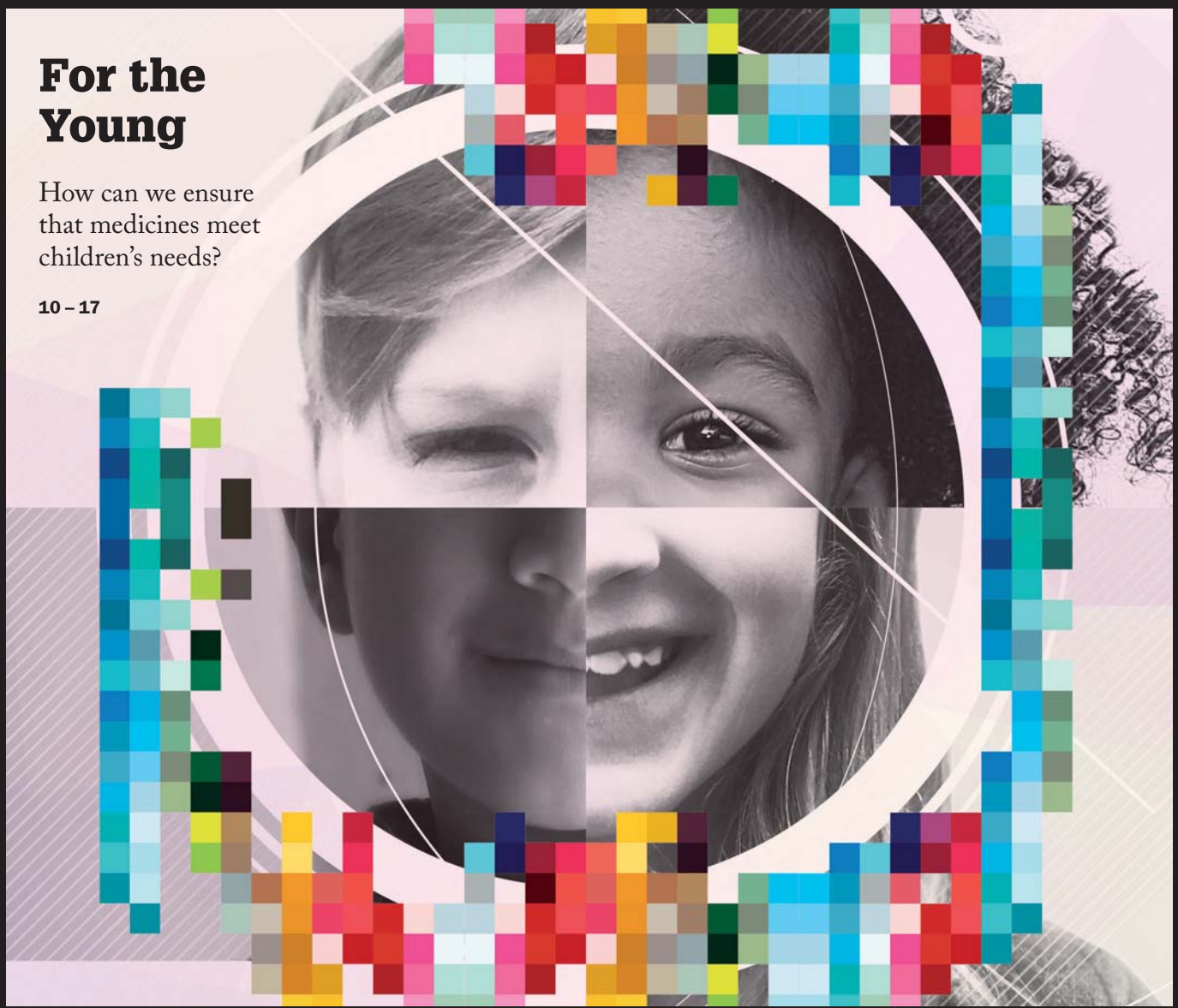
MAY 2020 # 05

the Small Molecule Manufacturer™

For the Young

How can we ensure that medicines meet children's needs?



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The New Fast Track

How pharma has risen in a time of true need

In February – which seems so long ago now – I wrote about the potential impact of the coronavirus on manufacturing supply chains. How many of us knew back then that COVID-19 would bring the modern world so abruptly to a halt? And yet here we are.

Speed is not typically synonymous with the pharma industry – it has been compared, more than once, to a slumbering giant. But now that the giant is awake, it is astonishing to see how fast it can move. Numerous vaccine candidates have been identified, approved small molecule drugs are being explored for potential repurposing, new treatments are being discovered by AI, human trials have already begun, and new collaborations emerge almost daily. The NIH in the USA has partnered with 16 pharma companies; Sanofi and GSK are teaming up on an adjuvanted vaccine; and the European Commission (DG Connect) is trying to round up partners for a project that will use supercomputers to analyze drug libraries for new medicines against COVID-19 (if you want to get involved, visit https://bit.ly/2VtnrWm).

Regulators are moving quickly too, keen to support pharma companies in any way they can. The EMA is offering free scientific advice for COVID-19 therapies and vaccines under development, and the FDA has set up the Coronavirus Treatment Acceleration Program (CTAP) to help get studies under way.

In other fields, engineering companies are designing better ventilators, and psychologists are looking into human behavior to teach us how to manage a pandemic – and the resulting mental health burden. Even app developers are creating tools to help keep us safe.

And that's just a tiny snapshot of what is going on. Who has seen the world's industries come together like this before?

True – we could and should have been better prepared; 2003's SARS and 2009's H1N1 pandemic were warning shots, but we did not want to listen or learn. According to the WHO, there were 18,449 confirmed H1N1 deaths by August 2010. COVID-19 has claimed ten times that number of lives – and counting.

The world has changed. And when we finally beat COVID-19, we must remember how we joined forces for the sake of global health, and eschew our old, siloed ways of working.

Stephanie Sutton
Editor

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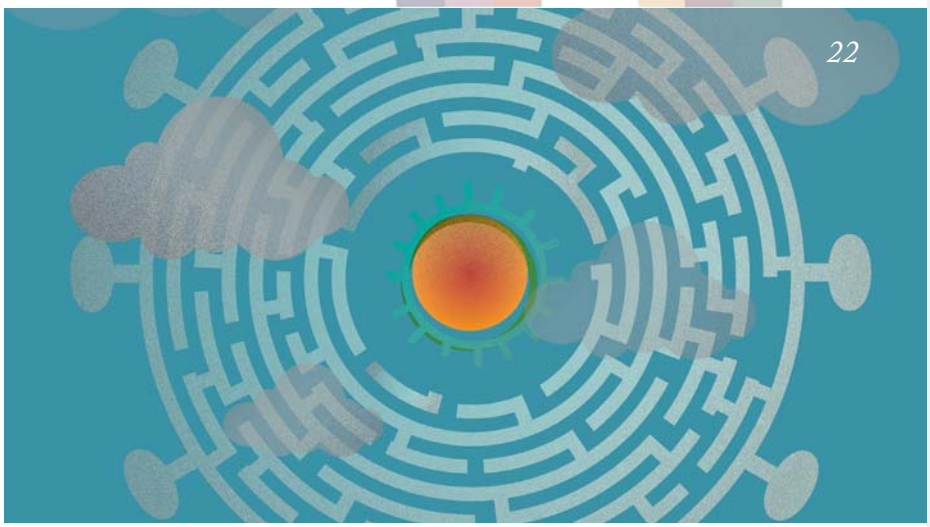
Contents



