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Preparing for the Third wave

Even if we need global help to meet today's needs, we have to shore up infrastructure for future disruptions

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Preparing for the third wave

Even if we need global help to meet today's needs, we have to shore up infrastructure for future disruptions

A recent International Monetary Fund (IMF) report's prediction that vaccine coverage in India could remain under 35 per cent of our population by this year-end, inspite of the government's claim that the full population would be covered, is worrying at several levels.

From a public health perspective, the under-vaccinated will still be vulnerable to the infection and therefore lead to many subsequent waves. From an economic perspective, while the pandemic is lowering business sentiment, it is also an opportunity for sectors like pharmaceuticals, medical devices and hospitals to scale up. Even if we need global help to meet today's needs, we have to shore up infrastructure for subsequent waves of this and future pandemics.

Indeed, even as overseas companies are holding out for pre-orders, advance payments and indemnity clauses, the government has finally given in and waived local clinical trials for "well-established companies". No company can ignore the size of the Indian population and the market it represents. Especially as it looks like annual SARS-CoV2 booster shots will be required for at least a couple of years.

Which is why Bharat Biotech has applied for approvals in more than 60 countries. Other vaccine manufacturers from India too will do the same, not just to shore up exports but to ensure that vaccinated citizens will be allowed to travel to as many countries as possible, once they have key approvals in place. The era of vaccine passports is already a reality today.

As the vaccine and medical device supply chains are being re-jigged, so must the API supply chain, especially for medicines required for COVID-associated conditions like mucormycosis, for example. Medicines to treat fungal infections were usually manufactured in small volumes as the number of cases were much lower. Now, Mumbai-based VAV Life Sciences, which is reportedly the only Indian company that makes the highly purified synthetic lipids needed to produce Amphotericin B formulations, the medication used for treating black fungus infections, finds itself scrambling to scale up from a monthly capacity of 21 kgs to 65 kgs by August, and a further increase to 130 kg per month by December, as per Arun Kedia, MD, VAV Life Sciences.

The clinical trials sector in India is also seeing a revival. Biotech and biopharma clinical trial sites in the Asia Pacific have increased by over 40 per cent each year on average, compared to just 11 per cent across the rest of the world, as per some estimates. Thus it is no wonder that major CROs like IQVIA Biotech recently announced their launch in India, along with across the Asia Pacific and Japan (JAPAC) region.

But as we rush repurposed medicines through clinical trials in the race to get emergency use authorisations for COVID-19 use, properly conducted clinical trials will be very important to determine the true value of such molecules.

Dr Arun Bhatt, a clinical research and drug development consultant points out the COVID-19 trials and tribulations in a recent article explaining how a majority of clinical trials of repurposed drugs in India suffer from a high risk of bias. Most have been conducted in a small population of mild and moderate COVID-19 patients, using viral clearance, or clinical scale as efficacy endpoints. He points out that viral load reduction, as an endpoint is difficult to assess because of sensitivity and specificity limits of RT-PCR, and discordance between detection of virus from nasal and oropharyngeal swabs. Also, there is no established predictive relationship between the magnitude and timing of viral reductions and the extent of clinical benefit for a patient.

Dr Bhatt mentions the most recent example of such a trial, for 2-Deoxy-D-Glucose, which recently received the DCGI/CDSCO nod. He flags one major concern as the safety in COVID-19 patients who can suffer from myocarditis and develop diabetes mellitus.

The WHO's recently released World Health Statistics report 2021 and global COVID-19 excess mortality estimates warn that the COVID-19 deaths could be at least two to three times higher, based on preliminary excess mortality estimates for 2020. Globally, and in India, deaths in 2021 have already surpassed cases and deaths reported in the whole of 2020. Thus, while we cannot afford to get complacent once more, neither can we rush through clinical trials or approvals.

CIPLA signs licensing deal with Lilly to manufacture and commercialise baricitinib in India

Baricitinib was issued a restricted emergency use approval by CDSCO to treat COVID-19

Cipla announced that it has signed a royalty-free, non-exclusive voluntary licensing agreement with Eli Lilly and Company, US for the manufacture and commercialisation of the drug baricitinib for COVID-19 indication. Baricitinib was issued a restricted emergency use approval by the Central Drugs Standard Control Organization (CDSCO), Ministry of Health, India for use in combination with remdesivir for the treatment of suspected or laboratory confirmed COVID-19 in hospitalised adults requiring supplemental oxygen, invasive mechanical ventilation, or extracorporeal membrane oxygenation (ECMO). This collaboration is a step further in Cipla's efforts to enhance access to critical treatments for patients affected by the pandemic.

Commenting on the partnership, Umang Vohra, MD and Global CEO, Cipla said, "Enabling access to high-quality treatment and medication is core to our purpose of 'Caring for life.' Through the pandemic, Cipla has been at the forefront of COVID care and our partnership with Lilly is a demonstration of our unwavering commitment to care towards patients impacted by COVID-19."

Lilly India gets nod for restricted EU of monoclonal antibody drugs, bamlanivimab and etesevimab to treat COVID-19

Bamlanivimab and etesevimab together have been authorised under Emergency Use Authorization in the US and select EU countries, for the treatment of mild to moderate COVID-19

Eli Lilly and Company, India announced that it has received permission for restricted emergency use of its antibody drugs, bamlanivimab 700 mg and etesevimab 1400 mg, in India for the treatment of patients with mild to moderate coronavirus disease 2019 (COVID-19). Bamlanivimab and etesevimab together are indicated for restricted use in emergency situation, IV route for the treatment of mild to moderate corona virus disease 2019 (COVID-19) for injection administration in hospital settings in adults and pediatric patients (12 years of age and older weighing at least 40 kg) with RT-PCR positive results of direct SARS-COV2 viral testing and who are at high risk for progressing to severe COVID-19 and/or hospitalisation and do not

require oxygen. The company informed that it is engaging in active dialogue with the Indian government and regulatory authorities to donate bamlanivimab and etesevimab in order to speed up access and provide treatment options for patients with COVID-19.

Bamlanivimab and etesevimab together have been authorised under Emergency Use Authorization in the US and select EU countries, for the treatment of mild to moderate COVID-19.

Luca Visini, MD, India Subcontinent, Lilly India, said, "We are pleased that we have another innovative treatment option to offer India's healthcare providers who continue to be at the forefront of the battle against COVID-19. Lilly is committed to contributing to the alleviation of the COVID-19 pandemic in India and around the world. We will continue to assess and evaluate how our existing portfolio and ongoing research can benefit patients with COVID-19."

