementation of track and trace legislation, which is now in place around the globe, intended to combat the problem of counterfeit drugs?

ARS: Manufacturing companies have put huge resources into meeting the legal requirements for serialisation and have seen benefits in terms of track and trace, but the supply of counterfeit drugs continues to rise. For instance, The Pharmaceutical Security Institute in the US estimates that during the past 5 years, the supply has increased by approximately 70%. Complex supply chains for many pharmaceutical products make them vulnerable to counterfeiting and diversion, and any security system focused solely on the packaging is open to abuse.

For criminals, counterfeiting is a low risk/high reward activity, with lenient sentences and the potential to make millions of dollars in successful operations. Last year, for example, Italian police seized 84 million Captagon pills that were allegedly produced by ISIS in Syria and contained amphetamines worth more than $1 billion. Chinese efforts to restrict precursor chemicals used in making fentanyl (for illicit products) may be contributing to the rise of India as a supplier of fentanyl and fentanyl ingredients, and Mexican cartels are also getting in on the act. In 2019, more than 2000 products in a range of therapeutic areas were targeted by criminals.

KSR: What has been the impact of COVID-19?

GFP: There is widespread agreement that the Internet is the primary market for counterfeit pharmaceuticals. The World Health Organization has said that more than half of all drugs purchased from online pharmacies are potentially counterfeit, and 100% of online searches for

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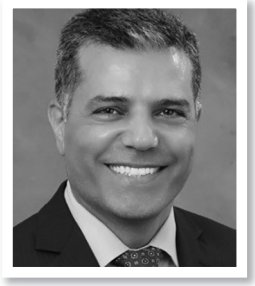
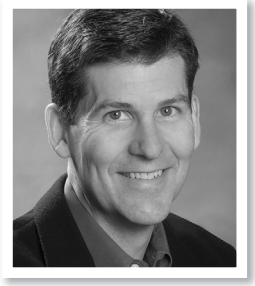
medicines return links to illegal websites. Since the beginning of the pandemic, online sales have increased dramatically and there's compelling evidence to show that legitimate online pharmacies are several weeks and thousands of daily registered domains behind the scammers. Every type of medicine is at risk of falsification; and, although counterfeiters often target lifestyle drugs, life-saving medicines are the fastest-growing category.

The Royal Pharmaceutical Society also suggested that the UK would see an influx of counterfeit medicines at the end of the Brexit transition period on 1 January 2021. Criminals view Brexit and the COVID-19 pandemic as an opportunity to expand their operations. The widespread use of tablet presses means that we're now dealing with counterfeiters who can change production and ingredients rapidly to satisfy market demand. They are also using sophisticated printing technology that can easily replicate much of the on-package security that is being implemented with serialisation.

We believe that serialisation is important and that, as it matures, it will be a valuable track and trace asset; but, we need to expand our product security solutions to continue to improve patient safety. The COVID pandemic has resulted in a greater reliance on digital interactions and that lack of human connection harms consumer trust. Our goal is to give supply chain partners, caregivers and even patients the technology to show that their medication is real.





FOR MORE INFORMATION

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KSR: I've often questioned how workable serialisation can be in more remote parts of the world, so on-dose authentication and the use of smartphones seem like a good solution. How close is that to becoming a reality and what's the prognosis in the new normal brought about by COVID?

GFP: Fortunately, it's not just a matter of proof of concept anymore — we're beyond that. The technology is now available and could easily be implemented across the world. We've been working with two different types of taggants, one produced from non-biologic DNA and one from silica. These taggants are not detectable with human senses, they are used in very small quantities and are easily detected using field instruments. A smartphone app is currently in development for the real-time detection of the silica taggants.