the Small Molecule Manufacturer

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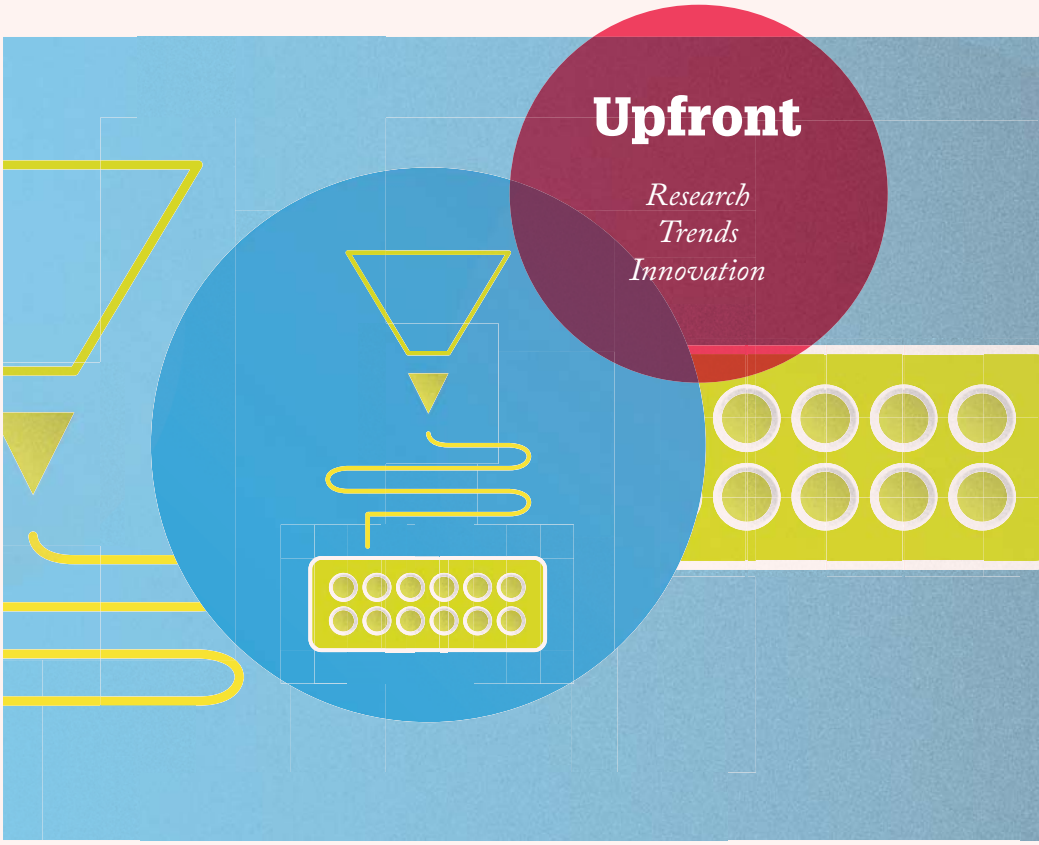


Prototyping for Success

New blister cavity designs become a rapid reality with additive manufacturing

Using 3D printing, Maruho Hatsujyo Innovations, a Japanese company focusing on pharmaceutical and medical packaging machinery, has developed a new prototyping service for blister cavity design. "Additive manufacturing is all the rage in manufacturing, with companies making everything from aircraft blades to components for small machines. Why not apply it to blister packaging too?" says Benjamin Voelcker, Product Manager at the Medical Packaging Machinery Division of Maruho Hatsujyo Innovations.

Clearly, it's better (and much less expensive) to find – and fix – a problem at the design stage rather than discovering an issue further down the line. And that's why extensive prototyping is attractive – but it's also time consuming. "Prototyping is particularly important for blister packaging applications because the production tooling for blister machines is expensive. Lead times for traditional prototypes can run from one to two months because of the metal tooling involved," explains Voelcker. "When testing cavity designs, brand owners want to be able to make changes quickly that take into account the properties of the film material and the behavior of the design." For blister cavities, drug manufacturers need to assess factors such as childproofing, and conduct tests for stability and material limits for filming/lidding.

But 3D-printed prototypes can be produced in days rather than months, allowing companies to easily test multiple blister cavity options, and then compare the benefits of blister packaging over other packaging platforms, such as bottles. "The 3D printing process is also less expensive than using traditional metal tooling," he says.

The company is also exploring how else 3D printing can be used in machine making. "Some customers need to shift sensors on machinery to different positioning for eye marks and print registration," says Voelcker. "Additive manufacturing can be used to create simple brackets and small components that secure devices properly."

INFOGRAPHIC

Artificial Impact

What role does artificial intelligence (AI) play in R&D?

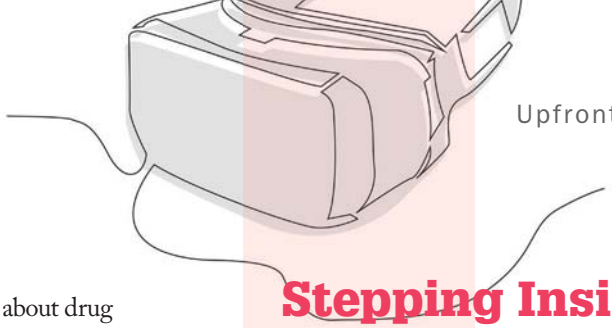
The AI R&D market increased from **$200 million** in 2016 to more than **$700 million** in 2018

It is expected to reach **$20 bn** IN THE NEXT FIVE YEARS

Computer-aided de novo drug design has identified a list of **200 billion** compounds with potential therapeutic activity

About **80%** of scientific data is available only in intellectual property files.

Small Molecule Manufacturer



COVID-19 IN BRIEF

COVID-19 clinical trials, lifted bans and an improving reputation… What's new in business?

- Both the FDA and EMA have issued statements about the potential dangers of using hydroxychloroquine and chloroquine, two antimalarial drugs, in COVID-19 patients. There has been high interest in using the drugs as potential COVID-19 treatments. Studies are ongoing, but some early results suggest they may not be effective.
- Indian officials have partially lifted the ban on the export of a number of medicines, including hydroxychloroquine and acetaminophen. The country initially banned the export of some drugs to quell the rising domestic concern about drug shortages. The decision to reverse the ban came after a call between Prime Minister Narendra Modi and President Donald Trump.
- Data published by APCO Worldwide indicates a shift in the American public's perception of the pharma industry; 58 percent of survey respondents said US companies are more likely to create breakthrough therapies, while 68 percent were optimistic that a treatment would be developed for COVID-19. "That shows me that the public has a hopeful attitude, and almost enthusiasm, about what companies can do to solve this problem. And what a change that is from years of people basically beating up on pharmaceutical companies," said Jack Kalavritinos, a senior director at APCO.

Stepping Inside Drug Design

An interactive VR tool helps scientists predict how drugs bind to protein targets

Researchers have developed a tool that combines interactive molecular dynamics simulations and virtual reality to allow users to step inside proteins and observe how drugs bind at the atomic scale (1).

"An important part of drug discovery is finding small molecules that bind tightly to specific proteins – and then understanding what influences this binding affinity because it helps us to design better drugs," Adrian Mulholland from the University of Bristol's Centre for Computational Chemistry, said in a statement. "Using the tool, we were able to accurately predict how drugs for the flu and HIV would bind to protein targets."

The researchers also demonstrated that it is possible to unbind and rebind drugs from protein targets on a simulation time-scale that is much shorter than using traditional non-interactive molecular dynamics engines.

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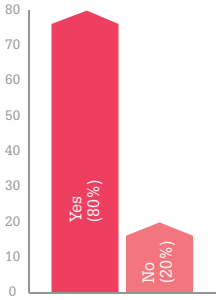
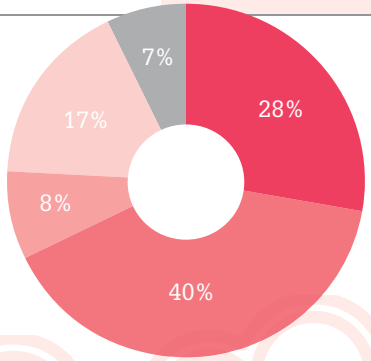
Are you using or planning to use AI or big data approaches to improve R&D performance?



How are startups using AI?



Finding new targets
Screening of small molecule markets to find new candidates
De novo drug design
Drug optimization and repurposing
Preclinical testing

Source: Deloitte, "Intelligent drug discovery: Powered by AI" (2019). Available at: https://bit.ly/2ybyTNc

An Orange a Day...

Researchers dig into the potential anti-obesity properties of a molecule found in tangerines

Nobiletin, a citrus flavonoid found in sweet oranges and tangerines, has been shown to reduce obesity in mice – and potentially lessen associated complications, such as heart disease and diabetes. Mice who were fed with a high-fat, high-cholesterol diet supplemented with nobiletin weighed less than those who hadn't ingested the small molecule, according to research published by scientists at Western University (Canada) (1).

