JULY 2020 # 06

the Small Molecule Manufacturer™

The War on (Counterfeit) Drugs

How is pharma working to stop the spread of fake medicines?

10 – 17

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Leading the Charge

The world is making progress against COVID-19 – and small molecules are on the frontlines

Many different therapeutic avenues for COVID-19 are being tested, but so far small molecules have emerged as the first treatments. In May 2020, the FDA issued emergency use authorization for remdesivir as a treatment for severe COVID-19. The drug has since received similar emergency authorizations in other countries, and been approved for severe COVID19 in Japan and recommended for conditional marketing authorization in the EU, under the brand name Veklury. Remdesivir is a nucleotide analog delivered via injection that, when metabolized, forms remdesivir triphosphate – an inhibitor of SARS-CoV-2 RNA polymerase, which prevents viral replication. Clinical trials for remdesivir are ongoing – but results are promising (1). Gilead also wants to commence new trials for an inhaled formulation that could offer a therapeutic intervention for earlier stages of infection.

In the UK, other trial results suggest that the corticosteroid dexamethasone could help treat critically ill COVID-19 patients. According to the study, the drug could reduce mortality of patients on ventilators and oxygen by around one third and one fifth, respectively (2). The WHO is conducting a meta-analysis to decide whether to include dexamethasone in its COVID-19 clinical guidance, but the drug has already been authorized in the UK for hospitalized COVID-19 patients.

It's true that we don't yet know how these treatments will work out in long term. Remdesivir was also previously tested against Ebola – and although early results were promising and safety was established, it was later found to be less effective than monoclonal antibody treatments. But, for now, remdesivir and dexamethasone are first to the fight, highlighting the importance of maintaining innovation and investment in small molecule drug discovery and development.

Biopharmaceuticals and advanced medicines are, of course, also being investigated as potential COVID-19 treatments – but progress is somewhat slower because of the inherent complexity. On the other hand, consider the extensive libraries of small molecule compounds that can be screened for potential; supercomputers are already working overtime in this regard – even NASA has joined the COVID-19 fight (3).

One thing is certain, the future of medicine will not depend on one drug type or a single approach. Small molecules, large molecules, gene therapies, cell therapies, and perhaps new but undiscovered avenues will all play a role.

Stephanie Sutton
Editor

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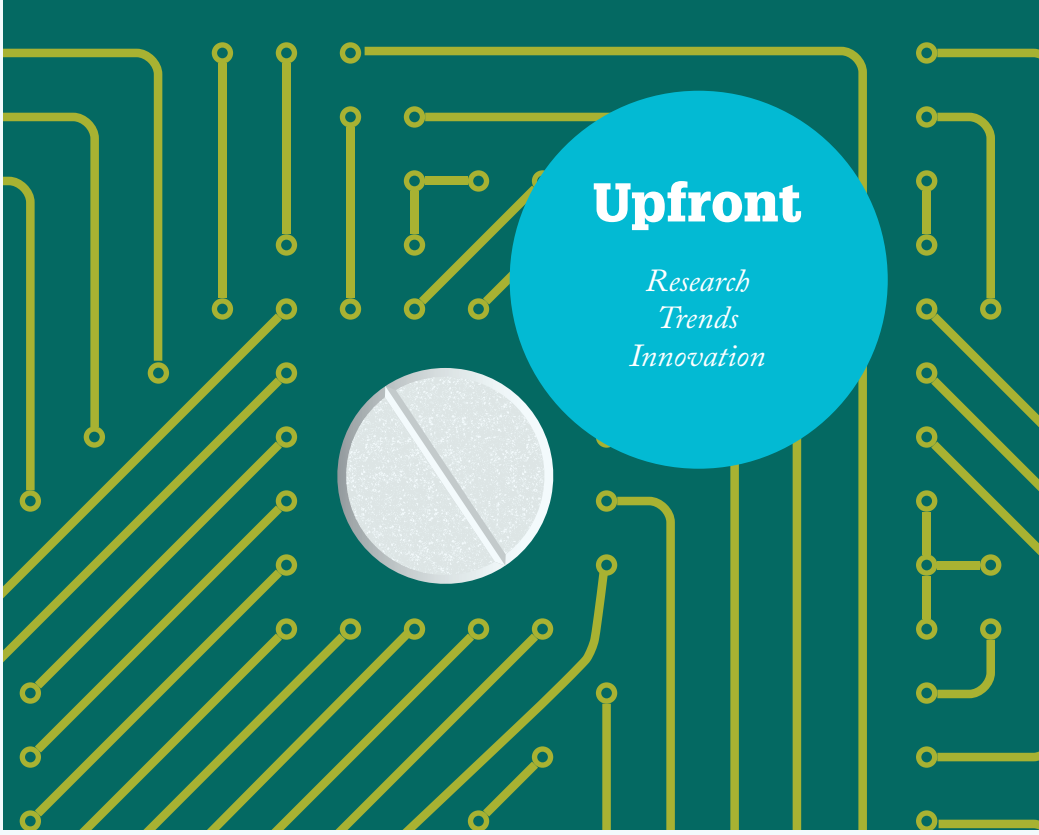

Intelligent Repurposing

An AI-identified drug enters clinical trials for COVID-19

Using its artificial intelligence platform, known as Knowledge Graph, BenevolentAI has identified a potential COVID-19 treatment: baricitinib. The drug, owned by Eli Lilly, has now entered clinical trials in the US, with planned expansion to additional sites in Europe and Asia.

"The urgency of the coronavirus outbreak means that it made sense to analyze already approved drugs that could be ready for large-scale trials within weeks," says Peter Richardson, VP of Pharmacology at BenevolentAI. "Rather than focusing solely on drugs that could affect the virus directly, we explored ways to inhibit the cellular processes that the virus uses to infect human cells. The idea was to identify approved drugs that could potentially stop the progression of COVID-19, inhibit the 'cytokine storm' and reduce the inflammatory damage associated with this disease."

Richardson and his colleagues identified 47 potential drugs but baricitinib, an approved treatment for rheumatoid arthritis, was the only appropriate candidate (1,2). As both a JAK inhibitor and an AAK1 inhibitor, the drug has anti-inflammatory properties and is thought to interrupt the passage of SARS-CoV-2 into cells and prevent intracellular assembly of virus particles.

"Of the potential treatments, we identified only six that inhibited AAK1 with high affinity, preventing endocytosis and therefore, viral entry. These included a number of oncology drugs, but these compounds have serious side-effects," says Richardson. "Only one of the drugs – baricitinib – was appropriate for use in the target patient population."

For Richardson, the work proves the applicability of AI to the drug discovery process. "It is difficult to predict the long-term impact of coronavirus," he says. "But AI can help expand the drug discovery universe by making predictions in more novel areas of biology and chemistry – and at speed, as demonstrated by our work on COVID-19."