Both taggant technologies are inactive, safe to use and easy to apply and detect. The structure of the DNA taggant means that different sequences of the same DNA molecule can make this product specific. In effect, you can code to make it identify with a company, specific region or individual manufacturing location, and these codes can then be detected using specific reagents (like a lock and key mechanism). To add either DNA or silica taggants to tablets and capsules is simple; they are simply incorporated into the film coating that is applied onto the tablet or into the ink used to print on the surface of the tablets or capsules. This is quite a straightforward process.

ARS: From an application point of view, we're making it as simple as possible by leveraging current film coating and printing technologies. This means no new capital investment is needed and the manufacturing process stays the same; the tablet coating or capsule printing will be done anyway, so it's just a matter of the addition of the taggants.

The silica tagging technology differs from DNA in that it uses microparticles that are spectrally encoded and can be detected by the way they reflect light. The interesting thing about silica is that it's already used in the majority of tablet and capsule formulations. Silicon dioxide is typically used as a flow aid in core formulations as well as in many of our film coatings. The development of these technologies using Opadry film coating is now at an advanced stage in terms of stability, application process and detection methods; and, through the SoteriaRx on-dose authentication platform, we're ready to bring these solutions to the market.

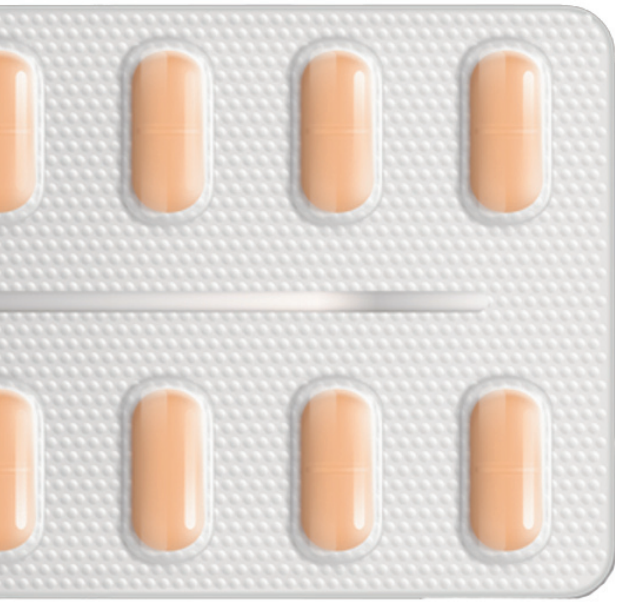
KSR: In the case of DNA, how stable is it, for how long and in what conditions?

ARS: DNA molecules are complex structures made of nucleotides and their sensitivity to environmental conditions is well understood. There's a large amount of data that demonstrates the stability of DNA for very long periods, and DNA technology has been used for many years in courts of law for legal cases. We've tested coated tablets to demonstrate that the detectability and integrity of the DNA remain consistent throughout the shelf-life of the product and we have supporting data to confirm that standard manufacturing procedures don't damage the DNA. Also, we have developed know-how around the application process and cleaning procedures to ensure that no residues of DNA taggants are left, which could contaminate the next product in manufacturing lines. The same goes for the silica taggants, which are equally stable throughout a typical manufacturing process.

KSR: I'm assuming that because you're not making any fundamental change to the production process, manufacturers using the tagged coating wouldn't have to revalidate their process to use it. Is it also safe to say that the integration of the taggants does not affect the friability or the dissolution and disintegration of the tablets themselves?

ARS: The application of the taggants in coating or inks is seamless from the start to the finish of product manufacture. The only thing that manufacturers need to do is validate their cleaning procedure to ensure no residues of taggants are left at the end of a batch, and we can provide support to assist in this. Some companies may not want everybody in their manufacturing facilities to know that the product has been tagged, and we can offer guidance on how to best manage this.

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. There is a DMF (Drug Master



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File) and we're already in discussions with the US FDA, so from a regulatory point of view, we don't feel that there's any significant hurdle to either the DNA or the silica approach. We can provide full advisory support to a client's regulatory department to ensure smooth implementation.