"Obesity and its resulting metabolic syndromes are a huge burden to healthcare systems, and we have very few interventions that have been shown to work effectively. This warrants the pursuit of novel therapeutic interventions," Murray Huff, a professor at Western's Schulich School of Medicine & Dentistry, said in a statement (2). "Nobiletin helps in the regression of atherosclerosis (the buildup of plaque in arteries), but although the positive effects of the molecule have been observed, we're still not entirely sure how it works."

Huff and his team predicted that the molecule was "likely acting on AMP kinase", a regulator that determines how the body is able to manage fat by activating the cellular machinery that enables energy to be expended. But when they began to study mice who lacked AMP kinase, nobiletin was still able to elicit an anti-obesity effect.

"Though nobiletin's mechanism of action remains a mystery, our findings suggest that the molecule won't interfere with other drugs that act on AMP kinases like metformin, a first-line medication for the treatment of type 2 diabetes," Huff added.

The next step for the Canadian researchers will be human trials.

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The Mitochondrial Trojan Horse

Shuttling anticancer drugs directly into the cell's powerhouse with MOFs

Researchers at the University of Cambridge have developed a metal-organic framework (MOF) that helps deliver cancer drug candidates directly into mitochondria (1).

According to David Fairén-Jiménez, a researcher at the university, the MOFs developed by his team enter cells via receptor-mediated endocytosis, "smuggling" drugs into mitochondria. "We loaded our MOFs with dichloroacetate, an anticancer drug candidate currently undergoing clinical trials, and found that the drug-loaded MOFs can reduce the drug dose needed to kill cancer cells, something that could lessen the side-effects of chemotherapy," he said (2).

Fairén-Jiménez admits the research is just "one piece in a jigsaw" of effort around the possibilities of MOFs for targeted drug delivery. His group is currently expanding its work to investigate the potential of different MOFs, anticancer drugs, and coatings.

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Weighing Up Granulation Options

Whether wet or dry, high shear or single pot, the best method is the one that matches your operational needs

By Andreas Znidar

Granulation is a long-standing process for tablet manufacturers – and a variety of technologies are available. But choosing the right system to fit your business needs is essential. What factors are the most important to your unit operations? Do you need the highest productivity, or will space constraints limit your choices?

First of all, do you need wet granulation or dry granulation? Wet granulation can be used to granulate a wide variety of products. It works by joining solid particles together using liquid solutions. The only major drawback to wet granulation is that, once granulated, particles must also be dried. And the drying process requires another piece of machinery or another process, depending on the technology. But, as the name suggests, the drying process can be avoided entirely using dry granulation, making it a more appropriate choice for products that are sensitive to moisture or heat. Dry granulation uses compacting rollers to produce a granular, free-flowing blend of uniform size. Though the process will work well for some products, it isn't universally applicable as it requires special raw material properties. And that's probably why wet granulation is the most popular approach.

Choose your technology

There are several types of wet granulators, and companies should remember to consider the drying capabilities of each before making an investment decision.

High Shear. For contract manufacturers looking for a technology that meets the needs of a broad spectrum of customers, high-shear granulation is a sensible option. With short processing times and the capacity to fully integrate upstream and downstream equipment, it is highly favored on an industrial scale, currently accounting for the granulation of roughly 70 percent of all wet-granulated products. The robustness of the technology allows it to function well with a variety of products. But high-shear granulation requires two specialized pieces of machinery – a High Shear Granulator and a Fluid Bed Dryer – and that means there is an increased risk of product loss and considerable cleaning effort to be taken into account.

Fluid Bed. Though less common than high-shear granulation, fluid-bed granulation offers tremendous flexibility, as it allows particle size to be readily controlled by varying key process parameters, such as spray rate, droplet size, air volume and temperature. In fluid-bed technologies, the powder is fluidized by the air that is drawn up through it. Binder liquid is introduced into the chamber as droplets through a binary nozzle, which causes the powder material to form granules. The resulting granules are dried in the same process chamber, limiting product loss. Notably, the agglomerates produced by Fluid Bed Granulators have different particle properties compared with the granules produced by High Shear or Single Pot Granulators, with high porosity and hence low bulk density. Companies considering a change from High Shear to Fluid Bed Granulators must assess how the differences in granules will affect the hardness of the tablets they produce and determine whether a re-registration of their granulation process will be required. Moreover, process times are longer when compared with high-shear granulation.

Single Pot Processors. Using one piece of machinery for both mixing and drying, single-pot equipment is easier to clean than other granulation technologies. Single Pot Processors produce wet granulates that are dried under a vacuum, meaning that they are, by design, contained systems. For companies who need to make frequent product changes or work with toxic products, the combination of easy cleaning and containment is attractive. They are also a great option for companies working with effervescent products, which are extremely moisture-sensitive, because no additional moisture is introduced. Single Pot Processors also have the advantage of requiring less floor space for installation than granulation lines or Fluid Bed Granulators.

Advice is on hand

Before moving to a new type of granulation processor, companies must always weigh up the advantages and disadvantages for their particular products and how they fit into the future needs of the business. If you are looking for a modern update to your processing systems, Diosna is on hand to offer the assistance you need – helping you make the transition from old-fashioned to contemporary with no headache.

Andreas Znider is Area Sales Manager at Diosna.

NOT JUST SMALL ADULTS

How are medicines being optimized for children?

By Maryam Mahdi

The Small Molecule Manufacturer

Children do not respond to medicines in the same way as adults. Despite this, pediatric drug development has been a sticking point for the pharma industry for decades, with doctors often resorting to off-label drug use. And even when medicines are licensed for use in children, they are not always formulated appropriately and can be poorly accepted by some patients. Regulatory agencies have been actively trying to change the status quo. In the EU, the Paediatric Regulation came into force in 2007 to ensure that high quality medicines for children were authorized appropriately; in the US, the 2003 Pediatric Research Equity Act mandated pediatric studies for certain drugs.

And progress is being made. In this feature, we highlight select companies pushing the boundaries of the pediatric development space – and ask a probing question: "What more can be done to optimize therapies for children?"

Closing the Treatment Gap

Over 1.5 million children live with HIV – and they don't have access to optimized medicines

In the 1980s, an HIV diagnosis was a death sentence. And though therapeutic options have since emerged, it remains a major public health issue. An estimated 37.9 million people live with the disease – including 1.7 million children (1). Many of the drugs currently available are tailored to the adult population, leaving children, particularly those in developing countries, with limited access to drugs. With drug development for children living with HIV lagging 8–10 years behind that of adults (2), many have resorted to the use of off-label and unlicensed drugs, which are unsuitable for the specific needs of the patient population (3). As resistance builds to these existing medicines, at-risk children are left with fewer options. In 2018, Médecins Sans Frontières (MSF) criticized the pharmaceutical industry for its failure to develop appropriate formulations of HIV medicines for children (3). But the tides are turning and the industry is taking action to address the problem; however, the complexity of the pediatric demographic makes the process challenging.

According to Harmony Garges, Chief Medical Officer at ViiV Healthcare, defining what the term "child" means is key to addressing the issue. "When talking about children, we are addressing a group that is made up of people at different developmental stages. From newborns to 18-year-olds, the patient group is broad and varied. In adults you can pick a single dose which will work across a diverse range of people but this can't work for children," she says.

As children develop from infants through to adolescents, their hepatic and renal functions change, affecting drug disposition and pharmacokinetics. Therefore, mean population dosing based on age subgroupings, such as preterm newborns, term newborns, infants, toddlers, children and adolescents aren't reliable because they do not consider metabolic development in relation to age. Though weight-adjusted formulations require different types of testing in different weight cohorts, they are becoming more commonplace as they allow companies to discern how the weight of a child influences dosing, metabolism and their response to a variety of drugs.

"It's also important to remember that the youngest of children are unable to swallow pills easily and simply crushing or breaking tablets does little to meet their needs," Garges adds. "And in countries where resources are lacking, the ability to swallow and tolerate medicines is the difference between life and death for many children."

With the child in mind

The majority of AIDS-related deaths in children still occur before the age of five (4), so developing a formulation that can be easily tolerated by children that fall into this group is imperative for pharma. Viiv Healthcare recently submitted regulatory applications to both the EMA and FDA seeking approval for a 5 mg dispersible tablet formulation of dolutegravir (DTG), as well as a simplified dosing regimen to optimize the use of the existing DTG 50 mg film-coated tablet in pediatric HIV patients. Previously, DTG had only existed as a solid dosage form.

