IMPLEMENTING ON-DOSE AUTHENTICATION TECHNOLOGIES for SOLID DOSE DRUG PRODUCTS

A Colorcon Whitepaper
2019

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Authentication Issues

Globalisation, outsourcing and the increasing prevalence of online sales have resulted in complex supply chains for the manufacture of pharmaceutical products. This makes products increasingly vulnerable to counterfeiting and diversion, resulting in significant loss of revenue and reputational damage for the brand owner, and health risks and loss of trust for the consumer.

It is essential that brand owners develop robust strategies to protect their supply chain from external threats. Innovative solutions, such as on-dose microtags, are now being used to mitigate counterfeiting and product diversion and to help with returns monitoring, quality control and product recall.

The Scale of the Problem

The prescription drug market has been estimated to be worth up to $900 billion/year worldwide, with about 85% of the world pharmaceutical market in the developed world. An estimated 1 in 10 medical products circulating in low- and middle-income countries is either substandard or falsified, according to new research from WHO.[1] In 2016, The Center for Medicine in the Public Interest estimated the illicit drug supply industry to be worth $95 billion. Other investigations put the figure at around $200 billion and estimate that internet sales of counterfeit drugs account for $75 billion of the total market.

WHO estimates that 16% of counterfeit drugs contain the wrong ingredients, while 17% contain the wrong levels of active ingredients. More than 30% of the counterfeit drugs that are available today contain no active ingredients. Counterfeit products may also include toxic compounds which can endanger life. According to a CNN report, between 100,000 and one million people, including 300,000 children die each year from counterfeit drugs.[2]

A more challenging and complex problem than counterfeiting is diversion. This may occur when an intermediary sub-distributor acquires the product intended for sale in a lower priced channel, then re-sells it for a higher price in a non-discounted market. This is generally illegal, but in the EU, repackaging is legal and allows companies to take advantage of differential pricing.

Another form of product diversion is the unauthorised return of products; when product is often in damaged packaging or not in the original packaging. This makes it difficult to determine whether such product is eligible for refunds. Cases have been reported of authentic pill bottles being filled with fake material and then re-sealed and returned. Many returns monitoring practices fail to verify the contents of packages and are therefore open to this form of abuse.

“Street” diversion is a particularly insidious form of drug diversion in which addictive prescription medication is diverted without controls, resulting in dangerous use and risk of overdose. The opioid crisis in the US is an example of consumers getting prescriptions that are not intended for the end users.

Legislation

In the past decade, governments have passed laws to enforce serialization, requiring product identifiers to be affixed to each package in order to provide product traceability throughout the distribution supply chain. In the EU it was the Falsified Medicines Directive (FMD)[3], enacted July 2011; followed closely by the Drug Supply Chain Security Act (DSCSA)[4], which was enacted in November 2013 and required to be implemented by November 2017, with a one-year reprieve to 2018 for compliance. This requires track and tracing of all Transaction Information (TI), Transaction History (TH), and Transaction Statements (TS). By the end of 2020, impacted parties will include the manufacturer, re-packagers, wholesalers, third party logistics and dispensers. By 2023, full unit level traceability will be required.

However, traceability and security measures focused at the packaging level are not enough to protect patients. Even if a package is authentic, it may be impossible to determine if the medicine inside is real or fake, and whether it has been diverted.

Authentication Measures

In order achieve true supply chain security, on-dose authentication measures are needed. These may include coatings, which are difficult to replicate, or chemical or molecular markers added to the drug formulation and/or coating. Microtags or taggants are uniquely encoded materials that are virtually impossible to replicate, or reverse engineer. They can be used to on finished products, ingredients or materials used to make products, and on packaging.

When their presence is detected in a sample (using hand-held devices) then authenticity is confirmed directly. The most useful taggants are those that can carry information or incorporate ‘fingerprints’ which complement packaging security and traceability systems and allow product diversion to be combated.

The use of taggants is becoming more common 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).[5] The agency issued two sets of relevant guidelines for pharmaceutical companies, considering the use of plant-based or silica molecular tags. These guidelines make it possible for drug manufacturers to incorporate

PCIDs without having to repeat clinical trials. The document defined molecular tags as a kind of PCID and stated that,

when PCIDs are 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.