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INFOGRAPHIC

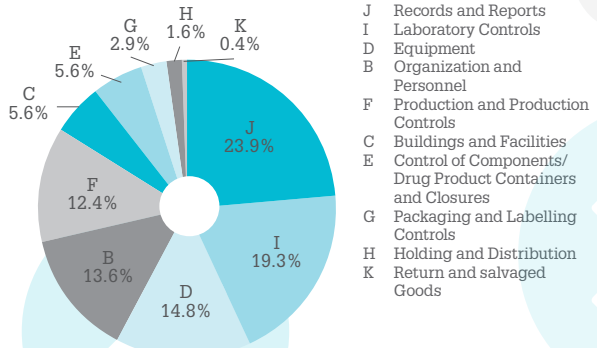
FDA Reflections

The FDA has published its report on the state of pharmaceutical quality in 2019

Source: FDA, "Report on the State of Pharmaceutical Quality: Fiscal Year 2019", (2020). Available at: https://bit.ly/2V4mZgK

Violations

The most commonly cited violations were for records and reports (**23.9%**); laboratory controls (**19.3%**) and equipment (**14.8%**)



BUSINESS IN BRIEF

Annual reports, leases, and lawsuits… What's new in business?

- Dr. Reddy's Laboratories has entered into a licensing agreement with Gilead for the right to manufacture and sell, remdesivir – the broad-spectrum antiviral with the potential to treat COVID-19. The technology transfer will make the Indian pharma company responsible for the regulatory marketing approval of the drug in target countries.
- The EMA has published its 2019 annual report. The document outlines the achievements and challenges the agency faced last year, including its move to the Netherlands in response to Brexit, and the completion of "Regulatory Science Strategy to 2025" – a plan for improved engagement in (and with) regulatory sciences. The report, which is available in a digital format for the first time, also explores the regulator's procedures and activities, highlighting the key trends observed over the course of the year. "With all the challenges

we are facing, getting fit for the future became a top priority in 2019," Guido Rasi, EMA executive director said in the report's introduction. "I approach 2020 with the hope that we can [...] focus on the future."
- Twenty-six generic manufacturers and 10 individuals are to be sued by states and territories across the US for price fixing of over 80 medicines, reducing competition and creating a monopoly in the generics market. The case isn't the first to be brought against the defendants; similar litigation was filed in both 2016 and 2019. Some of the companies named in the lawsuit include Teva Pharmaceuticals' Actavis unit, Mylan, and Pfizer.

Don't Forget the Excipients

How can pharma better ensure data integrity for excipients?

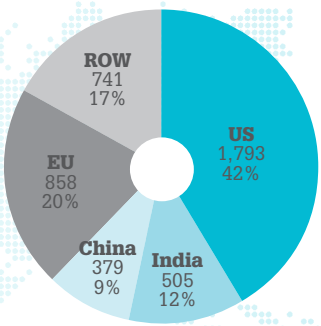
The International Pharmaceutical Excipients Council Federation (IPEC) has published a position paper urging pharma stakeholders to create strategies that ensure the quality of critical data for excipients. Though data integrity is an essential part of any GMP application, much of the regulatory guidance currently available does not outline data integrity requirements for inactive drug products.

IPEC suggested several ways excipient suppliers could improve their data integrity, including ensuring product life cycles are maintained, and using training and internal auditing to guarantee compliance with documented data integrity controls. Excipient users were also advised to "manage expectations appropriately when auditing excipient suppliers" as their data integrity controls may differ depending on the type of products developed.

The paper is available at https://bit.ly/2A2QYOJ

Manufacturing Sites

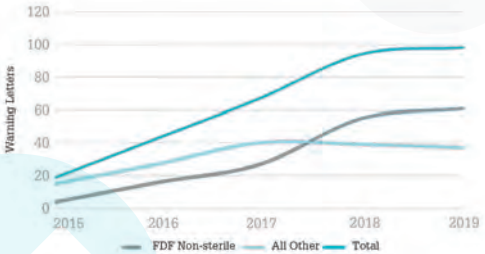
Of the **4273** drug manufacturing sites in the FDA's catalog, **42%** are in the US



Warning Letters

70%

of warning letter in 2018 and 2019 were for sites manufacturing products for the No Application sector



Preventing Preterm Problems

Researchers explore the use of small molecules to reduce the risk of preterm birth

Birth before 37 weeks of gestation accounts for 15 million deaths each year, but tocolytics – the drugs used to suppress labor – have limited use. "Currently there are no FDA-approved drugs that reliably halt spontaneous preterm labor (sPTL) – none of the most commonly used tocolytics can delay preterm birth beyond 48-hours," says Scott Barnett, a researcher at the University of Nevada's Reno School of Medicine.

With the aim of providing pregnant women with a more effective range of safe medicines, the Iain L.O. Buxton research group, of which Barnett is a senior postdoctoral fellow, has characterized a molecular pathway that contributes to the phenomenon of sPTL, and identified four drugs with the potential to prevent it (1). Specifically, the team has been investigating the unique pathophysiology of uterine smooth muscle that involves the metabolic dysregulation of nitric oxide – an endogenous smooth muscle-relaxing agent. It was once thought that direct administration of nitric oxide would help halt sPTL, but this route of administration was shown to be ineffective due to the overexpression of S-nitrosoglutathione reductase (GSNOR), an enzyme that metabolizes nitric oxide in women who experience sPTL (2).

"We discovered that GSNOR was overexpressed in some pregnant women, resulting in sPTL. With this information in hand, we identified and tested several GSNOR inhibitors on donated uterine tissue. When combined with an FDA-approved β3 agonist, nebivolol, and an experimental GSNOR inhibitor drug called N6022, the molecules prevented muscle contraction," says Barnett. He believes that the pharmacological "one-two punch" helps increase the availability of nitric oxide in the uterine smooth muscle, making it less inclined to contract.

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The Great Rebrander

A report shows that post-M&A rebranding bodes well for the pharmaceutical industry

According to research published by Brand Finance, pharma is the top-ranked industry when it comes to successful rebranding post-M&A – with average returns of 13.8 percent. But what makes the industry so proficient in managing corporate change? The report, which studied acquisitions worth $500 million or more across 25 sectors, attributes pharma's success to "superior marketing and client networks of larger players." The report explains that strategic divestment also prompts companies to rebrand.

Although pharma's post-takeover rebrands are often successful, they only occur in 31 percent of acquisitions – a figure that may seem small, but still places the medicine making sector ahead of other large industries, including the healthcare (30 percent), telecommunications (29 percent), and oil and gas (25 percent).

Reference

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IMAGE OF THE MONTH

From Food to Pharma

By fermenting discarded prawn shells and fruits, researchers at Nanyang Technological University, Singapore, have developed a sustainable method of producing chitosan, a sugar that can be used for the delivery of small-molecule polar drugs.

Find out more at https://bit.ly/2AGnnKR

Credit: NTU Singapore

Would you like your photo featured in Image of the Month? Send it to maryam.mahdi@texerepublishing.com

QUOTE of the month

"In an epidemic, speed is of the essence – and machines excel in handling data in fast-changing circumstances. Modern computing power and machine learning systems can be harnessed to work as tireless and unbiased super-researchers, analyzing chemical, biological and medical databases to throw up potential drug leads far faster than humans."