"DTG comes with the recommendation of the WHO due to the fact that it has comparatively fewer side effects than other currently available antiretrovirals. This makes access to the drug essential for all patients affected by HIV," Garges explains. "A dispersible tablet allows for the treatment of children as young as four weeks old, which helps simplify treatment options for patients and their caregivers, as the tablet will disintegrate in water offering improved swallowability and palatability."

"From a logistical perspective, medicines that remain stable across geographies and climates are also important for improved access."

Though it is certainly within the industry's capacity to create optimized pediatric drugs, access to these medicines will make all the difference in its response to the treatment of pediatric HIV. To that end, pharmaceutical companies are forming alliances with generic manufacturers and the organizations that support them to help reduce the cost of much-needed medicines.

"Viiv Healthcare has licensing agreements with the Medicines Patent Pool (MPP), a United Nations-backed public health organization working to increase access to medicines for low- and middle-income countries, to ensure that generic manufacturers can produce and sell single and combination versions of DTG to help treat children and adults alike," says Garges. "Currently, 18 generic manufacturers are authorized to produce and sell low-cost single or fixed-dose combination versions of DTG for low-income, lower-middle income, and sub-Saharan Africa countries, as well as some other upper middle-income countries (pediatric license only), totaling 94 and 121 countries for the adult and pediatric agreements, respectively."

From a logistical perspective, medicines that remain stable across geographies and climates are also important for improved access. "It is important to take into consideration the fact that the majority of the disease burden is in the developing world. Ideally, companies should aim to formulate medicines that don't require refrigeration as this comes with an associated expense that puts pressure on the governments of low- and middle- incomes countries," explains Garges.

Beyond treating existing cases of HIV, stopping new infections among children is another important target for pharma. The risk of vertical transmission – a mother passing a disease on to her child during gestation – can be reduced with appropriate antiretroviral treatments, but in emerging economies access is limited. "I believe it is important for the pharmaceutical industry to help provide holistic support for families, particularly those in the developing world, that need access to these drugs. This makes educating mothers and other caregivers essential to addressing the problem," says Garges.

The journey ahead

Current international targets are geared towards putting an end to the public health threat caused by HIV/AIDs by 2030, and though governments, pharmaceutical corporations and advocates are working towards meeting this goal, will the decade-long drug development gap prevent the target from being met? Garges is confident that the industry can ensure a better future for all patients living with HIV.

"The industry has come a long way in its ability to treat HIV. Thirty years ago, treatment options were scant, but now patients have the opportunity to lead long and fulfilled lives due to the innovation of pharmaceutical and healthcare companies," says Garges. "Pharma is constantly challenging the status quo when it comes to HIV, but the boundaries can and should be pushed further to help deliver more improved child-friendly options for patients."

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Natural Concern

Offering children living with neglected diseases a fairer chance at life

Chagas disease – described by the WHO as "silent and silenced" – is a public health concern for developing countries in Latin America where it is endemic. It is caused by the protozoan parasite, Trypanosoma cruzi, which is carried and spread by insects. Although the symptoms of the disease vary, it is responsible for approximately 14,000 deaths each year (1) and, given that the majority of people affected by the disease are children, appropriate treatments are needed. The Medicine Maker spoke to Bayer's Maria Luisa Rodriguez, Global Program Head for the development of nifurtimox, about the challenges posed by treating children affected by Chagas disease.

Why is pediatric drug development so important?

At the core of the pharmaceutical industry's motivations is giving people a fair chance at life. This should begin by ensuring that children are able to lead healthy lives with necessary treatments available to help see them through periods of illness. As a parent and a person who works in pharmaceutical industry, it is important for me and those who I work with to find solutions to the medical problems faced by children, regardless of whether they have chronic illnesses or acute conditions.

How does Chagas disease affect children?

Though typically asymptomatic, Chagas disease is a life-threatening condition that can cause severe organ manifestations like cardiomyopathy and gastrointestinal dysfunction years after infection. The parasitic infection relies on different routes to reach the host, but is generally caused by contact with the infected feces of blood-feeding triatomine insects. Vertical transmission, from mother to fetus, is another important, route of infection. Children born to infected mothers have a 5 percent chance of acquiring the parasite.

As a demographic, children are most affected by Chagas disease, which makes it important to focus treatment efforts on them to prevent associated complications following them into their later lives. Though the disease can stay latent for decades, between 10 and 30 percent of people will experience some of the more serious symptoms of the disease. By treating younger patients and addressing the issue as early as possible, the risk of developing severe disease symptoms is reduced.

How can dosage forms affect the treatment of Chagas disease?

The crux of the issue when it comes to treating Chagas disease is the availability of appropriate formulations for children. Big, bitter tasting pills are aversive to us as adults, so why would we expect children to want to take them? Furthermore, accurate weight-adjusted dosing is important. Though effective drugs like nifurtimox have been available for almost 50 years and can be used to kill the parasite T.cruzi which causes the disease, the dosage form that the drug is available in can make all the difference in how well it is tolerated by children. In the years since nifurtimox was first introduced to the commercial market, the tablets have been cut in pieces, crushed up and added to food or milk to treat children, resulting in poorly controlled dosing. The problem is only exacerbated by the fact that the drug has to be taken three times a day over a period of 60 days.

Bayer recently submitted an application for nifurtimox to treat pediatric patients with Chagas disease to the FDA. The drug was reformulated to easily dissolve in water, making it easier to administer to children who are unable to swallow whole tablets. The tablets, which are available in two dose strengths, can also be broken to divide the dose so that appropriate weight-adjusted amounts of medication can be given to patients of all ages.

What other challenges are associated with treating Chagas disease?

Though there are an increasing number of cases of Chagas disease in Europe and the US, the majority of people living with the condition are found in Latin America. Because Chagas disease is caused by an insect, cultural stigmas linked to poverty and uncleanliness can hold patients back from seeking diagnosis and receiving the treatment they need as they don't want their communities to be aware that they have the disease. But with that being said, in most of these countries, young children are the primary focus of treatment initiatives and there are a growing number of screening programs to test pregnant mothers. The industry now needs to create appropriate support channels for adolescents and adults, which should result in a more comprehensive approach to control and finally eradicate the disease.

What advice can you offer (smaller) companies wanting to develop pediatric formulations for neglected diseases?

It is important to keep in mind that the key requirements for pediatric formulations in developing countries differ from those in developed countries. Though general considerations must be made regardless of patient geography, like the use of childproof packaging and appropriate dosage forms, there are also logistical and storage considerations to take into account when transporting medicines to economically emerging countries. If a medicine is prone to spoiling at high temperatures, then there is little use in sending it to a location that lacks appropriate refrigeration facilities. Simply put, having a patient-centric mindset and understanding that the needs of children around the world differ based on lifestyle will help in the development of drugs best suited to the demographic.

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A Changing Landscape

As the pharmaceutical industry has evolved and grown, so too has its ability to develop child-friendly formulations

For much of the 20th century, research, regulations and formulation development have focused on treating diseases in adults, leading some to describe children as therapeutic orphans. With fewer options available and with dosages and administration routes that failed to satisfy the pediatric demographic, there was a clear need – and a gap in the pharmaceutical market. Here, Matt Ling, Director of Scientific Services, Oral & Specialty Delivery, and Andrew Parker, Senior Program Manager, Early-Phase Development, Oral Drug Delivery – both at Catalent – consider the progress the industry has made in the development of pediatric formulations and the issues that developers still face. And perhaps most importantly, they define the steps that need to be taken to bring truly child-optimized medicines to market faster.

How has the industry changed to make pediatric formulations a priority?

Andrew Parker: A decade ago, regulatory changes in the industry fostered a shift in attitude towards pediatric development. Before this, due to the limited potential revenue returns for large pharma, pediatric medicines were viewed with lower priority than other competing drivers. In Europe, incentives are now in place for companies to comply with the regulatory requirements of a Pediatric Investigation Plan or PIP (a medicines development plan to support the authorization of a medicine for children). PIPs must be drafted and submitted from late Phase I, and subsequent marketing authorization applications must include the results of studies conducted in the PIP. Applications that comply with this can be eligible for a six-month extension to their licenses (two years for orphan drugs). And so now the development of a pediatric drug has both strong financial and regulatory drivers. Similar regulations exist in the USA and, as of 2017, the RACE for Children Act authorizes the FDA to compel companies developing cancer drugs to also develop their drugs for children, if the molecular target of the drugs under development are relevant to a pediatric cancer.

