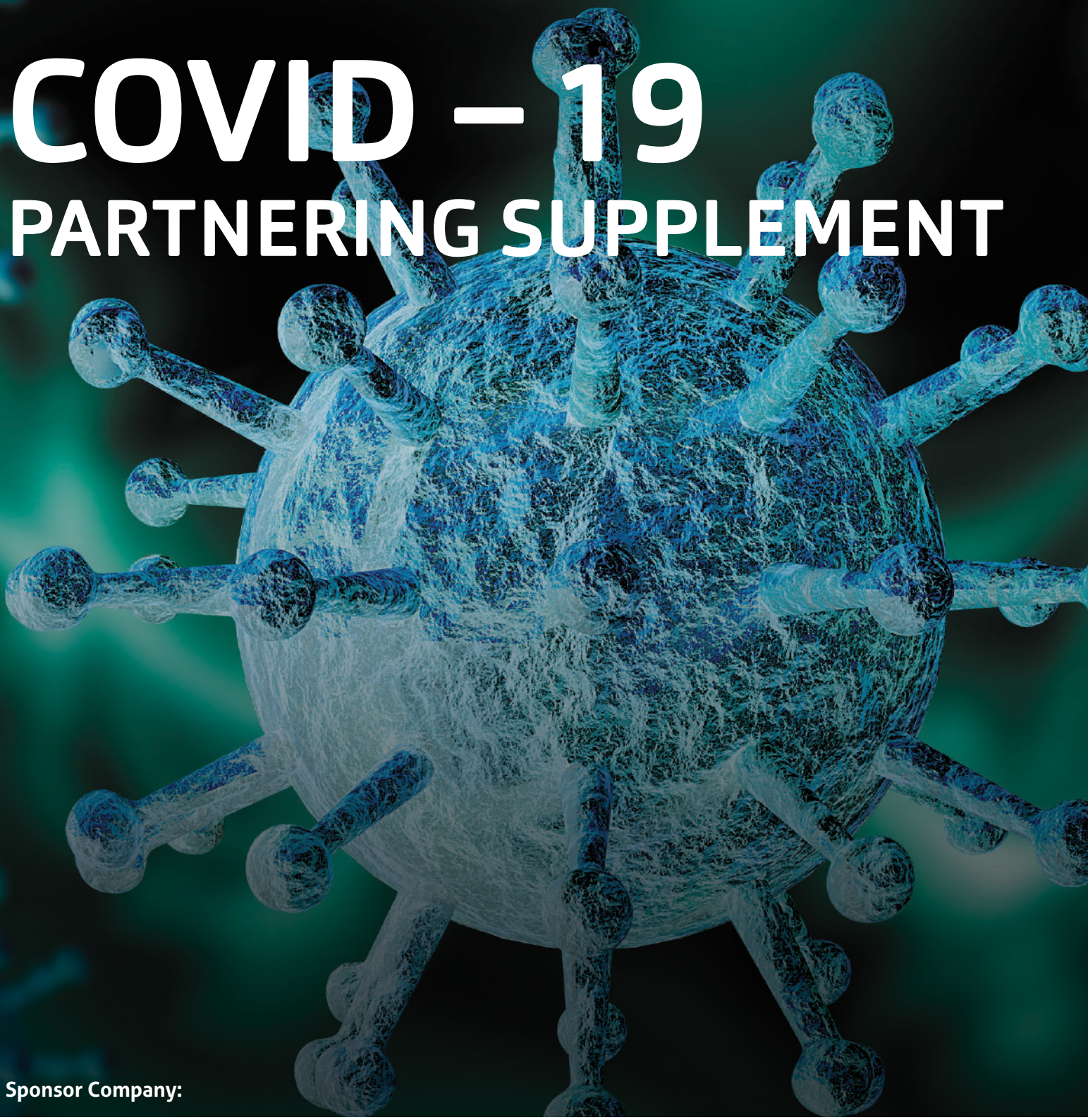
June 2020

PHARMA PUBLICATIONS
Supporting the Industry Through Communication

COVID – 19
PARTNERING SUPPLEMENT



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CONTENTS

COVID – 19
PARTNERING SUPPLEMENT

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PHARMA PUBLICATIONS
Supporting the Industry Through Communication

COVID-19 has touched every nook and cranny of our globe. Big and small, developed and developing have seen their economies grind to a halt; businesses buckling under the strain of lockdowns; toilet paper, hand sanitiser and pasta becoming rare and precious items; schools closing and major sporting events being cancelled. And, of course, it has exposed serious gaps in health services and systems. **Patricia Janet Scotland, Commonwealth Secretary-General**, rightly states that it is important that we never go back to the business as usual that we knew before coronavirus. We must use the opportunity to learn from this outbreak and decide, not only how we could have more resilient, connected and accessible healthcare systems, but also how we could address connected issues such as climate change and access to quality education for all.

Pharmaserve is a UK-based CDMO that has been combining in-depth knowledge, experience and constant innovation to develop and manufacture inhaled medicines for almost 50 years. With COVID-19 impacting countless businesses, many are finding themselves having to prioritise programmes. This is where Pharmaserve and a progressive partnership with them can be powerful. The Pharmaserve team has over 50 years' experience in manufacturing, analytical testing, supply chain and QP release and offer this service to support all or part of a programme, ensuring activity does not need to be slowed down. **Adam Kelliher *et al.* at Pharmaserve** describe how through experience and great partnership, they have streamlined the manufacturing and method transfer process, allowing this to be conducted effectively and efficiently with the assurance that your programme is in the hands of experts.

Tosoh Bioscience has enabled its biopharma partners to provide robust diagnostics solutions and safe and efficient therapies for life-threatening diseases for decades. During the ongoing battle against COVID-19, the necessary steps have been taken to ensure business continuity and to support the ongoing R&D and production activities to combat the coronavirus. **Dr. Romain Dabre, Senior Product Manager at Tosoh Bioscience**, defines how Tosoh Bioscience offers a variety of chromatography media and HPLC columns that can support the research, development, and production efforts in the fight against COVID-19.

The increasing frequency of prescription drug shortages in the United States can often be attributed to gaps in efficiency within the pharmaceutical supply chain. Drug shortages can impact the ability of hospitals, pharmacies, and other healthcare providers to deliver therapies at the intended time of treatment. **Matthew Hall & April Shen at Corning Pharmaceutical Technologies** explain how the drug shortage crisis in the United States can impact the quality and economics of healthcare. Numerous solutions to reduce drug shortages have been proposed, many of which focus on public policy initiatives. An alternative approach

to stabilising the supply chain enhances manufacturing with technologies that improve drug quality, increase throughput, and reduce waste. Innovative glass vials engineered with new features such as low COF coatings and chemical strengthening are a promising technology and a potential win-win for patient safety and manufacturers looking to improve quality and increase efficiency, while maximising the utilisation of capital-intensive manufacturing equipment.

18 **Proper Degassing Enables High-precision Dispensing of Chilled Solutions**

Dispensing precision is critical to the performance of modern diagnostic kits, where repeatability and accuracy in the amount of reagent dispensed form the basis for reliable results. For manufacturing and production lines, dispensing of chilled solutions warmed up presents a challenge as bubble formation caused by out-gassing threatens the precision. Deviation in the dispensed amount of solutions can affect the validity, economics, and possibly even the regulatory approval of a product. **Fritiof Pontén at Biotech** describes how in-line continuous degassing with Teflon® AF membranes effectively removes dissolved gasses from reagent solutions and avoids dispensing errors with greatly increased precision. Dispensing 1200 portions of water without degassing resulted in severe dispensing errors in 2% of the samples. An additional dispensing sampling of 800 portions of water with proper in-line degassing eliminated these dispensing errors.

22 **Bioquell Helping Pharmaceutical Companies Resume Operations Post-COVID-19**

As the world prepares to enter the next phase of the COVID-19 pandemic with the potential relaxation of lockdown restrictions, Bioquell, an Ecolab solution and leading manufacturer of high performance bio decontamination technology, is utilising its well-proven Rapid Bio Decontamination Service (RBDS) to help pharmaceutical companies ensure operational continuity and quickly ramp up capacity. **Guy Turner from Bioquell** explains how it will enable pharmaceutical companies that have reduced production during the coronavirus pandemic to quickly gain control of clean spaces and return to full capacity.

23 **Bioquell Rapid Bio Decontamination Service**

Bioquell RBDS returns converted COVID-19 wards back to normal. During the COVID-19 pandemic, many hospital wards were temporarily converted to solely treat COVID-19 patients. As these begin to revert to 'regular' non-COVID-19 wards, a solution is required to manage the increased potential environmental contamination risk facing the patients admitted to these wards.