Peter Richardson, VP of Pharmacology at BenevolentAI, in an interview with The Medicine Maker

A Doctor's Dream

A dramatic drug development story scoops top prize at WHO film festival

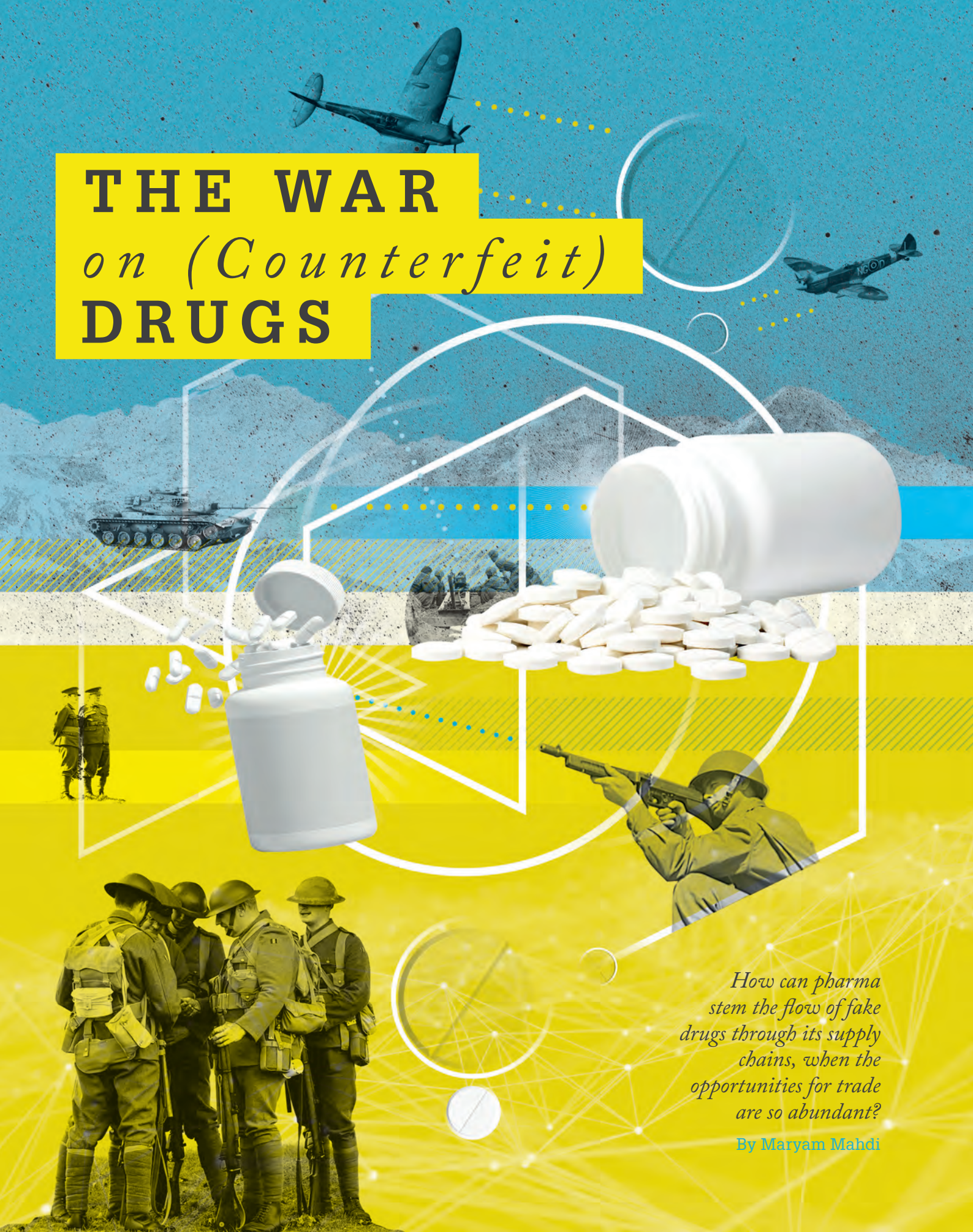
"A doctor's dream: A pill for sleeping sickness" by the Drugs for Neglected Disease Initiative (DNDi) was awarded the Grand Prix at the WHO's inaugural "Health For All" Film Festival. The The seven-minute film shows how Congolese doctors, non-profit DNDi, and drug giant Sanofi came together to develop the first oral treatment for sleeping sickness.

The drug, fexinidazole, was approved by the EMA in 2018 and is now on the WHO's List of Essential Medicines. Previous drugs were delivered intravenously – difficult and expensive for resource-limited settings. Doctors hope that the availability of an oral drug could help eliminate the deadly disease.

DNDi received a $10,000 prize, which they will use to make more films highlighting the challenges of drug development for neglected diseases.

Watch the film: https://bit.ly/3euvVUh

THE WAR *on (Counterfeit)* DRUGS



How can pharma stem the flow of fake drugs through its supply chains, when the opportunities for trade are so abundant?

By Maryam Mahdi

Counterfeit medicines put countless lives at risk. Pharma stakeholders are working hard to stop fake drug developers in their tracks, but the fight to protect patients, supply chains, and even reputations can feel like a game of cat and mouse. Here, five experts share their views on the technologies making a difference, the need for collaboration, and the rise of the pandemic scammer.

Creating Digital Infrastructure

How are end-to-end supply chain management systems helping in the fight against counterfeits?

By Shabbir Dahod

The pharmaceutical supply chain connects stakeholders from across the world in their shared goal of manufacturing effective medicines for patients. But the complex (and often international) transactions required to develop finished products provide counterfeiters with opportunities to infiltrate and introduce fake or falsified products. In emerging markets, where pharmaceutical supply chains and infrastructure may be frail, the problem is further exacerbated; in some countries, counterfeits account for 40–50 percent of available medicines (1). The consequence of this supply chain fragility is often death; many unwitting patients succumb to silent killers: falsified medicines with harmful or no therapeutic effects.

Manufacturers and other stakeholders are doing their best to mend these supply chain cracks. With serialization and traceability legislation in place across most countries, companies have the opportunity to improve end-to-end supply chain visibility and lessen the risk associated with counterfeit products. Although many companies have implemented or are implementing the technology to meet these laws, the timeframe for adoption varies across regions and implementation of software and solutions is at the discretion of individual companies.

In compliance with serialization and traceability laws, every pack of medicine is given a unique identity that can be tracked as it progresses through the supply chain. Information pertaining to each unique identifier can be relayed back to governments and trade partners, who can maintain a full trace history of any given product and flag suspicious activity. While some countries have already reached full traceability – the point at which all supply chain information is provided to centralized government authorities – others such as the USA, have taken a phased approach and the choice between the rapid adoption of full track and trace and its gradual implementation boils down to the complexity and broadness of a country's supply chain. Leapfrogging to a full track and trace endpoint is not feasible for larger entities like the EU or the USA, and many industry players in these regions feel that it is easier to maintain serialization and traceability measures in smaller, more controlled steps. No matter the strategy employed, all countries working on the implementation of these laws are taking different paths to the same destination: a more safe and secure supply chain with improved visibility.

A word of caution: the benefits of digital track and trace platforms can only be realized if they are implemented in accordance with regulatory guidelines – and in good time. Though many are eager to implement these systems, there are also laggards who seemingly hope that traceability legislation will not be enforced in their countries. Such an attitude can result in the need to cut corners when trying to catch up to peers. If you are not yet compliant with track and trace initiatives, you can make the process more manageable by drawing up a comprehensive implementation plan.

If we are to create a future where patients are exposed to fewer risks and where criminals have reduced capacity to introduce harmful products, every country and every company must fully embrace supply chain management.

End-to-end supply chain management systems

Supply chain management is also dependent on robust management systems. Without them, stakeholders across the industry fail to adopt standardized approaches to information sharing, which can provide opportunities for criminals to compromise the supply chain. Digital systems enable end-to-end supply chain visibility and collaboration that provides a clearer picture of medicine whereabouts as it travels from manufacturer to patient.