What are the most important developments of the last decade?

Matt Ling: One of the most important developments in the last decade has been the increased "noise" level, which has resulted in more companies devoting time to both development of pediatric drugs and, as a by-product, engaging in an increased number of conferences and publishing more peer-reviewed literature.

This increased activity is also reflected in the number of joint endeavors between academia and industry, which are addressing a variety of issues; for example, developing and refining new taste masking technology, creating new methodologies to assess taste, and developing improved in vitro and in silico approaches to simulate and predict the likely exposure of a pediatric formulation in children.

In the formulation space, mini tablets surfaced as a developable and acceptable platform for pediatric drug delivery. Typically only 2-3 mm in diameter, mini tablets may be dosed individually or as multiple tablets when mixed with soft foods. Mini tablets can be quick to develop because they adapt the adult tablet presentation. They can also be used where bioavailability enhancing technologies are required, such as for amorphous solid dispersions. Several studies have been performed to investigate the acceptability of administering multiple mini tablets to infants and children, demonstrating favorable acceptability when compared with a standard syrup formulation (1).

"Collaboration is always an important component when trying to either solve pan industry challenges or agree on general recommendations for scientific approaches to industry needs."

What are the key challenges of developing medications for children?

Ling: The most important challenges are ensuring the dose level is scaled correctly for the intended age and weight of the patient, and optimizing the formulation to give the correct release profile in the child. These challenges are compounded by more widely varying levels of absorption in children compared with adults. For example, if transit time is slower and solubility is higher than expected, there is potential for the absorbed dose to be higher than predicted, introducing the risk of toxicity – these attributes can vary significantly in children of different age groups. Alternatively, if transit time is fast and solubility is low, then drug absorption will be lower than predicted and there will be a risk of ineffective dosing. The physiological differences between adults and children demand scientifically-justified dose scaling to support safe and efficacious dose selection in the pediatric population. Formulators, therefore, need to understand that the correlation between drug exposure and body weight is not always linear.

To date, oral solid dosage forms have remained the formulation of choice within the pharmaceutical industry, due to the established advantages of long-term stability, ease of supply chain and low cost of manufacturing. But the degree of dose flexibility or dose adjustment required for a given product should influence the design of its formulation and give formulators pause for thought when developing products for children.

In addition, to establishing an effective dose level for children, issues of taste, acceptability and compliance in administering the dose as intended are important aspects that will often dictate the formulation strategy for the product. Most APIs have an undesirable taste and compliance failures are often manifested by a child spitting out the medicine immediately after dosing. Taste masking is, of course, an option to overcome this, often involving excipients such as coating polymers, sweeteners or flavorings. Guidance issued by the EMA in 2013 states that patient acceptability must be an integral part of pediatric drug formulation development. However, regulatory guidance is less clear on how acceptability is measured. Different approaches have emerged, with some research citing methods like the Visual Analogue Scale (a psychometric response scale) as a potential method for assessment, while others refer to the Hedonic scale (a test in which responses are rated on a scale from "dislike extremely" to "like extremely") as another potential form of assessment. Though these assessment methods have their benefits, they also create disparities in the ways that acceptability can be accurately measured. More recently, efforts have been made to standardize practices with papers published to try and provide a more harmonized assessment (2).

During the development of the formulation, assessment of the taste can present another challenge. The e-tongue, an instrument that measures and compares tastes, presents one in vitro method to assess the scope of the taste challenge. An e-tongue uses an array of electrodes to compare the taste pattern of the API to human calibrated standards for tastes – sweet, sour, bitter, salty and umami. It can also be used to compare the similarity between taste-masked formulations with or without the API to determine the degree of masking that can be achieved. Recently, more sophisticated preclinical models have been developed that can be used to assess how animals, such as rats, will respond to the presence of the API at different concentrations in drinking water. The results from such studies have been found to correlate well to similar studies in human volunteers (3).

How important is collaboration to the development of novel pediatric drugs?

Parker: Collaboration is always an important component when trying to either solve pan-industry challenges or agree on general recommendations for scientific approaches to industry needs. All voices need to be heard – and agreement on approaches is sometimes difficult to reach. Several organizations have been established to try and provide a vehicle for engagement and dialogue on the topic of pediatric medicines. The European Paediatric Formulation Initiative, a consortium working in a pre-competitive way on pediatric drug formulations, is one example of this. The group is made up of pharmaceutical companies, hospitals, and academics, who work closely with one another to resolve scientific, regulatory, and technological issues associated with pediatric formulation development. Through information sharing, lobbying, and building cross-industry networks they aim to foster improved awareness of the current challenges and opportunities faced by pediatric drug developers.

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Pediatric Formulation 101

The industry must move away from a "one-size-fits-all" approach when it comes to patients of any age

By Ralph N. Landau

The pediatric population is one group that has benefited from the industry's goal of becoming more patient-centric and, over the past 20 years, has seen gradual improvement in the number and quality of drugs available to them. In fact, over the course of the past two decades, there has been a five-fold increase in the number of pediatric drug approvals (according to Cambrex Market Intelligence, approvals increased from 10-20 per year to 50-70 annual approvals today).

Regulatory bodies are constantly working to update their guidelines regarding the implications of drug substances and excipients for pediatric patients. In the USA, Congress has passed several acts to accommodate pediatric drug development. These acts provide structure and guidance to companies developing drugs for use in children, as well as some incentives, such as a six-month extension of exclusivity on existing formulations if adequate pediatric studies are performed. The PREA act, for example, allows the FDA to require a pediatric formulation of a drug and the studies conducted must use appropriate formulations for each age group. PREA is triggered by one or more of the following criteria: a new indication, new dosage form, new dosing regimen, new route administration, or new API. The drug application must include a pediatric assessment unless the applicant has obtained a waiver or deferral.

Globally, agencies, such as the EMA, Health Canada and Australia's Therapeutic Goods Administration, also offer pediatric drug development guidance and regulatory requirements. If a company develops a pediatric drug product and receives approval from a USA regulatory agency and then wants to expand to Europe, for example, a separate submission for EMA regulatory agencies would be required for approval. The requirements vary somewhat by jurisdiction, therefore when developing a formulation intended for multiple jurisdictions, all requirements must be integrated into the development program.

On an international scale, however, regulatory bodies are demonstrating their desire to bolster the pediatric drug pipeline and are encouraging companies to find solutions for this patient group. In short, the problem of developing medicines for children can no longer be ignored.

Patient centricity

When developing medicines for the diverse population of pediatric patients, it's always best to establish what the requirements of the patient are in the particular therapeutic area. The most popular drug formats for treating pediatric patients are usually:

- oral liquid formulations
- oral solid dosage (OSD) formulations, particularly fast-dissolving or chewable tablets, or capsules
- multi-particulate formulations, such as mini-tablets and stick packs
- alternative oral delivery of liquid formulations via Medibottles and dose sipping

Liquid formulations are perhaps the most common approach as they bypass some of the issues associated with OSDs, but they do have their own constraints. For example, products in this format are often much less stable when compared with OSDs, leading to a shorter shelf-life. The use of multiple-dose

"While many excipients are considered safe in adult populations, the data for their use in pediatrics is either scarce or non-existent."

bottles to dispense them also introduces the risk of micro-contamination. For parents trying to administer the medicine to children, there is also the challenge of getting the child to swallow the liquid rather than spit it out! Taste masking can also be challenging with liquids, but can be helped with particle coating. By adding pH-dependent coatings to liquid formulations prior to their suspension, the liquid will not possess the taste of the API. The API will become available as the pH conditions in the GI tract erode the coating.

As new dosage forms, such as stick packs, become available, they open opportunities for companies seeking improved ways to deliver their products to pediatric patients. Stick packs are convenient to administer and also come with the advantage of making a medicine look far less like a medicine – an aspect that can encourage, in particular, pediatric patient compliance.

There is also continuing interest in fixed dose combination approaches, where more than one drug is combined into a single drug product. These products improve patient compliance by reducing polypharmacy issues, but can be even more challenging to design for pediatrics because drug-dosing recommendations may not be suitable across all weight or age groups. However, companies are now finding ways to successfully adapt these formulations so that they work well across different age groups.