24 **Stirred-tank Bioreactors and How they are Used in the Development and Production of COVID-19 Vaccines**

Increasing demands from governmental vaccination programmes and pandemic events such as the current COVID-19 outbreak require scientists to work under pressure to shorten the time-to-market of developed vaccines. Altogether, a need for new methods to increase speed and yield, and to produce new vaccines in a cost-effective manner to remain competitive is a constant concern for scientists. Although the competition in the vaccine market is high, a noteworthy effect of the current COVID-19 crisis is the fact that big vaccine manufacturers are forming and maintaining collaborations with comparably young companies, and former competitors are cooperating with each other in order to speed up vaccine development. **David Solbach at Eppendorf AG** analyses the trend towards collaboration in the biotechnology industry in order to accelerate the research, development and large-scale production of new vaccines.

26 **Together Beyond COVID-19**

We find ourselves in one of the most challenging situations in history. In a noticeably short time, the world has been consumed by a virus that has proved to be both ruthless and deadly. Countries all over the world are battling an invisible enemy and yet remain resolute in the face of such adversity. Whilst challenges create opportunity, never has such a spotlight been put on the pharmaceutical industry to react quickly and effectively and develop a cure or vaccine for COVID-19. However, despite the current crisis, product development continues and regulatory compliance, quality management and ongoing pharmacovigilance must be maintained. **Dr. Jürgen Hönig & Lisa Pascoe at PharmaLex** explain why it is important to also look beyond COVID-19 and have a strategy in place to manage this. Planning at a local level will help boost resources and ensure plans are aligned when the time comes. Now is the opportunity to put in place fail-safe measures that will ensure business can continue now and will continue and grow when the crisis is over.

31 **Importance of the Limulus Amebocyte Lysate (LAL) Assay in the Development of a COVID-19 Vaccine**

In December 2019, an outbreak of pneumonia was reported in the city of Wuhan, China. The causative agent behind the outbreak, a novel coronavirus called severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), was identified in January 2020. The World Health Organization (WHO) named this disease coronavirus disease 2019 (COVID-19). Since these initial reports, COVID-19 has rapidly spread to become a global pandemic. As laboratories across the globe focus their research efforts on the development of a vaccine for COVID-19, it is crucial that quality control standards are maintained throughout the research and development process. This report by **Lisa Komski FUJIFILM Wako Chemicals U.S.A. Corporation** will focus on the risks that endotoxin contamination poses for COVID-19 vaccine research, as well as highlighting the utility of the Limulus Amebocyte Lysate (LAL) assay for endotoxin detection during vaccine research and manufacturing.

36 **Pass-Through Autoclaves for Improved Containment**

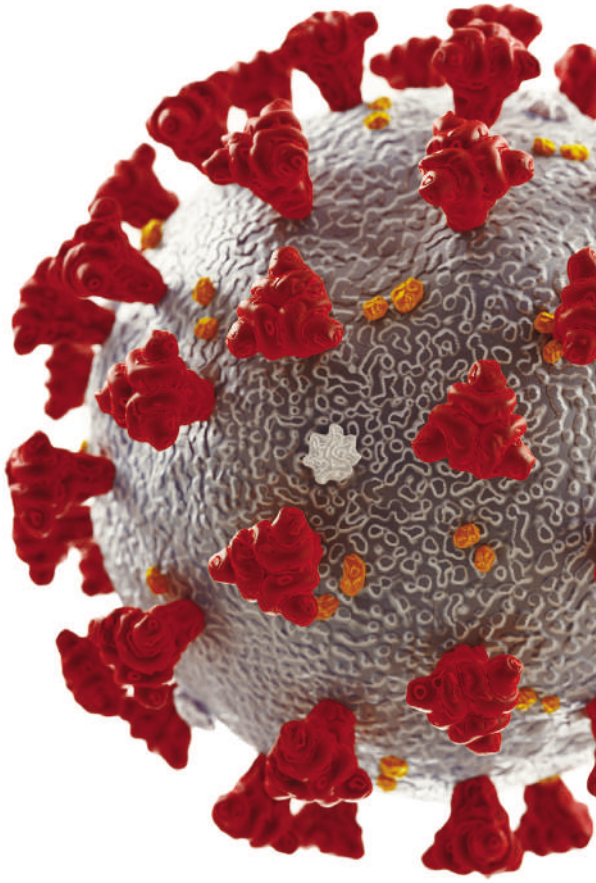
When Brunel University required a double-door/pass-through steam sterilizers as part of a new CAT III containment laboratory suite it was sourced from dedicated laboratory autoclave manufacturer, Priorclave, a British company with many years' experience in bespoke design and build of steam sterilizers. With years of experience in the design, manufacture and use of research grade laboratory autoclaves, **Lee Oakley** explains why, Priorclave is justifiably proud of its reputation as one of Europe's leading manufacturers. The company has a network of trained and certified technicians both in the UK and through accredited distributers throughout the world.

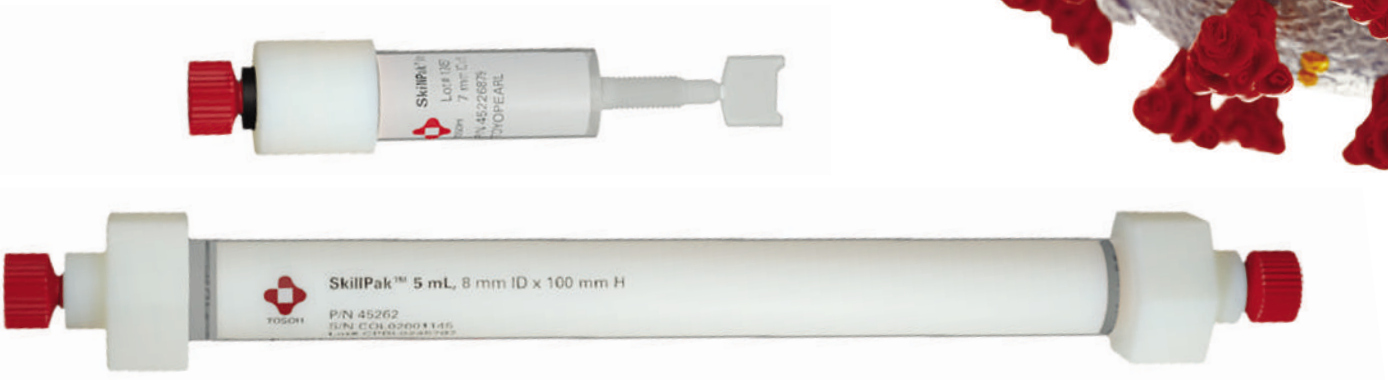
39 **Covid-19: The Real-World Applications of Photonic Equipment**

Techniques such as PCR and medical imaging are vital in the fight against the coronavirus, and rely on the continued supply of components by manufacturers such as Hamamatsu Photonics. **Tina Urbanek of Hamamatsu Photonics Deutschland GmbH** discusses how as a diagnostic tool of coronavirus, medical imaging techniques such as computed tomography (CT) and conventional radiography of the thorax are used.

TOSOH

#CHROMATOGRAPHY EXPERTS





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TOSOH BIOSCIENCE

FOREWORD

At the beginning of 2020, nobody could have realised what effect the corona pandemic would mean to everyone as the whole world was halted, nor have many people seen the type of world where borders have been closed and people have been unable go about their normal lives.

Being a British expat, but now a Swedish citizen living in Sweden, I have been in the position that our country never went into lockdown, but our lives have still been impacted as people worked from home or have been paid to stay at home due to companies' logistics issues.

I feel that the global pharma industry now has a great opportunity to educate and convince the whole world how hard it is to actually find a vaccine, which people may be hoping is a type of silver bullet that can eradicate Covid-19. The question is even if a vaccine is found, what cost is this going to have for the world and who is going to pay for this?

I also think it's been interesting to see what drugs we have available that can be reformulated into potential drugs that can help towards patients getting better, but I do think that blood plasma – and what we can learn from the patients who have been able to fight this virus – can help us understand about it more.

But inevitably, if there is a vaccine, then what are the potential side-effects and the future impact of antimicrobial resistance? Also, what is the next thing that will threat humanity on this scale?

One of the great ways this pandemic has been good is that the pharma industry, governments and everyone else have realised what knowledge and technology we have available, and the fantastic collaborations demonstrate what we really are able to achieve. However, companies are also really going to have to look at their logistic chain in this global world and ask if they are sustainable, should countries lock themselves down in future.