Without a digital supply chain, companies cannot track or measure how quickly products move from manufacturer to distributor and, finally, to patients. Digital platforms that ensure real-time information sharing contribute to companies' ability to comply with regulatory standards. And as adoption increases, the industry as a collective can begin to assess the steps that need to be taken to optimize the pharmaceutical supply chain as a whole.

Consideration must also be given to managing disruptions in supply, a challenge highlighted by the COVID-19 pandemic. Natural disasters, energy shortages, fuel crises, civil unrest – all can and will disrupt the pharma supply chain with little predictability; all require pharma to develop a more agile and transparent pharma supply chain with robust management systems in response. To negate the impact of these events, a collaborative platform is required to build end-to-end supply chain agility. The agility brought on by a single digital network would also enable businesses from countries around the world to communicate, coordinate and collaborate on a regular basis, ensuring the fluidity of pharma supply chain operations even when the unexpected happens. While these requirements represent a significant shift in how most companies currently manage their supply chain operations, the collaborative infrastructure needed to build this digital network has its foundation in the information-sharing networks developed to meet product serialization and track-and-trace regulations around the world.

Shabbir Dahod is Chief Executive Officer at Tracelink

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Beyond the Pack

Serialized packaging is not the only way to deter counterfeiters – integrated authentication technologies are here to help too

By Kelly Boyer

Counterfeiters have an arsenal of techniques that they rely on to dupe consumers – and their experience in making fake products means that they aim to copy the shape, color, and size of various medicines. The API, however, may be at the wrong strength, not present at all, or be a completely different active ingredient or even toxic material.

Parallel trade is one opportunity for counterfeiters to slip their product into the supply chain. This process allows them to introduce medicines to markets where the demand for them is high while inflating their prices to capitalize on patients' needs. Without a doubt, this type of illicit activity puts a strain on the relationship between pharmaceutical companies and customers.

The pharma industry has introduced serialization initiatives to counter counterfeits. Companies need to adhere to the Falsified Medicines Directive (FMD) in Europe and provide unit level traceability by 2023 per the Drug Supply Chain Serialization Act (DSCSA) in the USA. Both legislative measures rely on the use of 2D barcodes to verify product authenticity, but barcodes are easily copied and restricted to packaging, which can be discarded or reused. The problem is compounded by the fact that under legislation like FMD, the initially scanned pack is considered to contain an authentic drug product, which is not always the case. And even though pharmaceutical stakeholders and the companies who provide track and trace services are continually looking for ways to prevent the entry of such products into the supply chain, their efforts, much like the legislation for supply chain management and visibility, are focused on the developed world. Though counterfeiting undoubtedly occurs in the West, it certainly does not affect the region and its supply chains with the same detrimental effects experienced by developing countries (1). The cost of compliance with serialization can be prohibitive for many emerging nations, with most expected to develop their own policies, serialization standards, infrastructure, and implementation timetable. The high stakes situation means that pharma must look beyond packaging and begin to consider how security can be integrated into drug products themselves to better protect patients.

Integrated trust

Digitalization of physical tablets helps close the gaps in the supply chain by giving companies the power to track and trace individual tablets, regardless of whether they are within a pack or not. In 2019, in collaboration with PwC Australia and TruTag Technologies Inc., a tagging system was developed that connects physical tablets with Trillian – Google's scalable and cryptographic ledger system. The tags, made of silicon dioxide, contain nanopores that reflect very specific spectral patterns when scanned, essentially acting as edible barcodes. Silicon dioxide is recognized by the FDA as a Generally Regarded as a Safe (GRAS) agent and is currently used in various medicines and pharmaceutical products. The taggants are, therefore, safe to add to batches of tablets as part of the film coating system.

The technology can also actively engage patients in the authentication process as they can simply download a mobile application to scan their tablets and verify their legitimate status; plus provide patient information in a digital format. Information from the authentication application is then automatically transferred to Trillian, allowing companies to gain real-time information and identify instances of counterfeiting, diversion, and illicit trade. Not only can this type of approach help companies save money, that would otherwise be lost to counterfeiting, but it also establishes a stronger line of communication and trust with end-users, as many will be saved from potentially harmful incidents.

The FDA has also published additional guidance on physical-chemical identifiers, or PCIDs (substances that contain unique physical or chemical properties to authenticate drug products), in solid dosage forms (2). The guidance, which covers PCIDs includes inks, pigments,

flavors, and molecular taggants and informs manufacturers of the design considerations that must be made, and the supporting documentation required for the regulatory submission of such products. The existence of such guidance seems to suggest that, though the FDA is in support of more conventional serialization methods, they also recognize they are not comprehensive solutions. Adding additional layers of security, particularly at the dose form level, should be of interest to all pharmaceutical stakeholders who seek to improve the integrity of their supply chain and protect patient health and safety.

By incorporating microtags, the pill itself effectively becomes a barcode which can be digitally read and recorded, providing instant authentication. Colorcon's SoteriaRx on-dose authentication platform, provides a powerful tool for tracking medicines from plant to patient and provides a level of supply chain authenticity and transparency not previously available. The digitalization of medicines represents a major step forward in the fight against unauthorized and illegitimate pharmaceutical production and provides an opportunity to safeguard patients.

Kelly Boyer is Vice President, Film Coatings at Colorcon.

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The Supported Supply Chain

Alone, drug developers will struggle to reduce all the risks of counterfeiting. Further collaboration is needed. Staffan Widengren, Director Corporate Projects at Recipharm, and Dexter Tjoa, Chief Executive Officer at Tjoapack, describe the role that CMOs can play in the fight against counterfeits.

What challenges do manufacturers face when trying to prevent counterfeits?

Staffan Widengren: For the legal supply chain, one major challenge is improving efficiency during the packaging process. The serialization of a product is a complex process that requires the right equipment, the right software, and the right expertise. Even the smallest error can cause major disruption to supply, so companies either need to invest in internal resources or employ third party suppliers with the relevant experience.

Clearly, companies must also stay on top of evolving regulations. Many of the serialization measures are now a legal requirement, but there are likely to be further changes as we come to realize what works most effectively. For example, when it comes to the non-regulated supply chain and the online supply of medicines, there is still a long way to go. Ultimately, more regulations will be put in place to bring governance in line with the offline supply of medicines.

Aggregation (where the serialized data from each product pack is aggregated at the case and pallet level) is one way of overcoming efficiency challenges. This regulation is only required in some markets, but its implementation can streamline the journey of products through the supply chain, making packs more easily identifiable, if issues occur. The parent-child data relationship developed through the aggregation process also makes it harder for counterfeit medicines to enter the supply chain because of the level of data involved.

Currently, not all regulations are fully aligned across the globe and some, such as the US and Russian regulations, are more stringent than others. Serialization measures are a brilliant start, but represent just the first step.

Dexter Tjoa: I agree with Staffan; manufacturers are working hard to lessen the problems caused by counterfeiting. Over 40 countries are working towards or already have serialization regulations in place to ensure supply chain security and, ultimately, patient safety. However, the vast number of differing requirements and international standards as you move from market to market have made compliance very difficult.

Overcoming these complexities requires significant resources, CAPEX, and expertise. Many drug manufacturers are turning to contract packaging manufacturers for support in their adherence to regulatory requirements.