Earlier in May, Lilly had also received permission for the emergency use of baricitinib in combination with remdesivir, for the treatment of suspected or laboratory confirmed coronavirus disease 2019 (COVID-19 in hospitalized adults requiring supplemental oxygen, invasive mechanical ventilation, or extracorporeal membrane oxygenation (ECMO).

Understanding molecular actions may be key in treating severe COVID-19 cases: Study

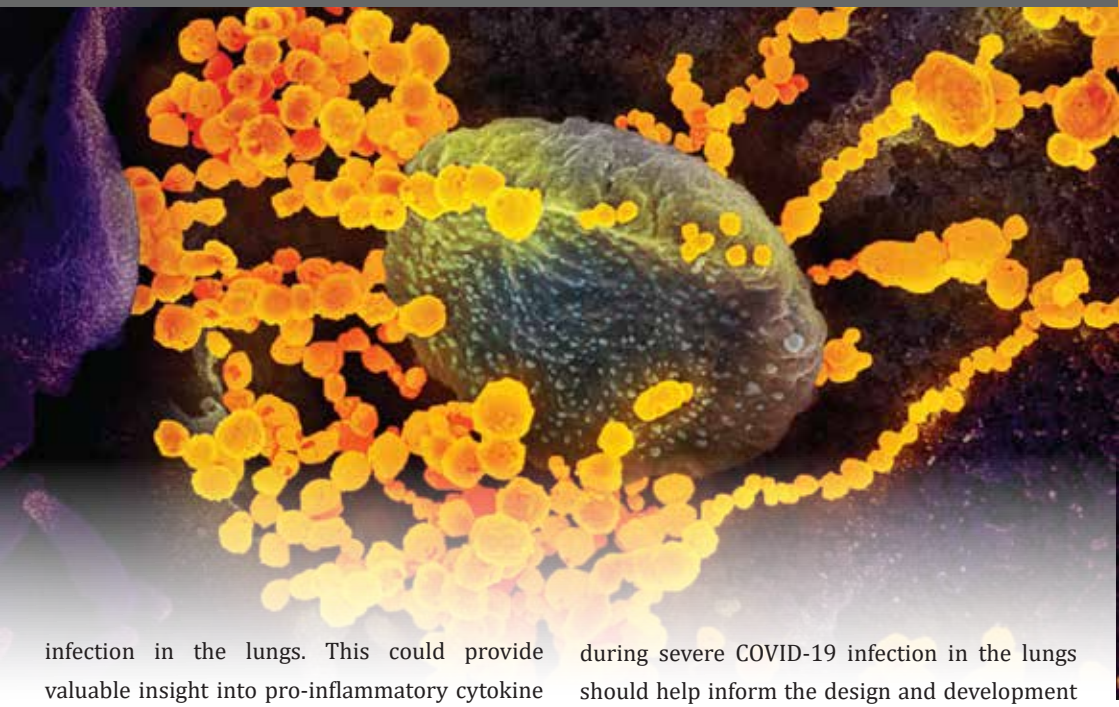
A recent study at the Bar Ilan University has found that RNA molecules play a significant regulatory function in immune response role in immune response, and their understanding their interactions might be a target of precision medicine

In a recent study conducted at the Azrieli Faculty of Medicine of Bar-Ilan University, researchers have reported the role of several lncRNAs in anti-viral inflammatory response regulation. Considering their significant regulatory function in immune response, the researchers sought to identify lncRNAs co-expressed with human genes involved in immune-related processes during severe SARS-CoV-2 infection in the lungs.

Recent studies demonstrated that patients afflicted with severe SARS-CoV-2 infections present increased levels of pro-inflammatory plasma cytokines, as opposed to milder cases, highlighting the release of inflammatory cytokines as being central to COVID-19 severity. However, the underlying molecular mechanisms responsible for dysfunctional immune responses during COVID-19 infection remain elusive.

In a paper recently published in the journal Viruses, the researchers demonstrated that lncRNAs are indeed potential regulators of anti-viral response during severe SARS-CoV-2 infection. Using the available transcriptome data from the lung cells of severely affected COVID-19 patients and SARS-CoV-2 infected lung-cell-lines, they constructed a gene co-expression network that can measure the relationship of gene expression patterns across a group of samples. This analysis enables them to identify four differentially expressed lncRNAs that are found to be strongly correlated to the protein-coding genes in a novel network enriched for different immune-related processes associated with dysregulated cytokine production. These four lncRNAs were also identified as "hubs" – important nodes in this co-expression network, signifying their association with cytokine over-production due to fierce immune response.

The finding suggests that the aberrant expression of lncRNAs can be associated with cytokine storms and anti-viral responses during severe SARS-CoV-2 infection. Thus, the present study uncovers the potential associations of lncRNAs in cytokine and interferon signalling during the response to severe SARS-CoV-2



infection in the lungs. This could provide valuable insight into pro-inflammatory cytokine production and how to mitigate it. It could also potentially be utilized as a future drug target to combat the hyper-inflammation caused by SARS-CoV-2 infection.

"It is remarkable that a major part of the human genome is filled in by non-coding regulatory elements, formerly known as "junk DNA". Among these are the long non-coding RNAs (lncRNAs). These lncRNAs are receiving more and more recognition as the potential regulators of several diseases," says Dr Milana Frenkel-Morgenstern, of Bar-Ilan University's Azrieli Faculty of Medicine, who led the study with Prof David Karasik.

This study sheds light on the mechanisms behind COVID-19 severity and dysfunctional immune responses. Understanding the molecular interactions behind the immune dysfunction during severe COVID-19 infection in the lungs should help inform the design and development of novel approaches for treating severe COVID-19 patients.

The researchers plan to validate their findings on human samples and further aim to determine which drugs from their COVID-19 drug database may inhibit the cytokine storm generation in COVID-19and will design experiments to test the efficacy of those drugs.

This study was supported by a grant from the COVID-19 Data Science Institute (DSI) at Bar-Ilan University and a PBC fellowship for outstanding postdoctoral researchers from China and India (to Dr Sumit Mukherjee, who participated in the research) from the Israel Council for Higher Education.

Scientists identify drug that prevents multiple coronavirus variants

Findings suggest that the drug diABZI activates the body's innate immune response, the first line of defence against invading pathogens

Scientists have identified a new drug which is highly effective in preventing severe COVID-19 in mice infected with SARS-CoV-2, and could also treat other respiratory coronaviruses.