The pandemic has certainly helped companies realise that working from home is something that is possible, and maybe that head offices will not always be needed. However it really makes you understand how important your professional network is, and how important networking actually is. I do miss meeting people and I don't think this is ever going to change.

The life sciences have always understood the need to be international and that people's networks reach outside their own market. Unfortunately, many networking events have been cancelled but they have made their way online, and I have been participating in two of these with the opportunity of virtual meetings.

With regard to the global economy, inevitably there is going to be an impact, and SEB Bank expect GDP in developed countries to shrink by 7 per cent in 2020. I feel that the economy is going to be okay but after the great restart, companies and people are going to look at what they really want from the planet and what the bigger picture is of global consumerism. The big question is whether this includes investing in our health, and what medicines or therapies are really going to keep us well.

I hope that this is the start of personalised medicine and preventive medicine instead of taking more and more drugs which we really understand so little about in the long run, and their long-term side-effects.

I hope you enjoy reading this edition of the magazine and that we all find some normality in this situation we find ourselves in.

Lucy Robertshaw

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WE SHOULD NOT GO BACK TO BUSINESS AS USUAL AFTER CORONAVIRUS, SAYS SECRETARY-GENERAL

Commonwealth Secretary-General Patricia Scotland on World Health Day (7 April 2020)

Today there is an eerie silence across the globe. Bustling cities have gone quiet, and highways that were once jammed with bumper-to-bumper traffic are empty. In homes, thousands of families are anxiously awaiting a phone call from a hospital about their loved ones. Many have already received the devastating news that their mother, father, child, spouse, sibling or friend has died from coronavirus complications – often without the comfort of someone familiar to hold their hands.

And in the very trenches of the war against this new disease that changed our world with astonishing speed, are nurses, doctors and other hospital staff. Every day they put on their uniforms and turn up to the frontline to battle, with or without the armour of personal protective equipment.

COVID-19 has touched every nook and cranny of our globe. Big and small, developed and developing have seen their economies grind to a halt; businesses buckling under the strain of lockdowns; toilet paper, hand sanitiser and pasta becoming rare and precious items; schools closing and major sporting events being cancelled. And, of course, it has exposed serious gaps in health services and systems.

But, even as we wake every day to this frightening and sometimes surreal experience, it is encouraging and comforting to hear the Head of the Commonwealth, Queen Elizabeth II, declare, on Sunday, that "we will succeed" in the fight against this global crisis.

So, on this World Health Day that has been rightly set aside to celebrate the contributions of nurses and midwives, it is important that we take the opportunity to re-evaluate the status quo and the current models that support our daily lives; and begin to assess the lessons that are already emerging from this catastrophe.

What we have already witnessed, for example, is that healthcare systems that are more equitable, providing access to basic healthcare to all individuals and communities without them experiencing financial hardship, are more equipped to respond to the pandemic. These countries that provide healthcare to all, known as universal health coverage, have been more successful in providing testing and treatment during the pandemic.

This particular lesson has been a top agenda item for Commonwealth health ministers at their annual summits for the last four years. Their meetings have critically assessed various strategies to help countries achieve universal health coverage. It is now undoubtedly clear that addressing human resources for health shortages, and financing sustainable healthcare systems that cater to the needs of those in poverty and the most marginalised in any society, are critical if we are to win the fight against COVID-19 and be ready for any future outbreaks.

Another challenge that this pandemic has exposed is the acute shortage of essential health supplies, drugs, equipment and tests. Prior to the COVID-19 outbreak, the Commonwealth had developed strategies to help countries to pool procurement of essential medicines. This was presented at the 2019 Health Ministers Meeting chaired by Fiji. And since the outbreak of COVID-19, we have been exploring how we can tailor approaches such as a price-sharing and pooled procurement platform to provide important information on these essential health supplies, drugs, tests and equipment necessary to combat the pandemic across the Commonwealth.

There is no doubt that this pandemic is affecting us all – its impact leaking into every aspect of our life. Both physical and mental health are on the line, as people lose their way of life, their livelihoods and their loved ones. Many of us will feel the long-term effects of poor nutrition, decline in fitness and the disruption of human relationships. But COVID-19 does not affect us equally. There is certainly a disproportionate impact, for example, on households that depend on daily paid labour and people at risk of domestic abuse. So, governments stand before a goliath challenge that requires a coordinated response involving all sectors.

But I again return to the wisdom of the Head of the Commonwealth, Queen Elizabeth II, that "better days will return". If we work together, share resources and equipment and follow advice of governments and the World Health Organisation, we will, eventually, be able to wake up our cities, return to work, school and leisure, to meet and chat, or to hug each other.

But it is important that we never go back to the business-as-usual that we knew before coronavirus. We must use the opportunity to learn from this outbreak and decide, not only how we could have more resilient, connected and accessible healthcare systems, but also how we could address connected issues such as climate change and access to quality education for all.

PATRICIA JANET SCOTLAND
Commonwealth Secretary-General

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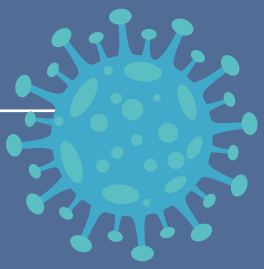

COVID-19: A CATALYST FOR INNOVATION

Adam Kelliher , Alex Hearn, Matt Tyler, Matthew Edwards

Pharmaserve is a UK-based CDMO that has been combining in-depth knowledge, experience and constant innovation to develop and manufacture inhaled medicines for almost 50 years.

Boasting large-scale, world-class filling equipment and a rigorous, in-house testing and release procedure, Pharmaserve has capacity to deliver over 70 million pMDI units a year across four GMP manufacturing lines and more than 10 million on a dedicated nasal line.

Due to the expertise and analytical capability of our development laboratory, many of the medicines supplied to our customers are developed and formulated in-house and our team has a demonstrable technical transfer capability, bringing already commercialised products into the facility.

Moreover, it is our approach to working with our customers that sets us apart. At Pharmaserve, we tailor each project to the exact needs of our customers, offering not only first-class support but a truly collaborative partnership whilst bringing products to market efficiently and effectively.

The partnership with Senzer is a great example – the speed and efficiency from both organisations have taken products through from reformulation and re-purposing drug products to being ready for clinic. The aligned thinking and shared knowledge and experience ensure that the critical steps are understood, allowing strategic approaches that accelerate development programmes efficiently, ensuring quality remains at the forefront.

With the challenges of the recent pandemic, inhaled medicines are at the forefront of innovation. The role of Pharmaserve as the choice of CDMO in developing and supplying essential inhaled medicines, with a committed and highly capable team, will see Pharmaserve and customers like Senzer set for a robust and promising future.

Pharmaserve

With COVID-19 impacting countless businesses, many are finding themselves having to prioritise programmes. This is where Pharmaserve and a progressive partnership with us can be powerful. The Pharmaserve team has over 50 years' experience in manufacturing, analytical testing, supply chain and QP release and offer this service to support all or part of a programme ensuring activity does not need to be slowed down.

Through experience and great partnership, we have streamlined the manufacturing and method transfer process, allowing this to be conducted effectively and efficiently with the assurance your programme is in the hands of experts.

Pharmaserve are unique, covering the product journey from formulation development to commercial supply, and including pMDIs, DPIs, nasal sprays, liquid sprays and creams/semi-solids as dosage forms. The laboratory covers both development and quality control, with an array of equipment:

- HPLCs (including Agilent 1200 and 1260 Infinity systems)
- GCs
- LC-MS
- Particle size by laser diffraction (Malvern 3000 & Sympatec)
- IR, UV-Vis, microscope, Karl Fischer, viscometer
- ACI, NGI, delivered dose apparatus
- A series of 'walk in' stability chambers
- Storage in accordance with ICH guidance at 25°C/60%RH, 30°C/65%RH, 40°C/75%RH and 2°C – 8°C

A dedicated, highly technical and experienced product development team guide products from formulation development through to commercialisation; with ongoing input from the wider organisation to ensure that a commercially viable product and process are created. Services and capabilities include:

- Analytical methodology (development, transfer and validation)
- Formulation development
- Brand characterisation
- Process development
- Pivotal batch manufacture
- Full-scale stability
- Clinical studies
- Product characterisation
- Technology transfer
- Scale-up
- Process validation
- S&OP
- Supplier management
- Manufacturing
- Packaging
- Quality control
- QP release

We believe that success comes from truly collaborative relationships, combining knowledge, experience and innovation. These close partnerships allow us to deliver molecule to market to the highest standard, taking products to market efficiently.