Is a more global regulatory approach needed?

Tjoa: As more countries legislate for serialization, the supply chain will become increasingly secure. Aligning regulations would be an ideal aspiration, but at the moment it's simply impractical; some regions lack the infrastructure or resources to implement the required processes. Market forces will more effectively resolve challenges related to different regulatory demands through their continued collaboration with regional contract partners who have the capacity to step in to develop and deliver the required serialization capabilities allowing businesses to maintain existing access as well as new markets.

Widengren: In my opinion, the industry should look towards developing a global program that could be implemented "as standard" across each country. At the moment, each country has its own legislation with individual requirements, which of course generates challenges. Introducing one global program would ensure that all companies have access to the required data and reduce inefficiencies throughout the supply chain. The more cohesive regulations become, the stronger the chance of completely removing counterfeit medicines from the supply chain.

Which emerging technologies and strategies are likely to have the greatest impact on the trade of counterfeit medicines?

Tjoa: As we move forward and as regulations evolve, there will be a number of opportunities for companies to review and transform their processes to allow for more efficient and secure packaging. Many companies are exploring data management systems that use technologies such as blockchain to create an immutable ledger that acts as a digital mirror of

the supply chain. Businesses will be able to use such data as the groundwork for platforms that can track logistics across the supply chain, and use analytics to improve current operational processes, such as inventory management.

Companies that adopt future-proof solutions now will find themselves with a competitive advantage when regulations do come into play; just like when serialization laws came into force, and the businesses that had already explored track and trace solutions were well equipped to meet compliance requirements quickly and efficiently...

Widengren: It is far too early to see the full effect of serialization and new legislation. But over time, as supply chain control increases and companies become more sophisticated at monitoring the movement of products, counterfeiters will find it increasingly difficult to push drugs into the market. As more standardization is introduced across various markets, it will become easier to monitor the overall supply chain. And many players in the industry have successfully managed to implement measures that can cater to numerous market requirements. At Recipharm, we invested in serialization right at the start of the industry discussion. We bolstered our resources and established a dedicated team to ensure we had the right measures in place. Those of us who took a proactive approach to tackling legislation are feeling the benefits now.

Over the years, huge steps have been taken to regulate the pharmaceutical supply chain, but problems still remain – especially when it comes to online platforms. Online drug sales make it incredibly hard to identify counterfeit medicines, track them, and stop them before they reach the patient. A higher level of governance is required to improve this situation. To prevent the non-regulated sales of counterfeits on the Internet, companies must face tougher penalties for failing to regulate their supply chains.

With all this being said, the supply chains of developed countries have generally been safe environments. Even before the introduction of laws like FMD and DSCSA, counterfeit medicines were very rarely found in the supply chain. And so, addressing supply chain issues in emerging markets will be crucial in rectifying the damage caused by the fake drug trade. Helping companies in these locations access new software and equipment should be a goal for everyone interested in protecting the global reputation of the pharmaceutical industry.

The Rise of the COVID-19 Scammer

The coronavirus pandemic has caused a surge in the number of counterfeit drug products available online and on social media platforms

As the COVID-19 pandemic has evolved, so too have the criminals operating websites, e-commerce platforms, and social media accounts that sell fake medicines to consumers. Preying on fear and misinformation of a much larger target "audience" has triggered a clear rise in the sale of falsified medicines and claims around treatments to cure COVID-19. We spoke to Mike Isles, Executive Director of The Alliance for Safe Online Pharmacy (ASOP) about the measures that should be taken to protect patients – and their data – from counterfeiters.

How has the COVID-19 pandemic affected the counterfeit medicine trade?

Lockdowns imposed worldwide have caused a surge in the number of people using the online environment to find medicines and other products related to the pandemic. Furthermore, pharmaceutical companies have had to adjust to managing changing supply chain demands from patients, governments, and other industry players, which has led, in some cases, to delays in access.

Criminals have adapted their activity to make the most of the crisis, as evidenced by the increased number of e-crimes reported to law enforcement authorities. For example, hundreds of thousands of domains containing COVID-related keywords have cropped up over the course of the past few months, leading patients to unlicensed online pharmacies.

The economic downturn and continued supply chain disruptions will, unfortunately, lead to further opportunistic criminal activity that could affect both patients and pharma well into the future.

How do counterfeiters use online platforms to market and sell their products?

At any one time, there are approximately 35,000 websites selling falsified or unlicensed medicines. This, combined with the fact that people are actively looking to buy medicines claiming to cure the virus, makes it easy for criminals to lure in consumers. Sophisticated organic search algorithms are set up to promote websites when COVID-related keywords are searched for. Criminals also infiltrate social media platforms. Consumers are open to various types of fraud, malware, and phishing attempts. And being "locked down" means many people are in front of their computers with more time on their hands and so, are more vulnerable to cybercrime. The FDA has set up the operation "Quack Hack" helping to prevent the sale of fraudulent medicine by working with online marketplaces, domain name registrars, payment processors, and social media websites to remove illegal platforms from the online ecosystem.

The US Homeland Security Investigations' special agents have also opened investigations nationwide, seized millions of dollars in illicit proceeds, made multiple arrests, and shut down thousands of fraudulent websites. On June 8, 2020, the FDA and the National Telecommunications and Information Administration (NTIA, part of the Department of Commerce) launched a pilot program to reduce the availability of prescription opioids and illicit narcotics available online. The program will work with three domain name registries – Neustar, Verisign, and the Public Interest Registry – to coordinate responses to registrants that don't appropriately respond to warning letters issued for online opioid sales.

What steps can pharmaceutical companies take to protect patients?

The pharmaceutical industry is already doing a great deal to protect the patients who use their medicines. Many companies belong to the Pharmaceutical Security Institute – a non-profit trade association whose mission is to address the problem of counterfeiting. Often, in the first instance, it is pharmaceutical security that discovers counterfeit medicines or breaches in the supply chain, and who then begin gathering evidence so that the national police can follow up and make connections with other law enforcement agencies, such as Interpol and Europol. In the EU, the Falsified Medicines Directive (FMD) has ensured that all prescription packs are uniquely identifiable in all Member States, which is a significant development in itself. However, I would strongly advocate that pharmaceutical companies join in the effort to educate the public and encourage all endeavors that attempt

to address the serious and growing challenge of counterfeit medicines. They should also advocate for upstream Internet governance legislation.

Do regulations for falsified medicines go far enough in addressing the problem?

Given the current scams around COVID-19, the answer has to be a clear no. The FMD is effective in dealing with the legitimate supply chain where there is a clear chain of custody, as a product moves from the manufacturer to the patient via the pre-wholesaler to the wholesaler (or distributor), to the pharmacist, and then to the patient (with some deviations from this due the movement of goods via parallel traders). However, it does little to address illegitimate Internet-based criminal networks. Here, order-taking and distribution are entirely Internet-based and involve both criminal and legitimate actors, such as national postal systems. While law enforcement is needed, I feel strongly that those who facilitate access to the Internet such as registries (these are the top-level domain names such .com, .eu, .co.uk) and the registrars (these are can be loosely termed as Internet service providers who have the right to sell domain names for website or email address). Other key actors that should also do more for good governance are social media companies

What other measures can be taken?