The findings, published in the journal Science Immunology, suggest that the drug diABZI activates the body's innate immune response, the first line of defence against invading pathogens.

"This paper is the first to show that activating an early immune response therapeutically with a single dose is a promising strategy for controlling the virus, including the South African variant B.1.351, which has led to worldwide concern," said Sara Cherry, a professor at the University of Pennsylvania in the US.

"The development of effective antivirals is urgently needed for controlling SARS-CoV-2 infection and disease, especially as dangerous variants of the virus continue to emerge," Cherry, the senior author of the study, said.

The SARS-CoV-2 virus initially targets epithelial cells in the respiratory tract.

As the first line of defence against infection, the respiratory tract's innate immune system recognises viral pathogens by detecting their molecular patterns.

The researchers first sought to better understand this effect by observing human lung cells infected with SARS-CoV-2 under the microscope.

They found that the virus is able to hide, delaying the immune system's early recognition and response.

The team predicted that it may be able to identify drugs that could set off this immune response in the respiratory cells earlier and prevent severe SARS-CoV-2 infection.

To identify drugs that would block SARS-CoV-2 infection, the researchers screened 75 drugs that target sensing pathways in lung cells.

They identified nine candidates that significantly suppressed infection by activating STING — the simulation of interferon genes which plays an important role in innate immunity.

The team tested a newly-developed drug molecule called diABZI, which is currently being tested in clinical trials to treat some cancers.

The researchers found that diABZI potently inhibits SARS-CoV-2 infection of diverse strains, including variant of concern B.1.351, by stimulating interferon signalling.

Interferons are a group of signaling proteins made and released by host cells in response to the presence of several viruses.

The scientists tested the effectiveness of diABZI in transgenic mice that had been infected with SARS-CoV-2.

Because the drug needed to reach the lungs, diABZI was administered through a nasal delivery.

Mice treated with diABZI showed much less weight loss than the control mice, and had significantly-reduced viral loads in their lungs and nostrils, and had increased cytokine production.

The findings provide further support that diABZI stimulates interferon for protective immunity, the researchers said.

The study also offers promise that diABZI could be an effective treatment for SARS-CoV-2 that could prevent severe COVID-19 symptoms and the spread of infection, they added.

Keeping pace

***Environmental risk, biosafety and other key regulatory considerations for cell and gene therapy trials* - By Dr April Marquick**

In recent years, the gene therapy regulatory landscape has evolved from a broad, general guidance to a narrower focus on testing and manufacturing considerations in specific disease states. This article explores how factors such as environmental risk assessment and biosafety can impact gene therapy clinical study start-up as well as the continuing evolution of guidances from the European Medicines Agency (EMA) and US Food and Drug Administration (FDA).Tracking the complexity in the global regulatory landscapeThe regulatory landscape in the United Kingdom (UK) and European Union (EU) is increasingly complex, reflecting the advancement of gene therapy research. Aside from the EMA, a gene therapy product will have to undergo review by individual member states' competent authorities (CAs), ethics committees (ECs), and/or genetically modified organism (GMO) authorities. To ease the complexity, the EMA has created the Committee of Advanced Therapies (CAT), whose responsibilities include providing scientific recommendations on the classification of advanced therapy medicinal products (ATMPs) as gene therapy medicinal products (GTMPs), somatic cell-therapy medicinal products (sCTMPs), tissue-engineered medicines (TEPs), or combinations thereof.

Since January 2020, the FDA has issued nine separate guidances specifically focusing on cell and gene therapy,1including recommendations regarding the design of long-term follow-up

studies.2 Additionally, the Recombinant DNA Advisory Committee (RAC) recently refocused its role to follow and provide advice on safety and ethical issues associated with emerging biotechnologies and renamed itself the Novel and Exceptional Technology and Research Advisory Committee (NExTRAC), reflecting its broader outlook.

These developments have led to faster approval timelines, with 68% of novel drug approvals in the US in 2020 using at least one of the FDA's expedited development and review pathways to speed approval.3 These include the agency's Fast-Track designation, and the Regenerative Medicine Approved Therapy designation, which covers a growing number of gene therapy products.

Environmental risk assessment and biosafety take centre stageSponsors seeking rapid and efficient study start-up must provide actionable information to facilitate regulatory decision-making. Such information should include assessment of potential risks identified in preclinical studies (eg, integration activities of the gene therapy product into the genome, genome editing, prolonged transgene expression, latency, persistent infections) and how they may affect clinical trial design.

Consequently, toxicology and biodistribution studies have become increasingly relevant in gene therapy trials. The strength of the preclinical package, therefore, often depends on biodistribution data that show where the vector travels, a factor largely determined by the route of administration. That underscores the importance of up-front collection of non-clinical data to shorten long-term follow-up, especially when the literature offers limited information on similar products.

Paralleling the industry's heightened focus on patient-centricity, regulators increasingly insist that clinical trial protocols incorporate strategies to minimise inadvertent horizontal and vertical transmission of genetic material and/or vectors. Though essential for ensuring trial participants' safety, such strategies may necessitate up to 15 years of long-term follow-up with regular collection of blood and other samples.2Mode of action and regulatory pathway selectionMode of action is a key consideration in product classification and regulatory pathway selection, though it can sow confusion among trial sponsors, particularly for studies conducted in the UK and EU. For example, the EMA may classify a genetically modified cell therapy product as a GTMP, even if the genetic manipulation was ex vivo, necessitating compliance with applicable gene therapy guidelines and regulations.

A GTMP incorporating a medical device would raise additional questions, including, "Is it really a combination product?" and "Is the mode of action really related to the medical device, or does the device merely supplement for administration of the investigational medical product (IMP)?"

The uncertainty underscores the importance of up-front discussion with the regulators, especially the EMA, as CAs in different EU member states seem to view these issues differently.

Managing the competent authoritiesThe varying perspectives of the different states' CAs largely reflect the two distinct decision routes to approval:

• *Contained Use, defined as 'any activity for which specific containment measures are used to limit their contact with, and to provide a high level of safety for, the general population and the environment'4*

• *Deliberate Release, or 'any intentional introduction into the environment…for which no specific containment measures are used'. 5*

Germany, for example, favours the deliberate release route and has specialised CAs for biologics and gene therapy, with specific gene therapy documents required for submission and an EC review and approval process that is the same as that for a standard IMP. The advantage of this approach is that one CA reviews the product not only from the clinical trial directive but also from the deliberate release directive.