Having worked with us before, Senzer knows from experience that Pharmaserve rise to the challenge quickly and effectively.

A partner's perspective: Senzer and Pharmaserve

Senzer is a leading respiratory pharmaceutical company, and we have been fortunate to have a deep and long-standing business relationship with Pharmaserve. We have a unique breath-activated inhaler, which delivers both synthetic and botanical cannabinoids for both medical conditions, and health and wellbeing. More recently, we have been applying our focus on emergency treatments for Covid-19.

Inhalation is probably one of the most exacting areas of healthcare. Within the already tight stipulations of pharmaceutical compliance, it can be very challenging to formulate actives that are tolerated in the lungs, which have very sensitive tissues. Any misjudgement can mean the difference between acceptance and rejection of the inhaled materials amongst patients and users, and so it is really important to work with a team who have broad knowledge of this space.

This is something that we have found in abundance with Pharmaserve, as their R&D team have a very deep understanding of what will work in a respiratory device. They are highly efficient, have an evident appetite for problem-solving, and it has been a very open collaboration, with clear communication between them and our development team on reaching our agreed goals.

Once the formulation has been resolved and approved, the obvious next challenge is to deliver commercial product, and in this too, Pharmaserve have shown great capability. They have real flexibility in their production, being able to scale quickly from thousands of canisters up to millions per annum. From a commercial perspective, it is imperative for us to know that if we have a demand surge, we have a supplier who will deliver.

All these capabilities have been shown in our emergency Covid-19 programme, in which we are looking to deliver anti-viral pharmaceuticals to where the viral load is highest, in the respiratory tract. We have achieved within weeks what would probably take more than one year in normal circumstances. Every day there have been new challenges and obstacles, and each have been dealt with head-on. Pharmaserve have shown themselves to be a committed and highly professional business partner.

Choosing the right partner has been crucial for Senzer to execute its goals as a world leader in respiratory therapeutics. We have two routes in this strategy; targeted and systemic. The former is the basis of our Covid-19 programme, in which we are delivering anti-virals straight into lungs, where we intend the actives to reside. So this path requires the formulation to have a larger particle size, about 5 microns, so the formulation will topically coat the alveoli cells and hopefully help heal patients.

The second route is systemic. This requires the use of our patented device, for Systemic inhaled Drug Delivery (SiDD) which

has the features of slowing down the flow of the delivery, and delivering in a much smaller particle size, typically about 1.5 microns. This means the actives are absorbed by the lung tissue and go straight into the bloodstream, providing systemic delivery. We have data showing that uptake occurs within two minutes (versus 1.5 hours by oral ingestion), and this route has a similar efficiency to taking drugs by injection or IV.

The genesis of our SiDD platform was some 14 years ago, when the novel approach was invented by Senzer's founder and CEO, Alex Hearn. The offering has been used to deliver medicinal nicotine, as a smoking cessation product (see www.voke.com). Senzer was created in 2017 to develop the platform to deliver pharmaceutical synthetic cannabinoids, and these have been used in FDA approval trials to help treat chemotherapy-induced nausea and vomiting, and neuropathic pain. The ability to be able to provide the actives in a precise dose-controlled presentation has potential for treating a range of conditions appropriate for cannabinoid therapy, which is a field that has great promise to help a number of conditions that have defied mainstream pharmaceutical treatment. And one of the most wonderful aspects is that this approach gives patients a high degree of control. Because the effect is near immediate, they can titrate upwards in a controlled manner, based on their need. The device is simple to use and can be used at home, as well as in hospital.

SiDD is a unique approach, and our differentiation is reflected in the breadth and depth of our IP portfolio, which has some 450 granted patents, based on 35 patent families, with coverage in 46 countries. We see our approach to be a genuine game-changer, and one of the more exciting projects we are working on is to develop the offering for delivery of CBD in a format appropriate for mass consumer use.

All of Senzer's actions are based on deep concern for helping the health and wellbeing of our users. Safety and effectiveness are crucial, in our requirement for consistent compliant formulations. On this journey, we have found Pharmaserve to be a trusted and reliable partner.

PHARMASERVE NW
Working for you

SENZER
PHARMACEUTICALS

ADAM KELLIHER

Originally from NZ and a former war correspondent, Adam has 20+ years of experience in the life sciences sector, taking companies from inception to high value. He founded, built and successfully sold both Equazen Ltd. and Equatec Ltd. Adam has experience in the public markets as CEO of Avita Medical plc.

ALEX HEARN

A graduate of Oxford University, Alex is an innovator and successful entrepreneur. He founded Kind Consumer and developed the worlds first medically approved smoking cessation device, Voke. He started Oxford Entrepreneurs, and has worked at Johnson and Johnson, and Altium Capital.

MATT TYLER

Graduating from Cardiff University with a degree in pharmacology, Matt has spent over 14 years in the pharmaceutical industry. His background includes QC, R&D, operations and projects. Most recently, Matt was the Head of Technical Operations for three years. In 2019, Matt took the role of Business Development Manager, bringing his technical expertise to support the existing Business Development team.

MATTHEW EDWARDS

A chemistry graduate from the University of Liverpool, Matthew has over 17 years of experience in the pharmaceutical industry, including roles at Sanofi and Bristol Myers Squibb. His experience spans the life-cycle of products; from formulation through to commercialisation, where he has successfully led numerous product submissions, including EMA and FDA. Matthew is the Head of Development at Pharmaserve, leading with his technical expertise in product development from lab-scale through to commercial manufacture.

PHARMASERVE NW
Working for you

Inhalation SPECIALISTS

Pharmaserve has been developing and manufacturing inhaled medicines for nearly 50 years, combining knowledge, experience and innovation.

- Supplying inhaled products worldwide
- Four established pMDI filling lines
- Capable of producing in excess of 70 million units a year
- Expert formulation & analytical capability
- Demonstrated technical transfer expertise

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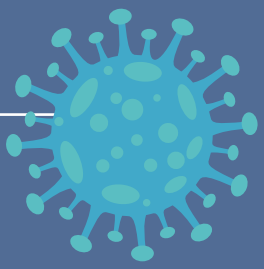


TOSOH BIOSCIENCE SUPPORTS THE BATTLE AGAINST COVID-19 ON ALL FRONTS

Dr. Romain Dabre, Senior Product Manager

Tosoh Bioscience has enabled its biopharma partners to provide robust diagnostics solutions and safe and efficient therapies for life-threatening diseases for decades. During the ongoing battle against COVID-19, the necessary steps have been taken to ensure business continuity and to support the ongoing R&D and production activities to combat the coronavirus.

In the diagnostics field, Tosoh is developing a reagent that can detect the new coronavirus in less than 50 minutes, slashing the six-hour waiting time required by current test kits[1]. In another division, Tosoh Bioscience's chromatography experts are focusing their technological leadership on chromatography materials to support the development of methods for the analysis and industrial production of therapies, vaccines, and diagnostic solutions at their biotech and pharma customers.

Let's dive into some of the major developments during the ongoing pandemic and discover the benefits of using Tosoh Bioscience's purification solutions for biotherapeutics.

Interfering with SARS-CoV-2

The oligonucleotide therapeutics field has seen remarkable progress over the last few years, and it has even accelerated since the beginning of the COVID-19 crisis. The first clinical trials using small interfering RNA (siRNA) are underway, as siRNA therapies have already proven their efficacy against former members of the coronavirus family, such as SARS and MERS. siRNA therapies could be used to hit the highly conserved regions of coronavirus RNA virus itself, and to improve critical lung symptoms[2].