The questions that might be raised by manufacturers will no doubt revolve around whether the use of taggants will affect how the coating is applied, if it will affect the stability of the product and/or the disintegration or dissolution.

Because the quantities of the taggants that are added to the film coatings or inks are small, there is no impact. There's also the question of changes with time: do you get any instability; does it cause any degradation or any impurities? Again, the answer is that there's no impact on stability and we have not seen any evidence of degradation or impurities.

ARS: We've been hearing a lot recently about the constraints of PCR (polymerase chain reaction) detection, which is used to detect the taggants, although this has probably been overplayed by the press. DNA is robust and there's no doubt about the identity of a tablet that's tagged; it's impossible to get a positive signal if you don't have the DNA taggant and the corresponding reagent for that specific taggant. You need to use PCR to detect it … but the latest machines are automated, portable and reliable, and a single molecule is all that's needed to identify the tag.

But the game doesn't stop there! Our goal is to go all the way to ensure that the patient has complete confidence that they are taking an authentic drug. That's partly why we started looking at other technologies. We have shown that it's possible to detect the silica taggants using a mobile laboratory based reader and a smartphone app. Now in the final stages of development, this app enables field use across the entire distribution network, including the supply chain, enforcement agencies as well as by patients or caregivers.

KSR: How does the incorporation of the taggants affect the cost of the coating?

GFP: The cost per tablet is a fraction of a cent. These taggants are advanced, complex technologies, so there will be a slight increase in product cost, but the film coating process doesn't change. As such, it's extremely cost-effective to apply. Compared with product costs and the detrimental impact of counterfeit drugs, the overall cost to the producer of the finished dosage form is negligible.

KSR: Is the global pharmaceutical supply chain secure enough to handle pills, tablets and capsules with your coating?

ARS: Fortunately, most diversion doesn't involve the raw materials … because this is of low value to the criminals. Pharma companies have security built into manufacturing plant and centres of distribution, but there will always be a risk during transportation. The chain of custody and the distribution network is something that the manufacturers must make as watertight as possible.

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

KSR: Can you tailor the coatings to specific requirements and/or quantities according to individual customer needs?

GFP: The products and services we offer through SoteriaRx are backed by advanced technology and significant investment made by Colorcon to develop a viable solution. For both taggant types, we've done extensive work to create solutions that work effectively with our film coatings and inks. Our position as a film coating leader and our reputation as a valued and trusted partner to the pharma industry is critical to success. Our customers rely on us to bring them proven solutions that effectively meet their needs. We work closely with our clients to understand their wishes and follow through with exemplary service and support from development to commercial manufacture. We thoroughly test our new offerings to ensure that we can provide the right solution for our customers with confidence. At this time, we have ongoing stability and proof of concept studies to ensure our recommended solutions are reliable and robust in use.

KSR: We are now operating in a "new normal" world in which technology such as this is going to become increasingly important. Is this the future of managing the global supply chain for drugs?

ARS: The most exciting part of this technology is when we look at the mobile phone app and its potential applications; in addition to authenticating the product, we can think about

what types of information it could be linked to. Through proof of concept, we've shown how you could track a product around the globe, leveraging the currently available serialisation technology and applying similar principles in terms of gathering the information to a central location. But you can also look at it from another angle: how can this medicine-related information directly impact the patient? The mobile phone app can utilise the data to set up an alarm system to remind patients to take the right medication at the right time, improving medication regime adherence.

An unexpected impact of the pandemic is its effect on clinical trials; participants have struggled to access testing centres. How can study units ensure that people who take clinical trial medication at home follow the correct medication regime? Failure to comply will give rise to misleading results, which can be enormously costly to pharma companies and significantly delay trial outcomes.

It may soon be possible to authenticate the tablet using a smartphone, video the volunteer taking the medication and use a smartwatch to monitor vital signs. There's currently lots of interest in the clinical trial aspect of the technology. We're not quite there yet, but this exciting future is close and COVID has accelerated a lot of technology. Where and when there is a need, the rate of innovation will increase.