Another crucial challenge for pediatric drug formulators lies in identifying safe ingredients. Importantly, while many excipients are considered safe in adult populations, the data for their use in pediatrics is either scarce or non-existent. The FDA is now expecting safety work to be done in pediatric populations for all excipients used, helping to improve the quality of medicines designed for children. Again, keep in mind that acceptance of certain excipients for pediatric products may vary by regulatory authority. Pediatric formulations must address the differences between adults and children. For example, it is not just body weight that drives dosing. Children's metabolism differs from adults. An extended release drug product may behave much differently in pediatric populations; formulators must consider this in their design. Notable differences between pediatric patients and adults include:

- Metabolic rate is higher
- Intravascular and extracellular fluid compartments are relatively larger
- Protein binding is decreased
- Infants have proportionately higher total body water

Each of which have the potential to affect drug performance and ultimately, influence the final drug product formulation.

The ideal medicine

What does the ideal pediatric medicine look like? In my view, the ideal formulation has yet to be developed, but I think that we're well on our way to seeing it happen. In 2020, there are more than 1,300 clinical trials underway investigating over 600 drug substances for pediatric use – a clear indicator of the industry's progress. To maintain momentum and demonstrate that we, as an industry, are developing drugs that are appropriate for the pediatric population, we must conduct robust clinical trials with clear endpoints.

At the same time, it is important to remember how a deeper consideration for the best dosage forms for children and true patient centricity can also benefit other vulnerable patient groups. End users who have difficulty consuming traditional medications, such as stroke patients, those with degenerative diseases like Parkinson's and Alzheimer's, or the elderly, can all benefit from formulations that take the stress out of the drug administration process.

Ralph N. Landau is Head of Development at Cambrex, Whippany, NJ, USA

Inside the Medicine Machine

The Future of Fluid Bed Granulation

Granulation is a staple step in pharma manufacturing, with fluid-bed processing a popular option. Guia Bertuzzi, Product Manager for Granulation at IMA Active, Italy, discusses the evolution of granulation machinery – and what the machines of tomorrow might look like.

How is granulation equipment advancing to meet the needs of drug manufacturers today?

Companies have historically looked for robustness, containment and flexibility – all at the lowest cost possible! And though these elements are still crucial, there is now also a growing demand for improved process control, and machines that reduce manual intervention and offer energy savings. Customers are also requesting granulators as a package, including more appropriate tools for scale-up, training, automation, and predictive maintenance.

There are a variety of granulation technologies available today that suit pharma's newer requirements, including dry, wet and melt granulation. Though these technologies don't compete with one another, wet granulation provides the broadest range of function. But ultimately, the right machine must meet a company's needs for product handling, productivity, cost, operator safety, and also work within their engineering and architecture constraints.

For instance, because pharma companies are increasingly working with highly potent APIs (HPAPIs), the granulation technology selected should allow for the proper management of air

displacement, which reduces the risk of airborne contamination. A high level of automation and a material transfer process that keeps the product away from operators and the environment is also essential. Single-pot processes are usually highly suitable for HPAPIs. As one example, our Roto Cube technology, developed in 1984, is a single-pot process that allows the entire end-to-end process of any type of product, from the loading of raw materials to the discharge of dry granules, to be carried out in a single, contained bowl, thus almost eliminating contact between product, operator and the environment.

The vast array of single pot-processors available means that finding one with the right specification should be straightforward for companies looking to invest in new equipment.

What should companies think about when choosing granulation technology?

Choosing the right granulation machinery will often involve a few compromises. The average lifespan of granulation equipment is around 20 years, so you need to think long term. The right machine should i) meet both current and expected future needs, ii) address productivity, iii) fit in the space the company has available, and iv) be capable of conducting processes in the shortest time possible.

I also believe that versatility is very important. You should look at versatility of the processes – drying, granulation, and coating – and versatility in terms of filtration technology. Different products and types of processing may require different forms of filtration, such as bag filters, star-pleated or stainless steel cartridges.

Be aware that, because of the long-life estimates of granulation systems, you may need to upgrade electrical components as infrastructure advances.

Take us inside the ARIA fluid bed unit. How does the system work?

ARIA is a fluid bed unit for the processing of powders, granules and pellets that allows different types of processes, including drying, granulating (top spray), and coating (bottom spray), offering flexibility of batch size processing in the same equipment. The system ensures a fully contained process, including closed product loading and unloading by means of pneumatic or gravity transfers to reduce manual intervention.

been a sustained effort to improve air distribution, augment the reliability of filtration processes, and improve the efficiency of spraying technologies. However, the pharma industry is changing as companies begin to emphasize Quality by Design (QbD), process analytical technology (PAT), and process control, and with the emergence of new technologies, such as advanced modeling and simulation. There has also been a dramatic shift in industry attitudes with companies no longer wanting "make do" equipment and instead placing greater emphasis on innovation and new approaches to manufacturing.

The application of PAT sensors and models that help to run processes and ensure granules are manufactured according to target specification are already becoming industry norms, but the industry must now become further invested in understanding the benefits of these tools.

Granulation is achieved by suspending the powder in heated air of the fluidized bed, and then spraying the binder solution from air-assisted nozzles. ARIA can be operated depending on the position of the spray system in either top-spray or bottom-spray to make granules or coated pellets.

ARIA supports various different forms of filtration that are kept clean during the process by pulses of air counterflow, which do not disturb product fluidization. The operator can inspect and change the filters using automatic movement of the supporting disk, minimizing the time required for a product change.

How can fluid bed machines be further improved?

Fluid bed is a mature technology, but in the last ten years there has

From my perspective, machine manufacturers need to find new ways of supporting customers focusing on support for a QbD approach. The challenge for the industry now is striking a balance between manufacturing standard equipment that integrates PAT and advanced process controls – and addresses the requirements of new industry standards – and the desire for customized machines.

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Business

COVID-19: Navigating the New Norm

Under pressure to deliver results, how can the pharmaceutical industry handle the current COVID-19 crisis to help patients around the world? We round up thoughts on the topic from eyeforpharma's virtual event.

By Maryam Mahdi

The COVID-19 pandemic has ushered in a new reality; businesses have closed and terms like "self-isolation" and "lockdown" have become common vernacular. For the pharmaceutical industry, the pandemic means striking the right balance between increased demand for therapeutic solutions to COVID-19 and the safety of employees who, just like everyone else, are vulnerable to the effects of the pandemic.

Pharma is under pressure to deliver and to help relieve some of the burden felt by the healthcare industry – a challenge that represented a major point of discussion at this year's eyeforpharma event. Originally planned to take place in Spain, eyeforpharma happened virtually, but still aimed to examine the "critical issues facing the pharma and med device industry." Pharmaceutical professionals came together to examine the ways in which the industry can use digital technologies to maneuver itself through the COVID-19 outbreak.