As previously mentioned, patient education is crucial in stopping counterfeiters. After all, it is the patient/consumer that creates the demand that criminals respond to. A survey conducted by ASOP EU showed that, depending on the country, between 35 and 58 percent of respondents had bought a medicine online at some point. Importantly, between 35 and 65 percent of customers were not aware that most of the websites selling medicines online were operating illegally. However, once they were informed, 96 percent of websites operating illegally were willing to change their behavior and seek out a local pharmacy or find an authentic online pharmacy. The results, though surprising, are a clear indicator of the support consumers need when navigating the online pharmaceutical environment. In my opinion, governments also need to play a more hands-on role in educational campaigns, ensuring that they are in line with the legal obligation of FMD and other serialization legislations.

One potential approach is to adopt the top-level domain name .pharmacy, which was acquired by the National Association of Boards of Pharmacy to verify the legitimacy of online pharmacies. Any person buying a medicine from a website with this internet address will be buying from a website that has passed all of the necessary regulations for the country they operate in.

In addition, and equally important, are new legal measures. ASOP EU and its partner organizations believe that any future laws must tackle the problem at the source. Put simply, those that manage and run Internet domain names should be brought to account and should make substantial attempts to ensure the safety and security of users. In other words, domain name registries and registrars need to be held accountable. The Digital Services Act in the EU will shortly replace the eCommerce Regulation that is now outdated. This piece of legislation is our best chance to put in place legislation that provides more robust Internet governance. For us at ASOP EU, it is all about going to the top of the Internet and ensuring that we stop the horse bolting – because once it's out then we are back to downstream law enforcement measures and we know how complex it can be to apprehend criminals who operate their businesses from different parts of the globe. If such actors can be held accountable, we should begin to see a huge difference in the way the falsified medicine crisis can be handled.

Inside the Medicine Machine

Fast, Non-destructive Solid-State Testing

How Raman spectroscopy-based technologies enable the pharma industry to streamline analytical workflows

Lee Dowden, Product Manager for Agilent's TRS100, worked in various analytical roles in the pharma industry – including product release testing, method development, stability testing, cleaning validation, and instrument validation – before entering the equipment industry. We catch up with him to find out how transmission Raman spectroscopy (TRS) works.

How is TRS used?

Laboratory techniques for the analysis of solid dosage forms have traditionally relied upon extraction of the API followed by chromatographic separation – either high-performance liquid chromatography or gas chromatography. Although advances have been made in these techniques, they have not fundamentally changed and tend to rely on time-consuming solvent extraction, which also creates a significant amount of waste. Spectroscopic solutions, such as near infrared spectroscopy, can help overcome some of the issues associated with chromatography, but still have limitations. TRS was developed to overcome key pain points and technological concerns.

TRS is a variant of traditional Raman spectroscopy that is particularly well suited to analyzing bulk content, including tablets and powder samples. It can be used for both formulation development and finished product testing. TRS only became commercially available around 10 years ago, with the launch of Cobalt Light System's TRS100 instrument. Cobalt was founded in 2008 as a spin-out from the UK Science and Technology Facilities Council (STFC), and developed technologies from the research and innovations of Pavel Matousek, a senior fellow at STFC, into commercial products for non-invasive analysis. The TRS100 was the first product to be launched by the company. Cobalt is now part of Agilent's Molecular Spectroscopy division.

"TRS is a variant of traditional Raman spectroscopy that is particularly well suited to analyzing bulk content, including tablets and powder samples."

TRS is a fast (typical analysis time of 10–60 seconds), non-destructive analytical test, with no sample preparation or solvent use, and is used in pharma QC labs for a variety of applications, including polymorph determination, analyzing crystalline content in amorphous dispersions, excipient compatibility assessments for formulation development, content uniformity testing, and at-line, in-process testing.

The TRS100 automates the qualitative and quantitative analysis of large samples (>100 at a time) of pharmaceutical dosage forms with fast measurement times. It can reduce content uniformity, assay, and ID tests from hours, or even overnight, to minutes per batch, cutting costs significantly and speeding up the quality control workflow.

How does TRS work?

The system works by using Raman spectroscopy in transmission mode, where monochromatic light (a laser), interacts with molecular vibrations,


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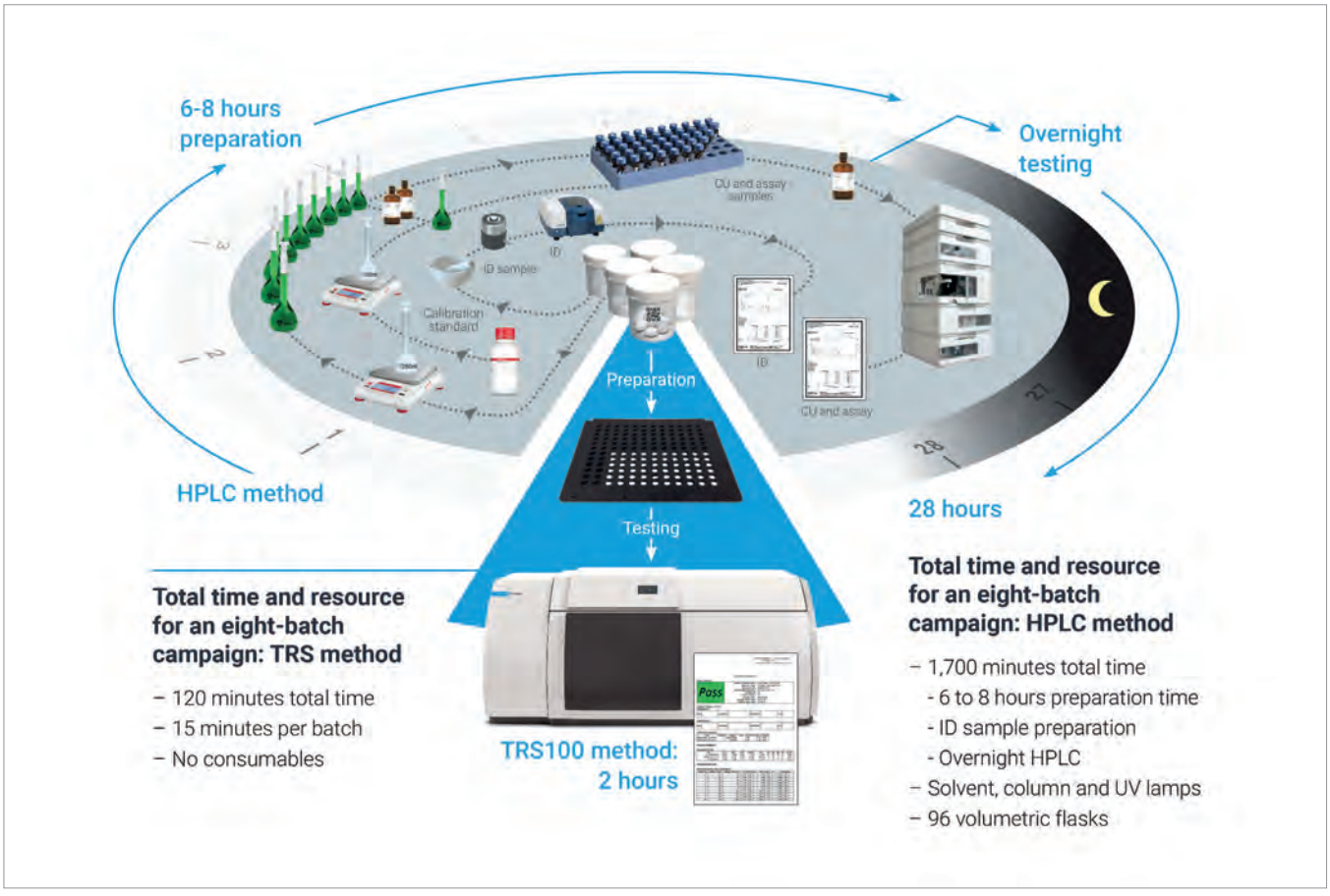
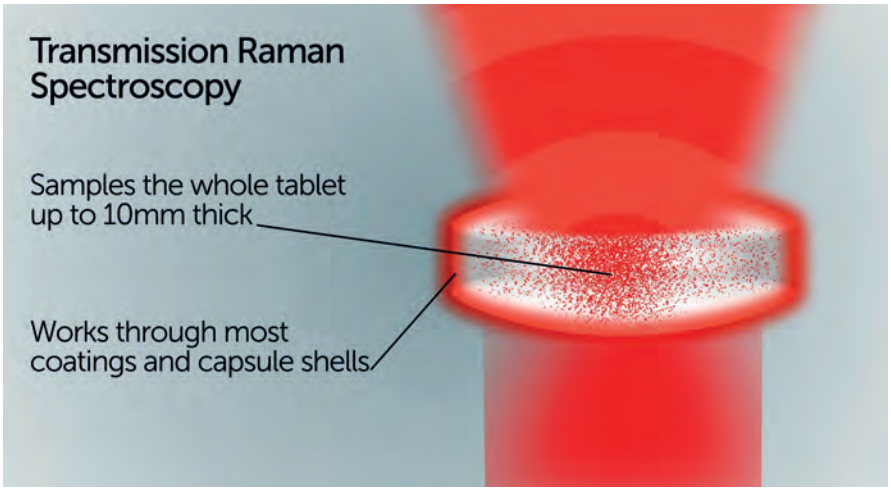