KSR: You mentioned that this research and development has been ongoing for many years. You've reached a point now where it all sounds very promising and functional. Is there a next stage, perhaps, or somewhere else you want to get to?

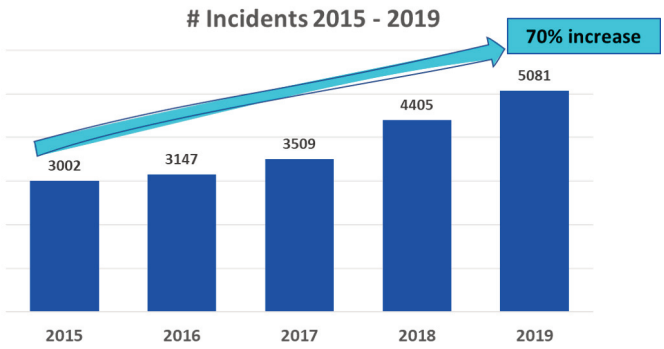
ARS: Right now, it's the beginning of the commercialisation process. We're in discussion with several companies, sharing concepts and talking about practicality and values. As with any new technology, it will take time for people to understand the platform and think about how it integrates and supports their current multilayered security strategy.

This also holds true for those in the commercial and patient-centric arena. It presents an innovative way to engage with their patients when dosing their medication. On-dose authentication is complementary to serialisation, but we believe that this technology safeguards the patient and brand to a new level by securing the actual product.

As it's a new technology, crossfunctional teams are being brought together within pharma to discuss its impact. We're working with companies to help them explore how this offering integrates with their current product security strategies, understand their challenges, then collaborate to develop and implement an effective solution. There are many new exciting options that companies need to think about, though, such as the role that patients play in authenticating their medication (overt versus covert) and how best to leverage the smartphone app to support patient engagement and build stronger brand loyalty.

Figure 1

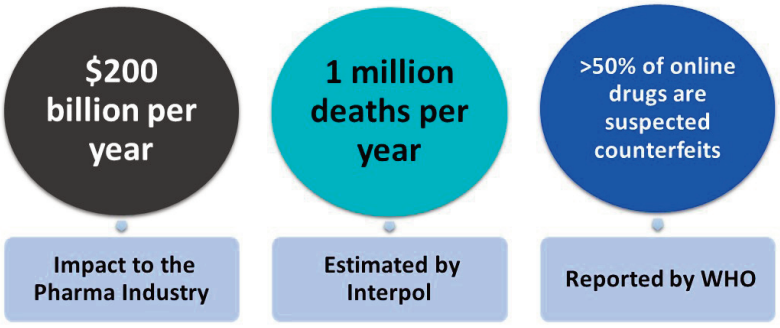
In the past 5 years, counterfeiting, illegal diversion and theft incidents have increased by 70%



Ref: https://www.psi-inc.org/incident-trends; accessed Nov 2020

Figure 2

The harsh facts about counterfeit drugs



Typically, when Colorcon develops a new product, our goal is that it is applied consistently to every tablet across a variety of conditions. In this case, the approach differs, as every product is different and each client has its own needs and different levels of security. For some companies, it may be important that each batch is identifiable at each location; others may just want one product with one tag around the globe. So, we're spending a lot of time together with our clients to understand their requirements. It's not simple … and launching this type of technology is more complex than bringing a new film coating system to market. As we learn more and understand the objectives and practices that clients wish to apply, we continue to innovate.

On the product security side, the primary questions we're being asked to answer are whether this product is real or fake, and what's its provenance. When you get to the commercial side, patient safety is paramount. Companies are keen to better engage the patient and help them to manage their disease and improve outcomes. So, there are two distinct areas wherein we can integrate product security with patient safety and brand awareness. We've come a long way and removed major technology hurdles to implementation; plus, we can share data to show the robustness of the solutions. We don't have to look into the future — it's already here.

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