Opportunities for start-ups

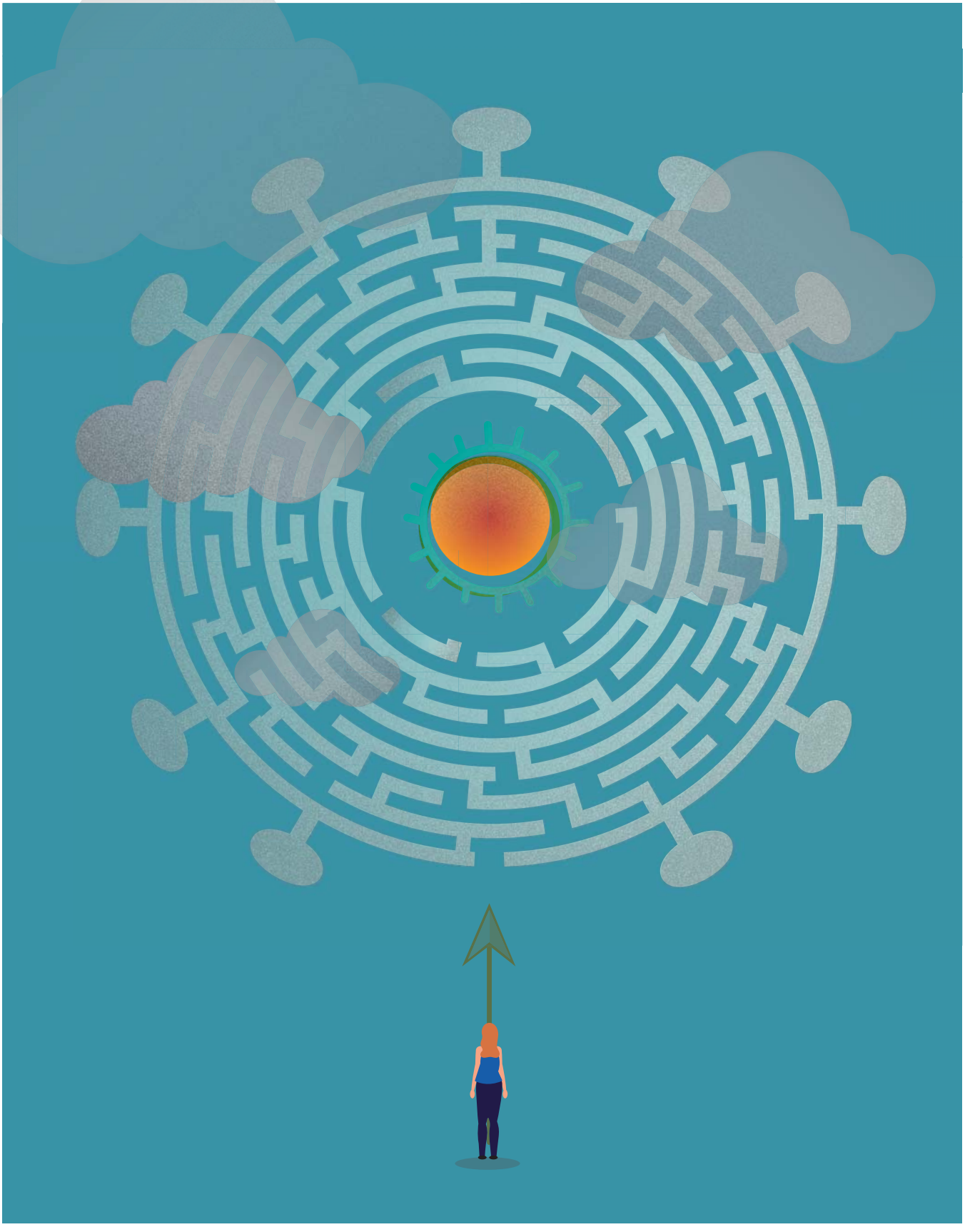
Start-ups aren't the most financially stable companies. And, in light of the COVID-19 pandemic, they have had to become even leaner to manage the change. But this doesn't mean they have to hide in the shadow of big pharma. According to Jessica Federer, former Chief Digital Officer at Bayer, who spoke at the eyeforpharma event, this is an opportune moment for start-ups to prove their inherent value to the pharmaceutical industry by showcasing the benefits of digital technologies for tackling infectious disease.

Start-ups are generally reliant on digital platforms (which are typically cheaper and more agile than conventional Customer Relation Management, or CRM, systems) and accustomed to remote engagement. They must, therefore, be able to "demonstrate their core capabilities" to both cement their place in the industry and weather the hard times caused by COVID-19. Federer believes they can do this by taking advantage of their expertise in data sharing. "The pandemic has left the global scientific community with the feeling that it has a duty to share and publish the data it has in relation to the virus. Though this information sharing is a positive step forward for the industry, it makes it difficult for physicians to weed through it to find the most pertinent data," she said. "Digital companies and start-ups can prove their worth to the industry by implementing technologies that improve information sharing and encourage transparency within the industry."

Tellic Health, which was founded in 2015, is an example, according to Federer, of a company working to improve the accessibility and availability of relevant material. The start-up helps pharmaceutical companies to apply data science technologies, and recently responded to the White House's call for the artificial intelligence community to develop new text and data mining techniques to help the scientific community answer high-priority questions related to COVID-19 (1).

"The company is launching a free tool, graph.C19, a product containing data on COVID-19 and other coronaviruses so that anyone who wants to see and search through all the COVID-19 related research can do so," Federer said. "It enables any researcher to log in and instantly access integrated knowledge from previous experience with coronaviruses, including SARS and MERS, as well as gain insights from the growing sea of biomedical data on COVID-19."

For Federer, these types of companies



can truly flourish in this environment by delivering value to the companies and patients who are currently in need. Across the industry, companies of all sizes are having to adapt and reshape their approaches to managing the consequences of a global pandemic. Though the loss of life and strain placed on the healthcare industry are heartbreaking, it is pushing pharmaceutical companies to work towards a better future.

Triggering change

Though nobody has a crystal ball, there are a number of things, according to Andreas Koester, Former VP Clinical Innovation at Janssen, that seem inevitable for big pharma companies after the crisis. "In this new climate, where social distancing has become commonplace, big pharma companies are beginning to see the advantages and the efficiencies of using digital tools," he said. "So, I think there is no way of going back to the old way of doing business."

The sentiment was echoed by Danilo Pagano, Vice President, Digital & Customer Engagement at Lundbeck. "Pharmaceutical companies will have to replace more traditional forms of communication with customers and clients with more digital approaches," he said. The two speakers, however, agreed that there was a learning curve for the industry to negotiate. "This situation is definitely pushing the industry in a positive direction and it is helping companies to adopt technologies that they may have previously been uncomfortable with. It's a new starting point for the industry when it comes to the technology at its disposal," said Pagano.

For Koester, much of the change he expects to see will be within the realm of clinical trials. "Despite the industry's efforts to introduce more innovative approaches to clinical trial development, we're still lagging behind what our inherent potential indicates we can do," he argued. "If anything is to come of this crisis, it would be the death of incrementalism – the industry's attitude of slowly introducing change to the clinical trials process."

"For too long, our risk-averse nature held us back from taking bold steps when it came to the clinical trial process."

Koester went on to explain that, while the industry has previously been satisfied with its progress, in many ways it had failed to prepare for dealing with a new infectious agent; it only became "painfully clear" to companies when the COVID-19 crisis began. "For too long, our risk averse nature held us back from taking bold steps when it came to the clinical trial process. What we need now is better point-of-care randomization, an improved ability to test known drugs for their potential efficacy and to be able to assess their safety. Every patient who enters a hospital with a coronavirus infection should be able to enter a randomized trial so that we can see, in a matter of weeks, which existing drugs work and which do not."

Koester also discussed how the crisis could be used as an opportunity for pharma companies to better interact with and educate the public. "There are people taking hydroxychloroquine phosphate, a substance used to clean fish tanks, in the hope that it will help protect them against COVID-19," Koester explained. "The industry's newfound digital savvy should encourage them to directly communicate with patients and create a more positive perception of the pharmaceutical industry."

Beyond how individual companies can use the crisis as a catalyst for change and improvement, Pagano believes that there are lessons to be learned by the global industry from China's management of the crisis. From the mass production of Gilead's experimental drug, remdesivir, to backing pharmaceutical companies' clinical trials for repurposed drugs, the country has, in the weeks and months since the crisis began, looked for multiple ways of dealing with the situation.

"In the past few weeks, China has transitioned from being in a state of lockdown to one where I am able to call my colleagues in the region who are now back in the office. We can now look at the way China has managed the pandemic and re-use and apply some of their initiatives to help the global community," said Pagano.

Will we need to re-examine the boundaries of privacy and data sharing? "There was once a time when the concerns about privacy and data sharing were so high that it would prevent good work being done in terms of trials. Now, in light of this global pandemic, it may be easier to accept that changes must be made," Koester said. "Those in leadership positions within pharma companies will have a big role to play in this. They must empower their employees to take new risks. In my opinion, these will be the companies that successfully make it out of the crisis."

The eyeforpharma speakers were united in a thought-provoking conclusion: those companies that believe we will ever return to the pre-COVID-19 world run the risk of succumbing to failure.