phonons, or other excitations within a molecule, resulting in a shift of energy of the laser photons. This shift in energy gives a specific Raman shift pattern for the molecule(s). In TRS, the bulk of the sample contributes to the signal (compared with the surface in traditional backscatter Raman), which means more of the sample is used in the analysis.



What are the challenges of designing and building an efficient TRS system?

In the pharma industry, instrument developers must always consider usability, serviceability, and reliability. The ideal is to have a user-friendly instrument that someone can use with very little training – and rely upon every day, with minimal upkeep. You also need to ensure the system is flexible enough to use with many different pharmaceutical dosage forms – tablets and capsules come in many different shapes and sizes, for example. A system also needs to incorporate plastic bags, vials, cuvettes

and well plates for use with powders, creams, pastes and suspensions.

One aspect that is often overlooked with instrument development is software. Not all users realize how much time goes into developing efficient and user-friendly software. It is very challenging for software developers to ensure that the programs they create are fully compliant with regulations and genuinely intuitive to use with simple routine workflows – while also ensuring there is full functionality for the advanced user.

With all this in mind, the team behind the TRS100 had to work hard to create a walk-up analyzer with both hardware and software explicitly developed for pharmaceutical users.

What is your advice in terms of care and maintenance to ensure a long system life?

When a lot of care is put into developing a system, it should not need significant care or maintenance. With the TRS100, routine instrument tests are performed automatically to ensure that the system is working correctly. However, periodic cleaning of the dust collection tray should be performed and an annual preventative maintenance visit by a trained engineer is recommended.

What industry trends will shape the development of future systems?

Increased demand for testing during the drug manufacturing process (both batch and continuous manufacturing) means that rapid analytical techniques play a crucial part in the process control strategy and real-time release. Finished drug product analysis should not just rely on the quality control laboratory and should be a necessity on-line or at-line in the manufacturing facility.

As more drug products based on complex formulation strategies emerge, the use of techniques for characterizing the API form (polymorph, amorphous, crystalline) will become increasingly important.

Another Raman technology helping pharma manufacturers with increased demand for testing is spatially offset Raman spectroscopy (SORS). Agilent recently launched the Vaya Raman raw material identity verification system, which uses SORS technology to analyze materials inside sealed opaque containers. Vaya verifies raw material ID through transparent and non-transparent packaging, testing more materials for the same cost by reducing the need for sampling.

The Next Big Thing?

Patient-Centric Printing

A proof-of-concept study indicates that stencil printing can be used to manufacture a range of flexible dosage forms

By Henrika Wickström, Researcher, Åbo Akademi University, Finland.

In recent years, additive approaches to the manufacture of medicines have become more popular, offering companies the opportunity to develop flexible and tailored dosage forms that better meet patient needs. And while 3D and 4D printing are exciting avenues for the industry to further explore, stencil printing has thus far been overlooked.

Stencil printing refers to a low-cost, high-throughput printing technique that is used across various industries to produce everything from electronics to artwork – but it has not yet found its way into the pharma industry. In stencil printing, ink is transferred onto a substrate through a series of apertures in a printing plate. And, just like the stencils used by kids, the apertures determine the pattern and design of the printed product.

The test case

With an increasing focus on patient-centricity, companies must consider the best dosage form for the target population. When it comes to patients who struggle to swallow regular tablets, such as children and the elderly, orodispersible films represent an interesting option for the administration of low dose drugs – and a good test case for stencil printing. In a proof-of-concept study, my colleagues and I explored whether stencil printing could be used to manufacture the antipsychotic haloperidol in an orodispersible disc formulation suitable for children aged between 6 and 17. We also investigated whether the printing technique would lend itself to a decentralized manufacturing model that enabled production of medicines in close proximity to patients. Pharmacies and hospitals, in particular, would benefit from this approach as medicines could be printed as and when needed – addressing potential deficits in product supply and giving them capacity to tailor doses to patients. Our findings supported this idea.

First, we designed a prototype flatbed printer that allowed us to produce orodispersible discs in a batch-wise manner. And then we turned our attention to the development of the API-containing ink – a significant hurdle for manufacturers looking into additive technologies. Indeed, we spent considerable time determining how the physicochemical properties of the API and its dispersion through the ink affected viscosity and therefore printing performance. Throughout the ink development process, we had to conduct a series of tests to assess i) the viscosity of the ink, ii) how well the liquid portion of the ink could adhere to the substrate used, iii) the removal of the dried film from the substrate and iv) if the binders and solvents would allow the ink to dry quickly enough to prevent delays to the overall production process.

"When it comes to patients who struggle to swallow regular tablets, such as children and the elderly, orodispersible films represent an interesting option for the administration of low dose drugs."