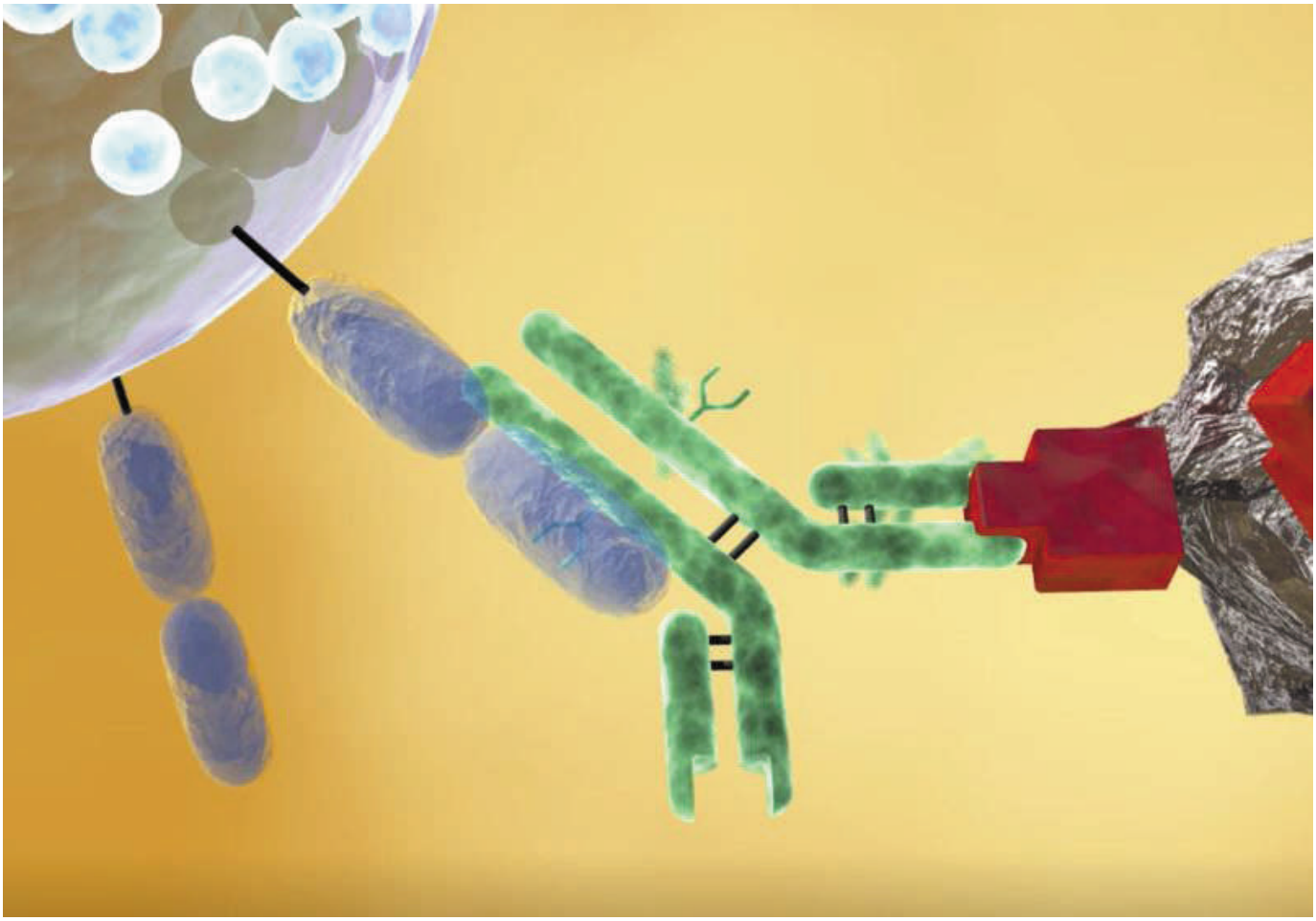
To ensure the best efficacy of such therapy approaches, the production of siRNA needs to be developed fast and efficiently while putting patient safety first. This is the reason why the key players in the siRNA field rely on TSKgel® SuperQ-5PW (20) for the purification of siRNA-based biopharmaceuticals. TSKgel SuperQ-5PW (20) offers high purity at high loading, accounting for more efficient production processes. For example, as published by a team of scientists from former Roche Kulmbach GmbH, now Axolabs, the separation between single and double strands of siRNA are better using TSKgel SuperQ-5PW compared with the competition[3].

Reduce Costs and Production Time by Switching to Tosoh's Two-step Platform

Antibodies are developed for many COVID-19-targeting projects. The most obvious one is for anti-COVID-19 therapies. One of the dramatic physiological effects of COVID-19 is the cytokine storm damaging the patient lungs, known in the literature as cytokine release syndrome (CRS)[4]. CRS is a systemic inflammatory response. In short, the virus binds to the alveolar cells and activates the immune system, releasing a large number of cytokines. This reaction leads to the release of fluids and cells in the lungs, resulting in dyspnea and even respiratory failure. Interleukin-6 (IL-6) plays a critical role in this acute inflammation process. Inhibiting its production is, therefore, promising for the treatment of patients in dangerous conditions, and antibodies such as tocilizumab or sarilumab can be very effective for this purpose. Some of the companies producing such antibodies, like Sanofi, Regeneron, or Roche, have started clinical trials with those molecules already.

Another use of antibodies is for the production of serological tests. The presence of antibodies to SARS-CoV-2 in the blood indicates whether the patient has been infected with coronavirus in the past. Such tests can be used to find out whether people, whether symptomatic or asymptomatic, have developed an immune response against the virus. Such information is critical to monitor the evolution of the pandemics and to evaluate upcoming herd immunity. Those serology tests require small amounts of anti-human antibodies to fix the SARS-CoV-2 antibodies[5].

All those diagnostics and therapeutics projects require a fast, reliable, and cost-controlled development and purification platform for monoclonal antibodies. At Tosoh Bioscience, we cut the time-to-market and reduced the development and production costs for our customers by developing an innovative purification platform. We started by optimising the capture step using the efficient and robust Toyopearl® AF-rProtein A HC-650F capturing resin. In a second chromatography step, after virus inactivation, we implemented the salt-tolerant Toyopearl NH2-750F. With this aggregate removal anion exchanger, there is no need for a third chromatography step, as it used to be in standard production processes. Both chromatography steps were combined into one integrated process. Protein A had a recovery of 98.8%, and anion exchange chromatography had a recovery of 91.3%, thus resulting in a total recovery of 90.2%. DNA, HCP, and leached protein A were removed to the limit of detection of the used assays. This approach can reduce downstream costs by 45% and increase production output by 58%.



The Purification One-stop Shop for Speeding up Vaccine and Therapy Development

The biopharma industry relies on Tosoh Bioscience's solutions for the robust and reliable purification of biomolecules. Scientists worldwide are currently developing many vaccine and therapy projects using Toyopearl, TSKgel, and Ca^{++}Pure-HA® chromatography media. The experience and reliability of Tosoh Bioscience ensure navigating safely through the clinical trials to launch the well-needed biotherapeutics as fast as possible.

Through well-thought measures, Tosoh Bioscience ensures the availability of those products on a production scale throughout the crisis. It is, however, not enough to provide large volumes of chromatography media. The ongoing race against coronavirus makes it more evident than ever: scientists need to develop biotherapeutics and vaccines as fast as possible. Tosoh Bioscience launched at the beginning of the year SkillPak™ 1 and 5 mL pre-packed columns. Those pre-packed chromatography columns provide a single-use toolkit that supports fast purification method development[6].

The Gold Standards for the Analysis of Antibodies

The characterisation of monoclonal antibodies is crucial for both diagnostic and therapeutic applications. In diagnostics, antibodies are used to produce the long-awaited serological tests, and avoiding false positives and false negatives are key. This can only be achieved if the renowned test kit suppliers such as Roche or Abbott can be 100% sure of the quality of the antibodies. On the other hand, when producing antibodies for therapeutic applications, a precise characterisation is mandatory to avoid adverse effects, to increase the chances of successful clinical trials, and to ensure patient safety when going into production.

Tosoh offers robust and reliable solutions for the analysis of antibodies at all those stages:

Size (and Time) Matters

The separation of mAb monomers from their aggregates is one of the essential assays at all stages of mAb development and manufacturing. For decades, the TSKgel G3000SW$_{XL}$ size exclusion chromatography (SEC) column has been the gold standard for aggregate detection in the biopharmaceutical industry. Many scientists are developing their analytical methods during the current crisis using this well-known and robust HPLC column.

Reducing the time needed for the characterisation of the impurity profiles for mAb is critical during the ongoing pandemic more than ever. This is why many scientists develop their SEC methods on UHPLC systems, where they can use columns offering shorter analysis time and higher resolution at the same time. The column of choice for the aggregate analysis is the TSKgel UP-SW3000 UHPLC column. Dr. Ruppert from Roche Diagnostics summarises his experience with the SEC-UHPLC column from Tosoh Bioscience: "We were testing several columns from different vendors with a variety of our pipeline products. Although several columns showed a comparable resolution, the Tosoh TSKgel UP-SW3000 column (2 µm, 4.6 x 30 mm) convinced us in terms of robustness, especially the high lot-to-lot stability, an absolute requirement for quality control under GMP conditions."

Many other mAb constructs, such as antibody-drug conjugates (ADC), bispecific mAbs, or coformulations, can potentially build the future of the COVID-19 therapies. The biopharmaceutical world will be able to count on the expertise of Tosoh Bioscience

in the size exclusion chromatography of such biomolecules, as published by a team from Genentech[7].