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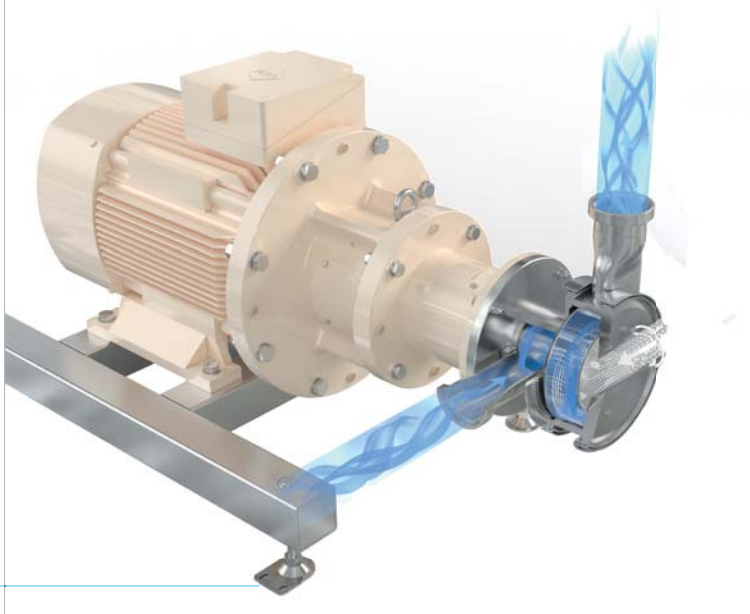


Achieving Excellence

Sitting Down With… Tom Moody, VP of Technology Development and Commercialization at Almac, Craigavon, UK

Has science always been a passion?
Science was always one of my favorite subjects at school. Initially, I loved the idea of just mixing things together, but as I grew I also came to appreciate the practical side of it. I was fascinated by how science could be applied to solve problems – especially when it came to chemistry. My passion pushed me to pursue a degree in chemistry and that is where I began to excel; I was proud to graduate from Queen's University Belfast, with the top grades in my year group and subsequent completion of a PhD.

What other interests have you pursued?
I've always been interested in the ways that businesses operate and, as I started work in the pharma industry, I wanted to understand how pharmaceutical companies, as commercial entities, were able to invest, reinvest and grow. I joined Almac in 2001 and quickly became a team leader. But I wanted to differentiate myself from others working in the organic chemistry department and bring value to the business. I realized I could only do that by offering up ideas and solutions that could have a meaningful impact on the company's future. Was there a technology that I could help introduce that could have benefits for the company? Or were there other avenues, yet to be considered, that were worth exploring?

In 2003, I decided to pursue a masters in business alongside my work at Almac to help improve my knowledge of the commercial world. During that period of time, I began to develop a business plan outlining the benefits of biocatalysis for Almac. I presented it to the senior management team, which must have gone well because they allowed me to begin developing the technology.

How did your role change?
My role expanded and I found myself in new territory. The success of our biocatalysis technology depended on a diverse international team. I began to work with microbiologists, enzymologists and in silico chemists and physicists who all spoke their own scientific languages. In the early days, I had to learn to communicate with people from these different scientific disciplines, which wasn't an easy feat! But it was necessary (and fun) because I was responsible for bringing the voices of these groups together so the project could achieve what it set out to do. We had a common goal and, in spite of our differences, our passion for innovation helped us work cohesively and deliver the new chemistry.

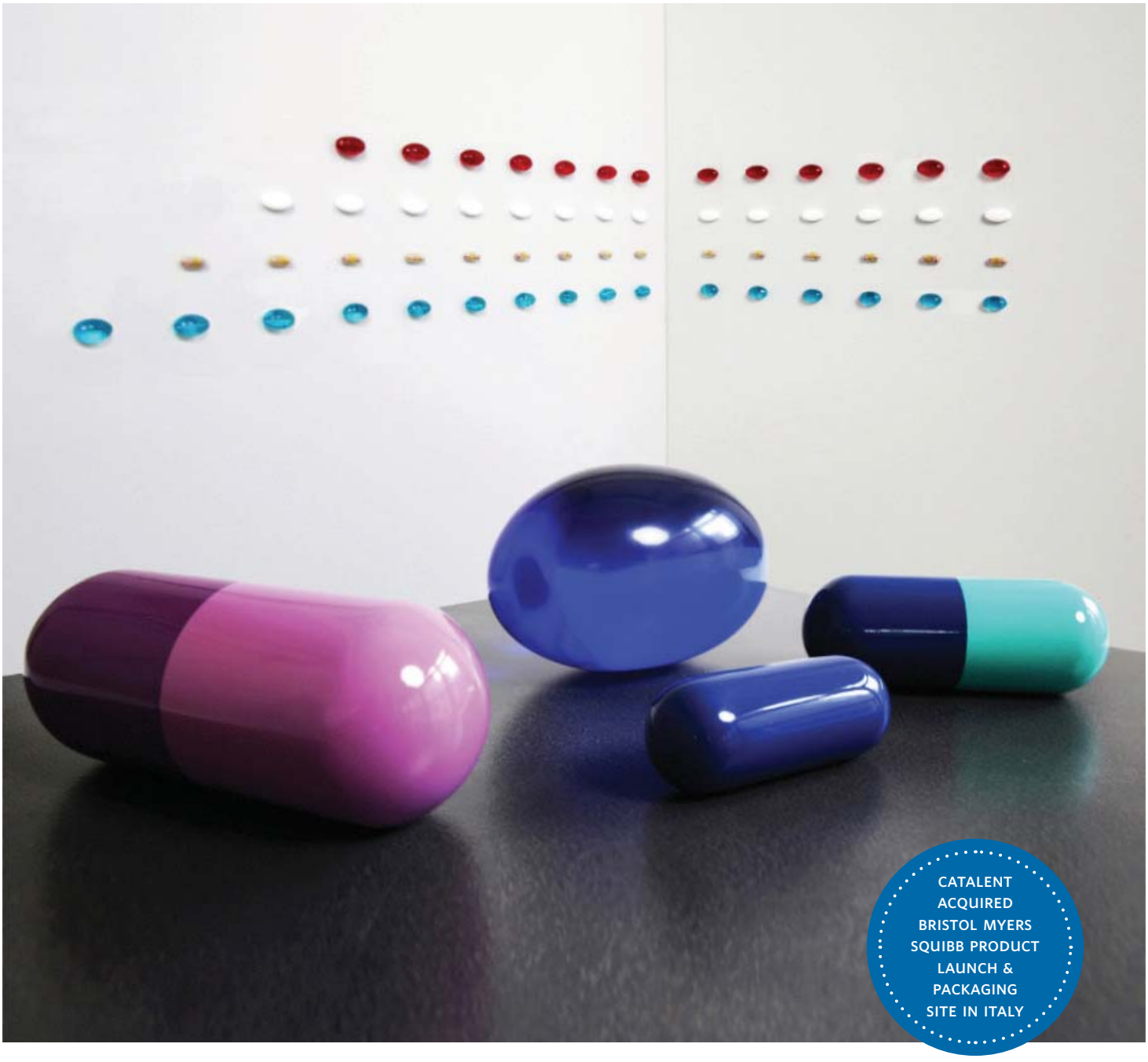
"We had a common goal and, in spite of our differences, our passion for innovation helped us work cohesively and deliver the new chemistry."

What do you do in your current role?
Essentially, I have to draw upon the experience that I've developed throughout my career. From assessing new technologies coming through the pipeline and making decisions about their commercial viability, to seeing R&D projects through from concept to completion; I get real satisfaction from knowing that an idea that existed on paper can be transformed into a commercial product that is of benefit to our customers in different countries.

What advice can you give to bench scientists who want a career in commercial operations?
Really ask yourself whether you'd prefer to be working on the technical side of the business or the commercial side. If science is your primary interest and you're not quite sure whether you are suited to the managerial aspects, then there's nothing wrong with climbing the "technical" ladder. I think that you really have to have drive and ambition to pursue a career in management. If you want to do this, there are ways of improving your knowledge of business. For me, I got an MBA, but others find mentors who will be able to give the guidance and support needed. It is important to take on board the ideas of people from different disciplines and set a development plan with your line manager. Try to expand your professional skill set to the best of your ability.

How do you engage with the wider scientific community?
I have an honorary professorship at Queen's University Belfast. The position allows me to write peer-reviewed papers and, by the end of 2020, I hope to have published more than 100 papers – something which I'm very proud of, as I'm not an academic 100 percent of the time!

One of my personal goals for 2020 is to help build science awareness for school students and graduates. There's definitely a need for young scientists to enter industry but, currently, many young people with an interest in science are pushed into medicine and other healthcare-related careers. I want them to be aware that there are fulfilling career options available to them in pharma too; I have certainly enjoyed the years I've spent in industry.



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