By contrast, the UK often assumes the contained use route. The Health and Safety Executive (HSE), the UK GMO authority, does not require additional approval for a Class 1 (no or negligible risk6) contained-use product, though trial sites need an HSE permit to certify that they have the right procedures in place for handling such products. Additionally, instead of a single standard EC review, the UK may require specialised reviews from each of the following:

• *Gene Therapy Advisory Committee (GTAC), which grants ethical approval for gene therapy clinical trials*

• *Gene Therapy Modification Safety Committee (GMSC), which reviews trial protocols and assesses potential risks and from which individual sites must also secure approval*

• *Clinical Trials, Biologicals and Vaccines Expert Advisory Group (CTBVEAG), a division of the Medicines and Healthcare products Regulatory Agency (MHRA) that oversees certain biologics and gene therapy products, and which may require additional meetings to discuss challenging or complex trials.*

Of all the EU member states, Poland presents what may be one of the most complex regulatory landscapes for gene therapy clinical trials. Poland requires prior GMO authority approval before a sponsor can submit the standard clinical trial application, parallel CA and EC review, and mandates a two-step process for GMO authority approval. The first step is a site permit that allows sites to work with specific classes of products.4 The second step is a study-specific approval, which can only occur once all study sites have appropriate permits. If a sponsor chooses sites that already have permits, it can accelerate the study start-up process.

3. No dedicated reimbursement and funding pathways

Efforts to integrate DHTs have resulted in a mix of nationally run access schemes and regionally funded programmes. Access and coverage often vary by private and government payers within each country, depending on the healthcare landscape. Each payer is likely to have its own guidelines for DHT adoption. Even in the absence of a definitive policy, public as well as private insurers reimburse for DHTs only when there is a strong rationale for their use.

In the US, the Prescription Digital Therapeutics to Support Recovery Act aims to change Social Security to support the use of DHTs, and individual insurance plans roll out specific programmes like the digital health programme 'Level2' by UnitedHealth for type 2 diabetes patients. In Latin America, the situation is more complex due to the mix of private insurers and high share of patients paying out of pocket, but there are examples of public/private digital health partnerships aimed at supporting access to medical services in rural areas using DHTs. In Europe, funding sources for DHTs are country dependent: in the UK, the NHS England's Innovation and Technology Tarif (ITT) and the Innovation and Technology Payment (ITP) are available at the national level and clinical commissioning funding at the regional level, whereas, in Germany, the Digital Healthcare Act allows doctors to prescribe health apps to patients which are reimbursed by the statutory health insurance.

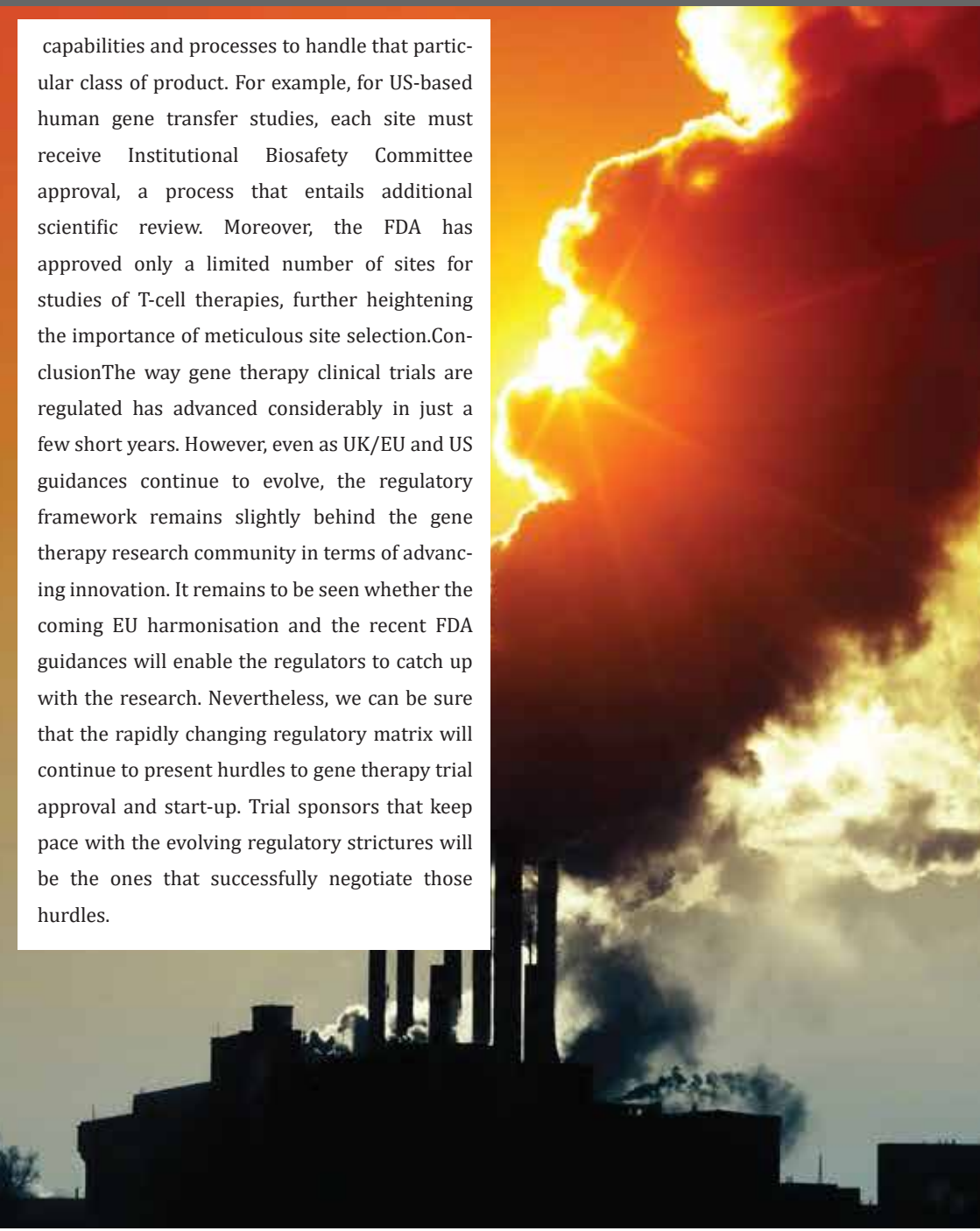
'Even as UK/EU and US guidances continue to evolve, the regulatory framework remains slightly behind the gene therapy research community in terms of advancing innovation'

EU harmonisation is comingEU Regulation 536/2014, expected to be implemented by early 2022 (with a three-year transition period), will institute a harmonised electronic submission process for CA and EC review and approval in all member states. That should eliminate the need for prior GMO approval in countries like Poland. However, GMO authorities will not be subject to the new regulation, meaning that gene therapy clinical trial applications will likely continue to be subject to additional review and approvals.