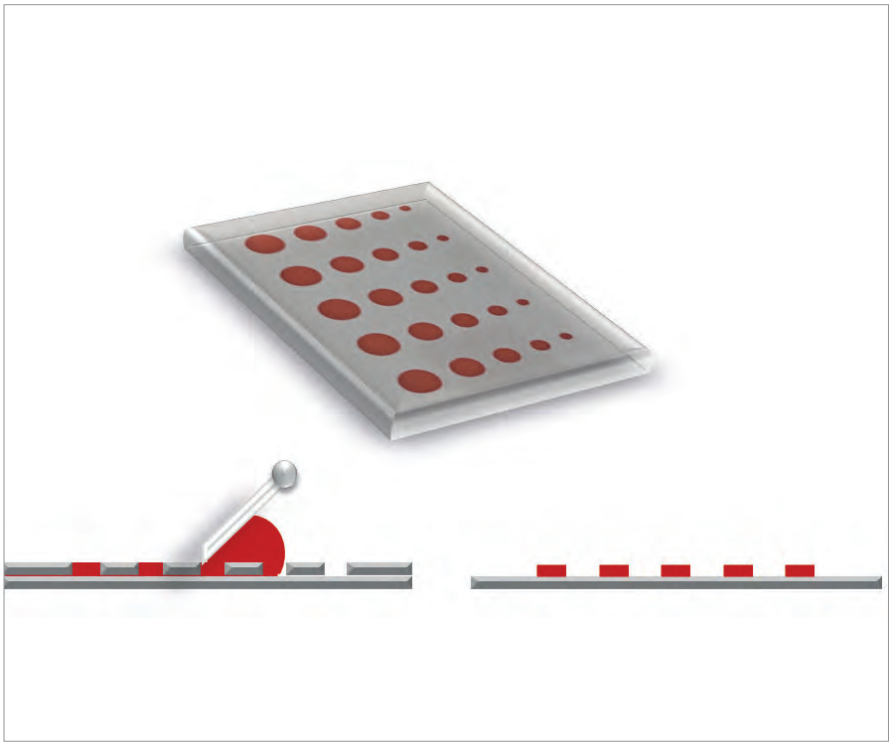


Figure 1. Stencil printing plate (top) and print result (right) of a flatbed process (left)

Success?

We were able to print our haloperidol-containing ink to produce final dosage forms that varied in strength between 0.5 mg and 2.5 mg of API, making them suitable for the treatment of children across the target age range. And, I must admit, we were excited by the results – they proved to us that stencil printing has the potential to be used as a pharmaceutical manufacturing technique. At the same time, we know we have to maintain a sense of realism about the technology. Though we were able to create a range of flexible dose forms with our stencil printer, the formulation of inks containing other relevant APIs is still a challenge.

We also acknowledge that we could optimize our drying times by adjusting the solvent composition and amount. It would also be interesting to study crystalline, pasty inks for stencil printing to evaluate the printability of another type of ink formulation.

"In short, our study established that stencil printing can be used successfully to manufacture orodispersible medicines, and we've already identified some technical areas for improvement."

The future

In short, our study established that stencil printing can be used successfully to manufacture orodispersible medicines, and we've already identified some technical areas for improvement. Next, we – and the wider pharmaceutical community – must answer additional questions to ensure the suitability and viability of stencil printing in commercial production; in particular, how can this technology be adapted to meet GMP requirements? Is it possible to develop an automated stencil printer with its own drug-containing ink supply? Can stencils be reused without compromising the integrity of drug products?

As with any technology, we must remember that different additive manufacturing techniques have unique strengths and weaknesses; though stencil printing was shown to be effective in this particular instance, another technology may be better suited to the development of other dosage forms. In-line quality control methods will need to be developed to ensure the quality of stencil printed products at various dose strengths. It will also be important to assess the benefit to patients versus the cost of production. I think it will be interesting observe the interplay between health professionals and those who develop specialist printing technologies over the coming years.

But in my opinion, there is a place in the pharmaceutical industry for a variety of additive manufacturing technologies, including stencil printing. They work well alongside more conventional manufacturing techniques, allowing companies to flexibly produce more niche products. With a broader range of manufacturing options, companies will be better equipped for their pursuit of patient-centric drug formulations.

The Adaptable Harbinger

Sitting Down With... Sauri Gudlavalleti,
Global Head of Integrated Product Development Organization (IPDO), Dr. Reddy's Laboratories

Why did you pursue a career in science?

From an early age, I knew I wanted a career in the sciences. My father was a nuclear scientist and we lived in a community full of scientifically-driven minds; our town in South India was adjacent to a major nuclear plant and R&D center. It was a place where professionals were solving problems in physics and chemistry – two subjects I had a keen interest in. I wanted to have the chance to do something meaningful with my professional life and I always felt that a career in science would help me achieve that.

How did you get involved in pharma?

I spent many years in my early career as a product development scientist in different engineering companies, working in a variety of areas including energy equipment, hydrogen production, and even mobile phone screens. I later moved into management consulting to help companies improve their R&D processes. Interacting with sectors as varied as oil and gas and farming equipment presented unique and interesting challenges, but I was drawn to the generic pharma industry. It was a complex area, but there seemed to be so many opportunities for improvement. And it felt like an industry that was meant for me because I'd really be able to have a meaningful and lasting impact.

What were the challenges of transitioning into the industry?

Generic pharma is one of the few industries that is truly cross-functional from end-to-end. On a daily basis, individuals are developing solutions that address everything from technology to patient health to intellectual property and government regulation. These factors, combined with the global footprint and multi-year product lifecycles, necessitate very robust systems and processes in everything we do.

When I first entered the industry, I found that I was able to bring my past experiences from outside of pharma to bear. Management consulting had taught me how best to deal with people; it gave me an understanding of their motivations and how different approaches can be used to get the best out of them. It became important for me to apply this knowledge to pharma R&D to help manage the scientific talent around me. I was also familiar with the use of Six Sigma for product development and bug tracking to minimize dossier deficiencies. I knew that by introducing these concepts to my colleagues, we would all stand to gain.

What experience had the greatest impact on your career trajectory?

In 2008, I decided to return to India from the US to pursue an MBA. It was a massive step as I had chosen to move from a predictable and stable job in Silicon Valley to India, where advanced technologies were just beginning to grow and flourish. It was truly an adventure! And, ultimately, it helped me handle even more professional challenges with an open mind and a versatile approach.

And your career highlights?

In 2004, as a bench scientist, I was part of a GE team that built a Solid Oxide Fuel Cell prototype. These electrochemical devices are able to produce electricity by directly oxidizing fuel. I was proud of the fact that our project broke the world record on certain performance dimensions! The goal appeared impossible when we started out, but we overcame multiple design, manufacturing, and experimental challenges over the course of a year to achieve this milestone.

As a business consultant, I led a team that turned around an auto component company with declining profits. Over 15 months, we re-energized the leadership and worked together to double the company's profitability and turn around several underperforming factories.

And now at Dr. Reddy's, I am part of a very exciting large-scale R&D transformation, which aims to double our global dossier submissions, crack complex technologies, and significantly reduce the cost of our products. We are doing this by implementing streamlined processes and governance, engaging the workforce, and adopting advanced experimental and modeling techniques across R&D. The most exciting part of it all is the digital transformation we have embarked on. Every process, every experiment, and every document we now create is fully digitized.

Has mentorship played an important role?

I am fortunate to have had several mentors throughout my career. Some have helped open doors for me, while some have helped me see and learn new dimensions in whatever I did. There are others who were not formal mentors but rather leaders from whom I learned by observing. What I have gained from all my mentors is a variety of tools and approaches to solve problems. Whenever faced with a challenging situation, I run through examples of how the best leaders around me have dealt with similar situations – and this helps me find the best way forward.

What advice would you give science and engineering graduates who are considering leadership?

Always be in touch with what is happening "on-the-ground" in any field you decide to work in. It is all too easy to get lost among computer simulations, spreadsheets, and slideshows. Even in a business leadership position, a scientist or an engineer is best placed for leadership because of their ability to connect with the actual operations of the business.

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