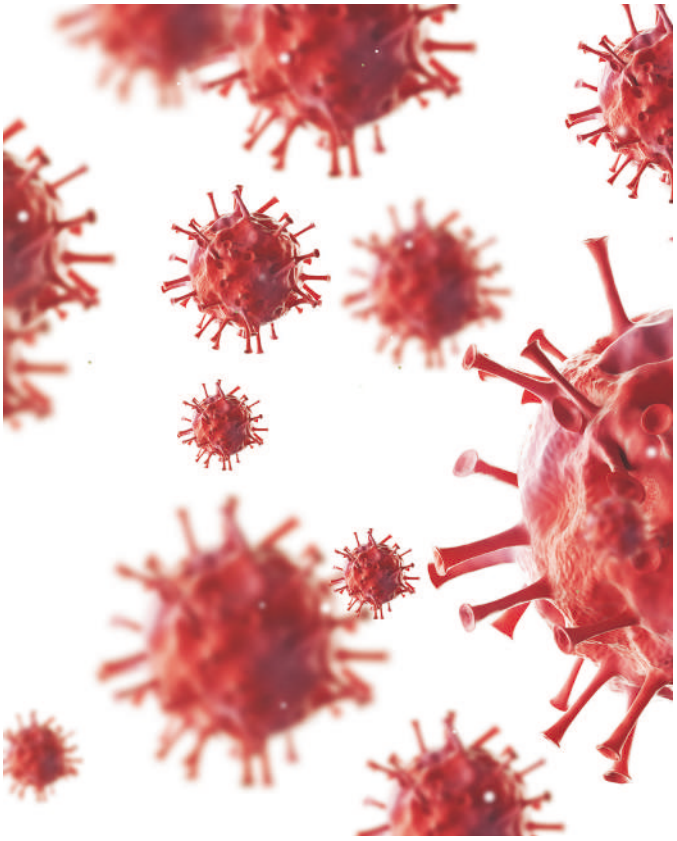
Fast Assessment of Biological Activity

One of the effects of antibodies on human cells is the cytotoxicity initiated by immune cells, such as natural killer (NK) cells and macrophages. Such cytotoxicity, known as antibody-dependent cell-mediated cytotoxicity (ADCC), might be beneficial in cancer therapies. However, for other applications such as the repurposing of anti-IL6 antibodies to reduce the cytokine storm in critical cases of COVID-19, random cytotoxicity should be kept as low as possible.

Fcγ IIIa receptor plays a crucial role in ADCC by forming immune complexes (IC) with the immune cells, leading to the release of cytotoxic molecules. There is a direct correlation between the intensity of ADCC and the glycosylation of Fc. Tosoh Bioscience made use of this property to develop a novel FcγRIIIa-immobilised column, TSKgel FcR-IIIa-NPR, as published by Kiyoshi *et al*. in Nature Scientific Reports[8].

A rapid thirty-minute separation allows the analysis of large numbers of mAb samples to gain valuable first information on the distribution of glycoforms and expected ADCC activity. This fast and efficient method can be applied to purified samples and supernatant alike. It can, therefore, be used in many phases of development and production, such as cell line screening in early R&D, biosimilar/originator comparison, upstream development and optimisation, monitoring of glycoengineering, or lot-to-lot comparison in QC.

Tomasz Walski, Project Group Leader in the R&D department at Mabion S.A., confirmed in a recent article that the FcR column will be extensively used in their current and prospective development projects[9]. He pointed out some critical benefits when developing projects in a high-pressure environment as we currently encounter in the fight against COVID-19: "The method was sensitive enough to use low microgram amounts of sample. On top of that, we got virtually the same results regardless of whether we used a highly purified sample of the antibody still in the cell medium. And that means we can perform high-throughput and highly informative screening of clones, cell culture conditions, and lead molecule selection with minimal sample handling. Not to mention that the lack of sample preparation makes this approach cost-efficient and environmentally friendly."



In a Nutshell

Tosoh Bioscience offers a variety of chromatography media and HPLC columns that can support the research, development, and production efforts in the fight against COVID-19. Moreover, they can help their biopharma partners avoid the common pitfalls, and they can speed up the ongoing development race through the pre-clinical, clinical, and production phases using their extensive expertise.

Contact one of Tosoh's chromatography experts to find out how their chromatography solutions can help you fight COVID-19: www.surveymonkey.de/r/Tosoh_COVID.

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TOSOH

DR. ROMAIN DABRE

Romain Dabre has dedicated his career to chromatography. After studying engineering at the ENSICAEN in France, he spent 5 years at Merck Darmstadt developing chromatography resins and HPLC columns while obtaining a Ph.D. Degree in Analytical Chemistry from the University of Vienna in parallel. He moved then to Tosoh Bioscience GmbH, where he occupied at first several sales positions before evolving in marketing roles. Romain is now Senior Product Manager, supporting the customers of Tosoh Bioscience in the EMEA region and contributing to the organization's success through global initiatives.

STABILISING THE PHARMACEUTICAL SUPPLY CHAIN

Matthew Hall, Application Engineering Manager and April Shen, Analytics Manager

Enhancing manufacturing with technologies that improve drug quality, increase throughput and reduce waste

The increasing frequency of prescription drug shortages in the United States can often be attributed to gaps in efficiency within the pharmaceutical supply chain. Drug shortages can impact the ability of hospitals, pharmacies, and other healthcare providers to deliver therapies at the intended time of treatment. Multiple factors including market dynamics, loss of patent exclusivity, quality issues, disruption of raw material supply, inventory practices, natural disasters, and manufacturing problems can lead to an unstable drug supply.[1–3]

Drug shortages can impact the quality and economics of healthcare. A retrospective study by Vail *et al*. evaluated the impact of norepinephrine shortages in the United States on the outcomes of adult patients admitted with septic shock.[4] Patients admitted to hospitals experiencing a norepinephrine shortage during the time period of the study were associated with an increased likelihood of in-hospital mortality. This outcome correlated with the use of less preferable vasopressor alternatives to norepinephrine such as phenylephrine and dopamine. Undesirable outcomes driven by the need to use alternatives during drug shortages have been observed with other classes of drugs, including anaesthetics, anti-infectives, and anti-neoplastics.

Hernandez *et al*. analysed FDA pricing data from December 2015 to 2016 – they found that the price of generic drugs in limited supply that were produced by three or fewer manufacturers increased by an average of 20%. The price of generic drugs that were not in shortage over the same period increased by 9%.[5] Healthcare institutions also incur substantial costs due to drug shortages. A 2019 survey conducted by Vizient estimated that US hospitals spent an annualised $359 million in costs associated with an additional 8.6 million labour hours to manage drug shortages.[6]

A number of solutions have been proposed to help alleviate drug shortages, including:

- Financial incentives to manufacturers that establish and maintain additional manufacturing capacity to prevent drug shortages
- Financial incentives to invest resources in manufacturing generic drugs with less desirable economics
- Mandated inventory levels for critical drugs
- New business models for stabilising the supply of drugs that are subject to frequent shortages.

Recent innovations in glass packaging provide another strategy to secure the pharmaceutical supply chain by improving quality and increasing manufacturing efficiency. These innovations address issues that have historically limited the performance of glass packaging, such as delamination, breakage, and particulate generation. Improved glass packaging is particularly relevant to the issue of drug shortages – statistics show that injectables are the most frequently impacted therapeutics affected by shortages in the United States. Between 2001 and 2018, injectables represented ≥50% of new shortages in 14 years of this 18-year time period.[7]

Glass Delamination

Delamination is a response primarily observed in converted tubing glass vials in which thin flakes release from the interior surface of the vial into the liquid formulation (see Figure 1). The propensity for delamination is dependent on multiple factors, although its origin is the surface chemical heterogeneity that is created during conversion of glass tubing to vials. Potential risks of delamination flakes include inflammatory responses that injure tissue, stimulation of undesirable immune responses, and/or tissue injury through occlusion of vasculature.[8] As a result of these potential risks, drug lots affected by glass delamination are recalled, thereby impacting supply.