For clinical trial applications involving environmental release, certain information from documents such as Environmental Risk Assessment reports, the Summary Notification Information Format Form, and the Common Application Form for viral vector-based therapies will often go straight into an EU public registry. Biological samples may also require additional import and export licences. The new regulation will therefore heighten the need for transparency, awareness and data-sharing between sponsors, regulators and trial sites.

Optimising site selectionThe determinants of product classification, and their implications for regulatory pathway selection, make site selection critically important. Sponsors must therefore ensure that each site has the requisite

capabilities and processes to handle that particular class of product. For example, for US-based human gene transfer studies, each site must receive Institutional Biosafety Committee approval, a process that entails additional scientific review. Moreover, the FDA has approved only a limited number of sites for studies of T-cell therapies, further heightening the importance of meticulous site selection.ConclusionThe way gene therapy clinical trials are regulated has advanced considerably in just a few short years. However, even as UK/EU and US guidances continue to evolve, the regulatory framework remains slightly behind the gene therapy research community in terms of advancing innovation. It remains to be seen whether the coming EU harmonisation and the recent FDA guidances will enable the regulators to catch up with the research. Nevertheless, we can be sure that the rapidly changing regulatory matrix will continue to present hurdles to gene therapy trial approval and start-up. Trial sponsors that keep pace with the evolving regulatory strictures will be the ones that successfully negotiate those hurdles.



Government issues operational guidelines for pharma PLI scheme

The applications are invited in the three groups based on the Global Manufacturing Revenue of FY 2019-20 of the applicant.

A special carve-out for MSMEs has been kept under the scheme

The government issued operational guidelines for the production linked incentive (PLI) scheme for the pharmaceutical industry.

The Department of Pharmaceuticals has notified the "Production Linked Incentive (PLI) Scheme for Pharmaceuticals, for which the approved outlay is Rs 15,000 crore, Ministry of Chemicals and Fertilizers said in a statement.

"The scheme envisages to create global champions out of India who has the potential to grow in size and scale using cutting edge technology and thereby penetrate the global value chains," it added.

Based on a series of consultations with the pharma industry and stakeholders in the government, the operational guidelines for the scheme have been prepared and issued on June 1. The scheme is now open to applications from the industry, the ministry said.

The applications are invited in the three groups based on the Global Manufacturing Revenue of FY 2019-20 of the applicants. A special carve-out for MSMEs has been kept under the scheme, it added.

The application window is for 60 days starting from June 2, 2021, to July 31, 2021, the statement said.

"The products covered under the scheme are formulations, biopharmaceuticals, active pharmaceutical ingredients, key starting material, drug intermediates, in-vitro diagnostic medical devices, etc," it added.

A maximum of 55 applicants will be selected under the scheme. An applicant, through a single application, can apply for more than one product and the products applied by an applicant can be in any of the three categories, it added.

The category-1 and category-2 products attract 10 per cent incentive and category-3 products attract 5 per cent incentive on the incremental sales, the ministry said.

An Empowered Group of Secretaries will undertake periodic reviews of the scheme to ensure its smooth implementation along with the other PLI schemes of the Government of India, it added.

SIDBI, the project management agency selected for this scheme, will be responsible for implementation and will be the interface with the industry for all issues concerning online applications, selection of applicants, verification of investments, verification of sales and disbursal of incentives etc, the ministry said.

Future of pharma marketing lies in 'Hybrid Model'

Preetha Vasanji, MD (India), Doceree emphasises that digital is here to stay, and for pharma marketers, it can't act as a band-aid anymore. She opines that the pharma marketing ecosystem will have to evolve to a hybrid model consisting of both offline and online modes

Just more than a year back, the world witnessed a grave health situation arising out of the COVID-19 virus attack. Not just it was unprecedented, it happened all of a sudden, not giving ample time to anyone to take a grasp of the situation. World leaders scrambled to contain the spread of the virus that fanned out like a wildfire, and then happened what was never thought of – the lockdown, globally. The pandemic and simultaneous clamping of lockdown crippled all industries and the pharma industry was no exception. Perhaps, it was much tougher for pharma brands as their sales representatives were shut indoors and engaging with physicians almost became impossible for them. The restlessness in not being able to manage the system was very much palpable among pharma marketers.

Digital became a saviour for pharma marketers

Amidst the chaos, pharma marketers looked for ways to keep the interaction with physicians going, but in vain. Healthcare practitioners themselves limited physical meetings for fear of contracting the virus and even shifted to online mediums to consult their patients. The physicians' shift to digital mediums pushed pharma brands too to take the digital route to engage with healthcare practitioners. Until now, digital was not more than a checkbox activity for pharma marketers. The hesitance for digital technologies dwindled in times of crisis and the medium became much sought for. Brands tested the medium, and for the very first time experienced the value it offered in terms of improved business outcomes. With the activity around digital gaining pace, the next big question was 'what the future of pharma marketing would look like?'.

Digital's popularity dipped as the first COVID receded

As opposed to how euphorically pharma marketers reacted to digital mediums in the initial days, its popularity dipped as the virus outbreak faded in various parts of the world. Most of the pharma marketers went back to their comfort zone and meetings with physicians the offline way resumed. A bunch of marketers, however, stuck to the medium, understanding full well that the medium can't be ignored. But overall it appeared digital failed to make an impact on marketers, who now stopped short of giving digital medium the due importance it

deserved. Some of those who benefitted from the medium during the days of the first COVID wave struggled to replicate the experience of digital at an enterprise level. Did it mean the future of digital technologies was bleak and the medium could never make a strong impact upon pharma marketers as it did on consumer marketers?

Digital gains ground with COVID's resurgence

Just when the popularity of digital medium seemed to be waning, COVID-19 resurfaced – this time in a more ferocious manner. The resurgence of COVID-19 has once again put a halt to physical interactions. Physicians are limiting meeting sales representatives and pharma marketers are again moving to digital channels to keep the flow of communication going with healthcare experts. The use of digital mediums is quite need-based at the moment with no clear view of how essential the medium is for marketers.