Innovative Technology

Several companies have developed a range of innovative technologies using inert materials that pharmaceutical manufacturers can implement to protect the individual dosage form and associated supply chains. These technologies are classified as overt or covert.

Overt technologies are features that are visible to consumers and are incorporated on to a product or its packaging. Such technologies may offer low security as counterfeiters become more sophisticated. There is also a risk that consumers will see a feature like a hologram or watermark and assume that the product it genuine. Pearlescent pigments incorporated into tablet coatings are an example of an overt technology that is difficult to mimic, reducing the counterfeiter's ability to replicate the real product.

Covert technologies are designed to be difficult to identify and require 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. Covert taggants can be incorporated into inks used on tablets or capsules, into the coating on tablets, and into active pharmaceutical ingredients. Taggants can also be used in the fillers and binders, as well as coatings used to make medicines. Crucially this requires no additional manufacturing equipment or processes.

The TruTag® Platform is a covert technology which uses microscopic silica particles, each of which bears a unique spectral signature. This means that each pill can be labelled, allowing tracking of individual items by product, dosage, plant, manufacturing line, and even batch. The particles are virtually invisible and can be incorporated on the surface of, or as part of, a critical product or component.

The solution is safe (silica is "generally recognized as safe" (GRAS) by the US FDA) and resilient, with the microtags lasting for the entire product lifetime. These microtags can also be customised with unique information for product verification and traceability.

For microtags an in-field optical reader can confirm the genealogy of the product without needing to send it back to a central laboratory for verification. This gives pharmaceutical companies the power to scan a pill found

anywhere in the world and immediately confirm its authenticity, place and date of manufacture, lot number, and other product intelligence directly from the dosage form itself, without needing the product packaging.

A unique DNA tag, produced by Applied DNA, is a form of covert molecular tagging and a platform for use across a wide range of applications. DNA tagging of inks, coatings, and other ingredients can be used in the pharmaceutical supply chain, securing authenticity of an individual dose from the manufacturer, to the distributor, and finally the pharmacy.

Authentication is possible, even when the product is separated from packaging, making it a solid complement to serialization. The DNA tag has no capacity for gene function and WHO has determined that intact, gene sized DNA may safely be included in oral dosage formulations. It acts like an individual barcode that cannot be broken, and which is traceable at parts per billion/trillion.

Choosing the Best Solution

Manufacturers now recognise they can no longer rely solely on packaging security features alone to ensure the authenticity of the product within it. Brand owners, risk officers and senior management must determine the most appropriate solution for their product. It is important to understand how effective and reliable the authentication process will be, and what benefits will be gained as a trade-off for the time and resources required to implement an advanced technology.

On-dose authentication solutions offer more sophisticated features that will not be susceptible to defeat within months, as is often seen with current packaging measures. If an authentication solution is machine readable, it will be faster and more reliable and suitable for high volume applications. An authentication system that can differentiate drug product at the batch level also offers powerful product identification potential:

- Distinguishing between expired and unexpired product
- Showing if a product has been improperly diverted
- Allowing rapid recall in the event of a quality incident
- Providing a digital lock between the product and its packaging.

Colorcon, a world leader in the development and supply of film coating systems and excipients, can offer multiple technologies depending on the needs of their clients, thus helping to protect patients and brands. No one solution is perfect, and a multi-layered approach can incorporate the strengths of the best technologies. Brand owners should fully evaluate options and implement the solution that fulfils their specific requirements.

Previously, the cost of on-dose markers would have been hard to justify and the need to repeat clinical trials for existing drugs incorporating markers prohibitive. With new guidelines from regulators and more accessible technology, the real barrier to the widespread use of taggants is now the complexity of global pharmaceutical supply chains. Despite this, most drug manufacturers agree that marking individual doses is where the industry is

heading, allowing products to be traced every step along the way to the consumer. On-dose technologies provide a more robust and reliable means of deterring and identifying counterfeiting, verifying product identity, and ensuring product traceability.

References

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