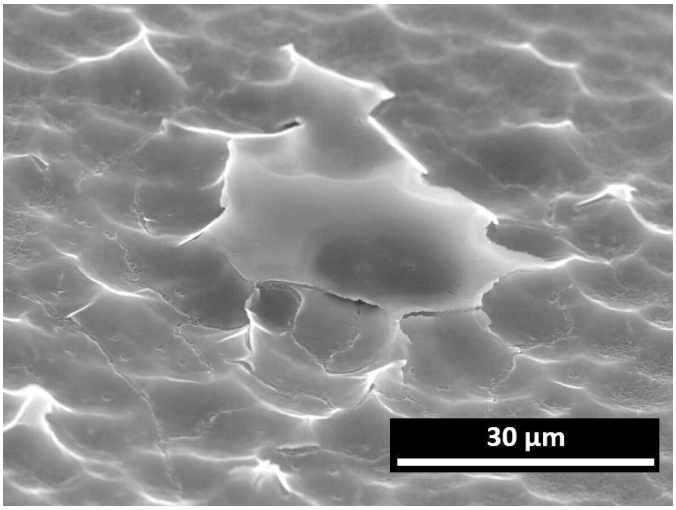

Figure 1. SEM image of corroded glass vial surface with flakes that are indicative of delamination.

Subsequent work on new glass formulations has led to solutions that address the root cause of delamination.[9] In particular, boron-free aluminosilicate glasses eliminate the volatilisation-prone component leading to chemical heterogeneity and subsequent delamination. These aluminosilicate glasses also meet the hydrolytic performance requirements of Type I glasses used for parenteral packaging as outlined by the USP.

Glass Particulate Contamination

The presence of glass particulates is another frequent source of recalls.[10] Frictive contact between vials and vial impact events during filling can generate particulates (see Figure 2). Complete breakage of a vial can also generate glass particulates. In either case, the resultant particles can lead to contamination, loss of product, and expensive recalls that jeopardise the supply chain. Potential health risks of glass particulate contamination of a parenteral product are similar to those related to delamination events.[8]

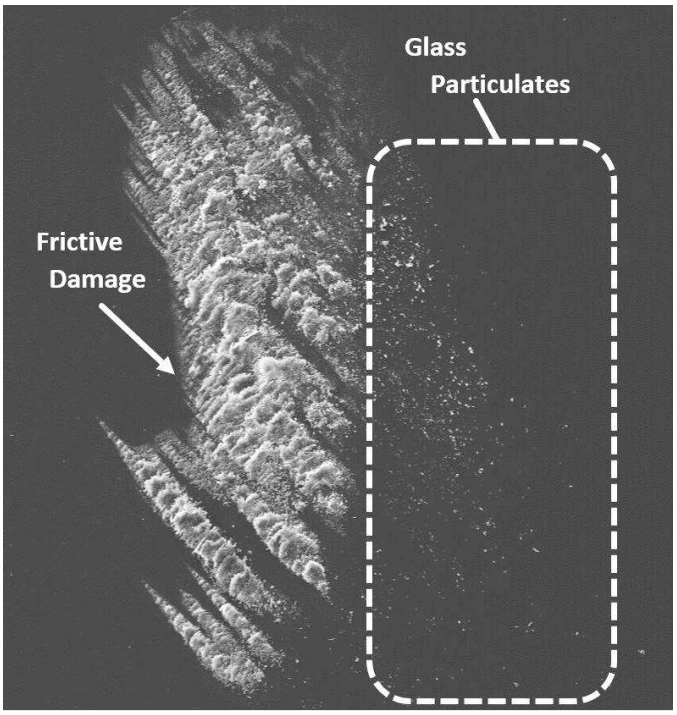

Figure 2. Scanning electron microscopy image showing frictive surface damage and glass particulate generation resulting from glass-to-glass contact of vials.

One approach to mitigating glass particulates focuses on operational parameters of the manufacturing process. Limiting vial residence time on a moving accumulator table decreases vial-to-vial contact that can lead to glass particulate generation. Careful assessment of line transitions (e.g., between bulk handling to singulation) can also control the extent to which high-velocity vials impact stationary or slow-moving vials.

A second approach is to increase the vial's inherent ability to withstand damage that generates particulates. Vials enhanced with a low coefficient of friction (COF) coating on the exterior surface can significantly decrease glass particulate generation on a filling line by reducing the forces generated by vial-to-vial contact. In one study, low COF vials were found to provide a 96% reduction in peak levels of particles greater than 0.5 µm in size.[11]

Increased Throughput in Drug Fill-finish Manufacturing

Fill-finish operations are generally the most capital-intensive stage of the drug manufacturing process – heavy asset utilisation is therefore critical to profitability. Product that has reached the fill-finish stage of manufacturing has the greatest value. Process changes that have the potential to negatively impact yield are generally avoided to mitigate risk. As a result, adoption of new technologies within fill-finish operations has historically been conservative and incremental.[12] These manufacturing innovations can also be limited by the glass packaging used on the filling line.

Glass packaging performance in fill-finish operations is evaluated by multiple metrics. Glass particulate contamination is one type of defect that occurs during filling operations. If particulates are detected during post-filling inspection, the resulting root cause investigations can lead to significant downtime. Other glass-related factors that impact yield include tip overs and broken vials that require operator intervention and/or line stoppage in addition to loss of product.

Low COF coatings provide additional benefits that improve manufacturing throughput. The ability of coated vials to smoothly flow on a line reduces tip overs and jams. Coatings also provide protection against the creation of strength-limiting surface flaws that render a vial more susceptible to breakage. The benefits of damage resistance extend to the inspection stage – less damage during filling leads to fewer cosmetic defect rejects.

Additional features can be designed into a glass vial to augment breakage resistance. One solution is to chemically strengthen the glass surface using an ion exchange process. The resulting compressive stress layer imparts additional breakage resistance to a vial by closing surface flaws and resisting applied tensile stresses encountered on a filling line.

The cumulative benefits of using new vial technology with low COF coatings and chemical strengthening have shown an average throughput improvement of >20% for filling lines operating at the same set speed used for conventional vials. As a result, pharmaceutical companies can realise an immediate boost in capacity without investing in expensive fixed assets or increasing their manufacturing footprint. Contract manufacturing organisations that are frequently engaged to fill the additional demand of pharmaceutical companies can also benefit from the increased efficiency and improved yield of quality product that is enabled by innovative glass packaging.

Capacity can also be hypothetically increased by operating filling lines at faster speeds. The efficiency of current high-speed filling lines is typically 60–70% with extensive breakage throughout the process, and the efficiency continues to decline significantly when using conventional glass packaging. The improved machinability and breakage resistance of enhanced glass packaging enables a new, previously unattainable trajectory in efficiency and throughput relative to conventional packaging, as shown in Figure 3. The increased productivity that is realised by innovative glass packaging can therefore provide pharmaceutical companies with a drop-in solution to addressing manufacturing-related issues such as drug shortages.

Summary

The drug shortage crisis in the United States can impact the quality and economics of healthcare. Numerous solutions to reduce drug shortages have been proposed, many of which focus on public policy initiatives. An alternative approach to stabilising the supply chain enhances manufacturing with technologies that improve drug quality, increase throughput and reduce waste. Innovative glass vials engineered with new features such as low COF coatings and chemical strengthening are a promising technology and a potential win-win for patient safety and manufacturers looking to improve quality and increase

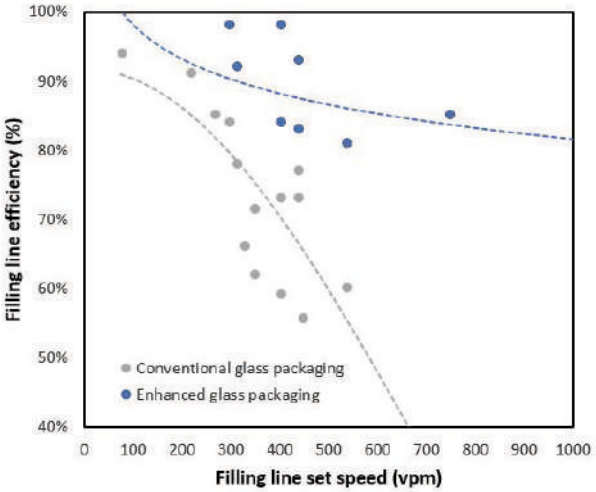

Figure 3. Line trial results demonstrate that enhancements to glass packaging enable improved efficiency and throughput in fill-finish operations compared to conventional glass packaging, particularly when operating at increased line speeds. Trendlines are added as guides to the eye.

efficiency while maximising the utilisation of capital-intensive manufacturing equipment.

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CORNING

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PROPER DEGASSING ENABLES HIGH-PRECISION DISPENSING OF CHILLED SOLUTIONS

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Dispensing precision is critical to the performance of modern diagnostic kits, where repeatability and accuracy in the amount of reagent dispensed form the basis for reliable results. For manufacturing and production lines dispensing of chilled solutions warming up presents a challenge as bubble formation caused by out-gassing threatens the precision. Deviation in the dispensed amount of solutions can affect the validity, economics, and possibly even the regulatory approval of a product.