Digital, more than a stopgap arrangement

The pandemic has underscored one thing: digital is here to stay, and for pharma marketers, it can't act as a band-aid anymore. The pharma marketing ecosystem will have to evolve to a hybrid model consisting of both offline and online modes. Digital would deserve a more sustained and continuous approach to build brands. The ad hoc efforts will not yield desired outcomes and would not unleash the full potential of the medium. It needs investment of time and efforts, and an unflinching commitment by marketers to understand the digital platforms and strategies that could work in their favour and increase the brands' ROI substantially. Creating a brand story without involving digital in all seriousness would now be only a half-baked attempt. Marketers will have to move to a hybrid model to improve business outcomes.

Pharma brands that had understood the importance of digital medium and integrated it into their plans, had leverage. When the resurgence happened, they did not have to jostle all over again to shift to digital to gain access to physicians. Creating gaps in digital marketing will only hamper the efforts as marketers will not be able to understand the medium fully, nor could they be able to explore the positive impact it can have. A hybrid ecosystem is every industry's future and the pharma industry, certainly, is not an exception.

In the genes

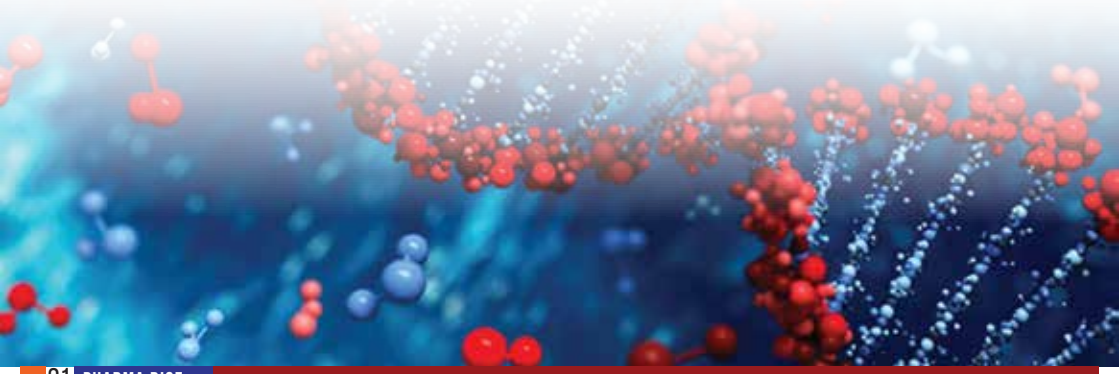
COVID-19 and the rapid rise of genetic sequencing By Joe Henderson and Dr Michael Roberts

While the United Kingdom's original response to the COVID-19 pandemic has drawn criticism, there are ways in which the UK has performed well. Some aspects perhaps even warrant the accolade 'world beating' or, at least, 'world leading'. One of these is the recent success of the vaccine roll-out. Another less heralded but equally impressive achievement has been the use of mass genetic sequencing of the virus.

Over time, the genetic material of viruses, including COVID-19, mutate. Mutations can affect the virulence of the virus, its severity and, arguably most importantly, the effectiveness of vaccines. In spring 2020, a consortium now known as COVID-19 Genomics UK (COG-UK) was set up to apply genome sequencing on a vast scale to enable tracking of the virus, and these mutations, within the UK population. The sequencing is typically carried out on samples from the UK's COVID-19 testing programme.

COG-UK has sequenced samples from roughly 5% of the UK's positive COVID tests. This has enabled the UK to quickly detect, analyse and act against COVID-19 variants of particular concern – such as the Brazilian (P.1) and South African (B.1.351) variants – and has informed public policy and containment strategies.

Few other countries have come close to matching the UK's sequencing output. For example, the Welsh branch of COG-UK sequenced roughly 4,000 genomes of Sars-CoV-21 over a seven-day period – more than the whole of France has managed throughout the entire pandemic. The success of mass genetic sequencing in the UK in response to the COVID-19 pandemic has led to the evolution of the 'New Variant Assessment Platform', directed by Public Health England (PHE), the NHS Test and Trace, as well as the World Health Organization's SARS-CoV-2 Global Laboratory Working Group, to help countries improve their expertise in the field and boost global capacity to understand new variants so we're all better prepared for whatever lies ahead.



Until recently, such a high level of sequencing would have been impossible. In the last couple of decades, huge strides have been made to establish a series of sequencing techniques known collectively as second-generation sequencing that have enabled low-cost and high-throughput sequencing. Meanwhile, so-called third-generation sequencing, which addresses some of the shortcomings of second-generation sequencing, has been made commercially available. COG-UK have been able to make use of both second- and third-generation sequencing in response to the pandemic.Second- and third-generation sequencing

In second generation sequencing, the sample to be sequenced is split up into fragments which are each sequenced in parallel. This reduces sequencing time and the chance of errors. Thus, second generation sequencing has significantly reduced the cost of sequencing while increasing speeds.

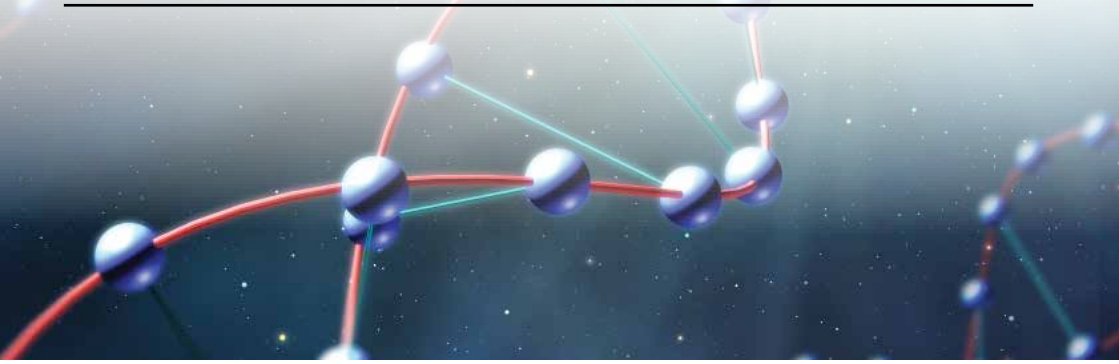
Illumina is the market leader in second-generation sequencing with its sequencing by synthesis systems forming the backbone of COG-UK's sequencing efforts.

Second-generation sequencing is computationally complex, particularly if the expected full sequence is not already well known, as it involves piecing the sequence fragments back together. For example, COVID-19 samples are split into hundreds or, more likely, thousands of fragments before being sequenced.

Third-generation sequencing attempts to remove or substantially reduce the computational complexity involved in piecing together full sequences by providing systems capable of reading much longer sequences in one go. The problem is that the longer the sequence, the more accurate the sequencing system needs to be if errors are to be avoided. Producing such a system is technically challenging. Only in recent years have there been any commercially available third-generation technologies that can cheaply sequence long strands of DNA with an acceptable degree of accuracy.

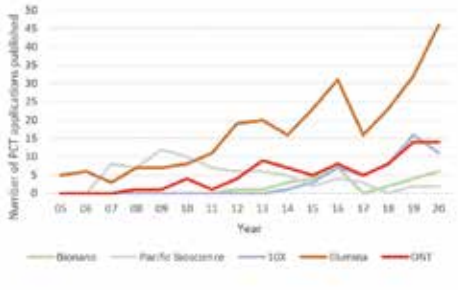
COG-UK has been able to use third-generation sequencing systems provided by Oxford Nanopore Technologies (ONT) to assist with their sequencing effort.

'Few other countries have come close to matching the UK's sequencing output'



The Future

The far-reaching benefits of second-generation sequencing have been evident in the scientific community for some time. The pandemic has perhaps for the first time given the general public a glimpse of this technology's potential. This, combined with the rise of third-generation sequencing techniques, demonstrates how we are in the midst of an exciting time for this field with much potential for development in the future.



Graph 1 Published PCT applications by year in the IPC categories: C12Q1 and G01N33Patent application numbers

Patent application numbers can be used as a proxy for innovation. It is important to file a patent application for an invention before that invention has been made available to the public (and so before it has been commercialised). So, when a company is filing lots of patent applications this is a good indication that exciting developments are in the pipeline.

COG-UK's main partner, the Wellcome Sanger Institute, identifies five companies whose equipment is used in their sequencing. Graph 1 below shows the number of PCT patent applications published each year between 2005 and 2020 belonging to those companies in the IPC categories: C12Q1 and G01N33. C12Q1 includes measuring or testing processes involving enzymes, nucleic acids or microorganisms. G01N33 includes investigative methods involving various entities including entities relevant to sequencing.

Although the number of publications has decreased or flat-lined for some companies; ONT, Illumina and 10X Genomics have a clear upward trend over the last 15 years. Illumina's rise is particularly marked, perhaps an indication that the clear market leader in genetic sequencing technologies has upped R&D given the competition from disruptive newcomers such as ONT and the rise of third=generation sequencing. In any case, the patent filings from this sample of companies demonstrates how we can expect significant innovation in this field in the coming years.

There is a delay of 18 months between the filing of a patent application and its publication. So, the data of Graph 1 does not include filings made since the start of the pandemic in early 2020. It will be interesting to see if there has been a flurry of patent applications relating to COVID-19 specific applications of sequencing systems filed in the last year. For example, ONT has recently released the LamPORE COVID-19 system, which is a highly sensitive COVID-19 test employing third-generation sequencing technology.

Conclusion

It is critical that countries work more closely together to identify changes in the COVID-19 virus and ensure stronger preparedness for further health threats. New variants of coronavirus can be a threat to the vaccine roll-out, so it is vital that the global community is always one step ahead of any mutations and subsequently react to them quickly and decisively.

Moreover, the COVID-19 pandemic has demonstrated how genetic sequencing has become a mature enough technology to be implemented en masse and that has value in informing public health policy. With the rise of commercial third-generation sequencing systems, the availability and power of sequencing will surely only increase while costs decrease.

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The shape of it

Should pharma companies consider protecting the shape of their products? - By Rebecca Anderson-Smith

Most people will be familiar with the fact that brand names and logos can be registered as trade marks in the majority of countries worldwide. However, there are other lesser-known types of trade marks which can be protected in a number of jurisdictions. One that is particularly relevant to the pharma sector is shapes.

What shapes can be registered?A unique or memorable shape to a product or its packaging can, in some circumstances, function as a badge of origin, a role traditionally performed by the brand name and logo. Of course, the more iconic a shape becomes, the more likely it is that it will be copied, causing confusion. A case of mistaken identity in the pharmaceutical sector can have very serious consequences. Trade mark registrations for shapes which are key to your branding, such as blister packs, tablets and bottles, can be used to try to prevent third-party use of identical and similar shapes for similar products.

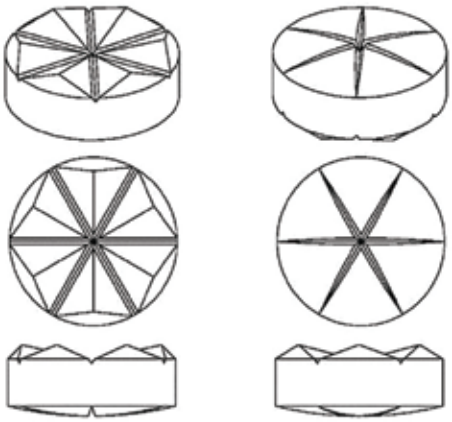
In the European Union (EU), Novartis has protected both the packaging of its cancer drug Glivec (imatinib) and the shape of the tablets themselves (with the word imprinted onto the surface of the tablet).

It is also common to protect the shape of products designed to deliver medicine, for example, Luye Pharma's EU trade mark (EUTM) Registration No. 12927935 covering 'rod-shaped medicine implants' and 'cannula devices for holding and administering rod-shaped medicine implants'; and AstraZeneca's EUTM Registration No. 5695341 covering 'inhalers'.

What are the challenges?To be accepted for registration as a trade mark in the UK and EU, the representation of the shape must comply with a number of criteria established by the Court of Justice of the European Union. It must be clear, precise, self-contained, easily accessible, intelligible, durable and objective. For a 3D shape, this is likely to require submission of several images from different angles.

In addition, the shape must be distinctive enough to function as a badge of origin. Shapes are often not considered to fulfil this role as a matter of course, as consumers will typically see them as decorative or functional, rather than as indicating the origin of the product. This can lead to objections from the trade mark offices.

By way of example, Abtei Pharma Vertriebs' application to register a pill shape under EUTM Application No. 6093141 was refused on the grounds that the disc shape of the pill is commonplace and that the other main feature, namely the grooves, is purely functional, facilitating the breaking of the pill into two or more pieces.



EUTM Application No. 6093141Gathering and filing evidence of extensive use and arguing that consumers have come to see the shape as a trade mark through use may help to overcome an objection like this, but it can be a laborious and costly exercise. Furthermore, if the application is an EU trade mark application, it is likely that evidence from across the whole of the EU will be needed, whereas many companies will have only sold their product in certain specific countries.

One way round this problem can be to include additional distinctive elements in the shape when filing the application. Pfizer's EU trade mark registrations for the shape of its Viagra (sildenafil) 'little blue pill' include the Pfizer name as it appears on the tablet and therefore no evidence of use was required for registration.

EUTM Registration No. 1909472If choosing this option, it will be important to bear in mind that the additional words will also be taken into account when assessing whether there is infringement in the future. If the contested shape does not contain an element similar to the distinctive word contained in the registered shape mark, there may be no risk of confusion on the part of consumers. Furthermore, if the mark is not used as registered for five years or more, it is likely to become vulnerable to cancellation for non-use.

'A unique or memorable shape to a product or its packaging can, in some circumstances, function as a badge of origin, a role traditionally performed by the brand name and logo'

UK and EU trade mark law also include some specific provisions which preclude marks from registration if they consist exclusively of (a) the shape or another characteristic that results from the nature of the goods themselves, (b) the shape or another characteristic of the goods that is necessary to obtain a technical result, or (c) the shape or another characteristic of the goods that gives substantial value to the goods.

Pharmaceutical shapes may be particularly vulnerable to objections based on technical function. In October 2012, Novartis applied to register the following mark:

EUTM Registration No. 11293362Registration was granted in March 2013 in respect of 'Pharmaceutical preparations for the treatment of dementia of the Alzheimer's type'. The registration corresponded to the product Exelon, administered by transdermal patch, which enjoyed patent protection until July 2012. The active pharmacological substance was rivastigmine.

Shortly after registration, SK Chemicals GmbH, which manufactures generic medicinal products, including transdermal patches for the administration of rivastigmine, applied to cancel the registration.

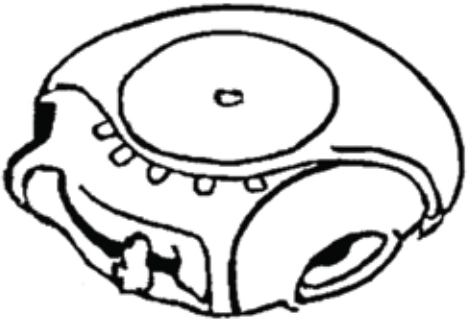
The EUIPO concluded that all the essential elements of the mark, namely the square shape of the patch, the overlapping protective plastic layer represented by the white stripe in the background of the mark, the circular area in the centre and the arrangement of knobs around the central circular area, were all designed to perform a technical function. The registration was therefore declared invalid, a decision which was upheld on appeal.

Novartis still owns trade mark registrations for variations of the mark with additional elements, but this particular registration could have potentially broadened its rights.

Can shape marks be enforced?The circumstances in which it will be appropriate to try to enforce a shape mark are likely to be more limited compared to enforcement of more traditional trade marks. In addition, in view of their weaker inherent distinctiveness, they may have a more limited scope of protection and you may be required to submit supporting evidence. However, if validly registered, shape marks can be enforced effectively, just like any other type of trade mark.

To illustrate this, we can consider a case decided by the Board of Appeal of the EU Intellectual Property Office from 2019. An EU trade mark, No. 9849191, registered for 'inhalers' and 'inhalation products used for the treatment of asthma and chronic pulmonary disease' was found to be invalid and cancelled following a challenge by Glaxo Group based on their Hungarian Trade Mark Registration No. 173643 for a similar shape, which covers 'inhalers'.EUTM Registration No. 9849191

Hungarian Registration No. 173643



A shape trade mark registration can therefore be a valuable asset to your business if you are able to navigate the potential pitfalls along the way to registration.

Safety first

Professor Saad Shakir reflects on the gap in public knowledge about routine drug safety and pharmacovigilance activity

It's natural for people to enquire about a new drug or vaccine. Even more so when some adverse reactions, even if very rare, attract publicity. But what our COVID-19 experience has reminded me is the gap in public knowledge about 'routine' drug safety and pharmacovigilance activity. We are seeing people wrongly assume that a 'post authorisation' safety study means a failing in clinical trials. Or that a very rare side effect means a vaccine is unsafe.

As a pharmacovigilance service, we need to do more to help the public understand our work, to show that far from being a cause for alarm, our work is a normal, planned part of the drug development process to ensure we keep people as safe as possible.

In the UK there is good take-up of the vaccine. But still, one in five Britons don't feel the COVID-19 vaccines are safe and effective. In America, confidence in the Johnson & Johnson (J&J) vaccine is only 46%; it is expected that the figure would be similar for the AstraZeneca vaccine, which uses the same methodology to deliver the vaccine.

What's more, the decision to pause distribution of the J&J vaccine in the US resulted in 24% of Americans saying they had lost confidence in the vaccine. Only 1% said the pause increased their confidence. Yet the pause was so researchers could assess the very latest data, check again whether the vaccine was safe. It should have been reassuring. Clearly it was not.

The fact people misunderstand our work shows we must communicate it better.

We need to show that uncovering rare side effects, studying these and working out how to minimise risks for certain affected groups is a sign our safety process is working well. It can be alarming to read about harmful side effects of new drugs or vaccines. But we must remember how rare they are. Many widely used medicines and vaccines cause very rare adverse effects, which do not stop people using them because their benefits outweigh the risks.

We need to reiterate that very rare side effects only appear when drugs are used by tens of thousands of people, something not usually possible to detect during clinical trials. And that drug safety monitoring and research after medicines have been authorised means any detected side effects, however rare, can be picked up and acted on immediately. This enhances the safety and well-being for everyone.

The recent reports of rare blood clots linked to the AstraZeneca and J&J vaccines are legitimate safety concerns. They are rightly being thoroughly investigated and risk minimisation measures, such as people aged under 40 being offered alternative vaccines, are in place in the UK. But the context is important. Contracting COVID-19 also can be associated with rare serious and fatal outcomes in people in this age group.

Air travel is considered safe. Very occasionally, it's not. But that doesn't stop us flying. We need to apply this kind of context to COVID-19 vaccines.

The COVID-19 vaccines are truly a success story. They've been highly effective in reducing the number of affected people and deaths from a terrible disease. As drug safety experts, it's our role not only to scrupulously monitor and research any possible side effects of the vaccines but also to help people understand the process and not feel alarmed by it.

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