In-line continuous degassing with Teflon® AF membranes effectively removes dissolved gasses from reagent solutions and avoids dispensing errors with greatly increased precision. Dispensing 1200 portions of water without degassing resulted in severe dispensing errors in 2% of the samples. An additional dispensing sampling of 800 portions of water with proper in-line degassing eliminated these dispensing errors.

Discussion

Current state-of-the-art diagnostic testing kits are designed to make the actual test procedure as straightforward and robust as possible, avoiding any end-user induced mistakes. This frequently allows the patient to use the kit as a self-test leading to increased compliance and testing frequency resulting in significant savings to the healthcare system. A robust and easy-to-use test would be highly desirable for Covid-19 given the immense pressure on healthcare systems.

Releasing the demand on precision in sample dosing by switching from sample-dependent response to reagent-dependent response releases the burden of laboratory competence from the testing environment. On the other hand, it creates high demands on the precision of the dosing and dispensing of reagents building up the diagnostic kit. This is in most aspects very useful and effective but puts pressure on the manufacturing facility all the way from bulk containers to dispensing nozzles. Regardless of how carefully the fluidic path is designed, or which technology is used for the dispensing, dissolved gasses present a major challenge by readily forming microbubbles in the fluidic system. Bubble formation is typically induced by negative pressure transients in the pump or at the check valves. This tendency becomes even more pronounced when the aspiration speed is high as is very prevalent in high-throughput production situations.

Solubility of gasses in liquids generally decreases with increased temperature and reduced pressure as shown in Figure 1. From 4°C to 24°C, the solubility of air in water drops from 14.5 to 8.8 mg/mL and with that follows the potential to release 4.3 mL of gas bubbles per litre of water[1]. The liberation of this gas can be held back by maintaining a positive pressure in the system but out-gassing will occur as soon as pressure is released. This typically happens during aspiration as a response on negative pressure transients in pumps and check valves. This is also further catalysed by sharp edges and hydrophobic surfaces within the system.

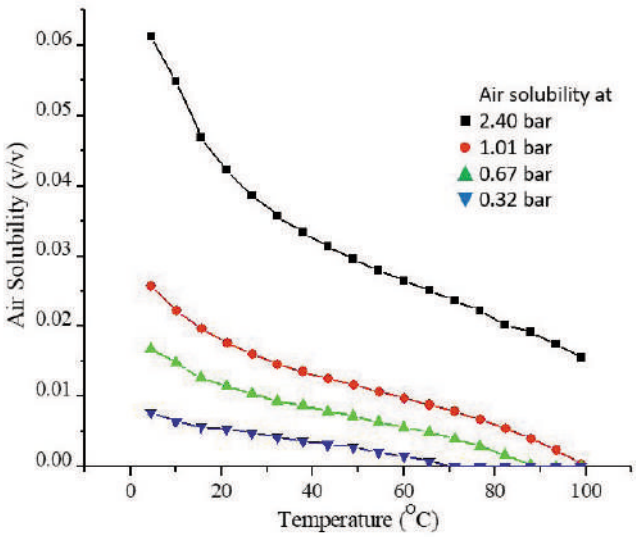

Figure 1: Solubility of air in water at different pressures as a function of temperature. The solubility of air decreases with approximately 40% on warming up a refrigerated solution to room temperature. Reduced pressure or negative pressure transients, frequently produced by pumps, reduces the solubility even further resulting in out-gassing and dispensing errors.

In-line Degassing

Removal of dissolved gasses long presented a significant challenge within the field of liquid chromatography (LC). Solutions used to address this challenge include vacuum degassing in-batch – with or without sonication – heating to reflux, or sparging with helium. It was early discovered that batch degassing was unable to provide reproducible results due to the quick reabsorption of gasses to the liquid. Continuous sparging with helium is very effective, with very low levels of residual gasses; however, it is a cost-prohibitive solution. As helium is a limited resource with several other important applications this is not a sustainable solution.

In-line degassing using gas-permeable membranes was introduced nearly 25 years ago within high-performance liquid chromatography (HPLC)[2]. In a modern in-line degasser, the liquid flow is passed through a Teflon® AF membrane situated within a vacuum chamber with a well controlled vacuum (Figure 2). The degasser preferably operates on the low-pressure side of the system, before any pumps or mixers. In this way, each component is properly degassed before any dissolved gasses can disturb the pump work cycle. Over the years, degassing technology has become so well-established that degassing units are routinely built into most LC systems, which many users may not even realise.

The use of in-line degassers has also spread outside the field of liquid chromatography and is widely implemented in a range of analytical systems. One example includes biosensors such as surface plasmon resonance (SPR) detectors, where microbubbles disturb the readout by increased noise. Today, effective in-line degassers are available for flow rates from less than 1µL to 100 mL per minute, chemically compatible with all regularly used solvents. A controlled and stable vacuum of 50 or 80 mmHg is supplied by small and virtually silent vacuum pumps, with integrated vacuum sensors such as the ZHCR pumps from IDEX Health & Science[3], as shown in Figure 2.

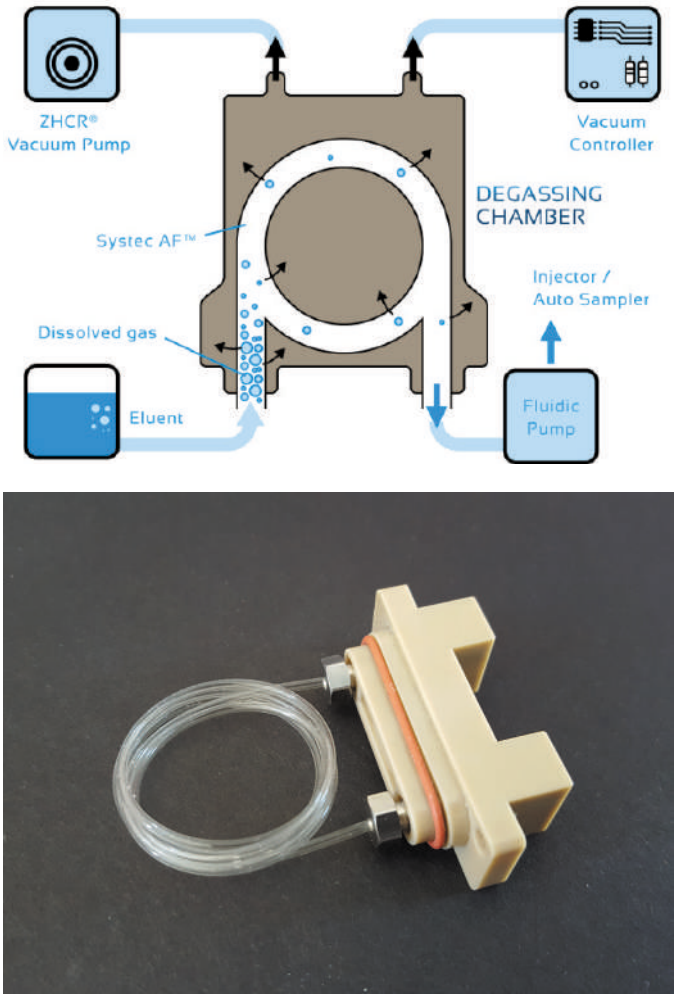

Figure 2: Schematic of the IDEX Health & Science Systec AF membrane of degassing chambers (upper) and the in-line vacuum degasser (lower). The well controlled vacuum in the degassing chamber (brown) provides the driving force for the dissolved gas to pass the degassing membrane (right).

Results

To demonstrate the power of proper degassing for increased precision and reproducibility during water dispensing, a validation experiment was performed with and without an in-line degasser in an otherwise identical system. Portions of 50 µL water saturated with air at room temperature were dispensed using a 500 µL syringe pump and the output was measured by gravity. The refill flow rate was set to 25 mL per minute, giving a syringe filling time of 1.2 seconds. In the degassing experiment, the degasser used a Teflon® AF tubular degassing membrane, with a length of 0.47 m and an internal volume of 480 µL, corresponding to one syringe volume. With the next aspiration portion of liquid standing still in the degasser tubing, the actual degassing occurred during the dispensing cycle of the preceding run.

The result of dispensing 1200 portions of 50 µL water without degassing is shown in Figure 3a, (degasser off). Dispensing anomalies (errors) were defined as giving less than 45 µL (90% of expected) occurred in 25 (2%) of the cases. Deviations of more than 2% by weight was observed in 96 (8%) of the dispensions.

In the next experiment, the procedure was repeated under identical conditions, but with an active degasser. The outcome

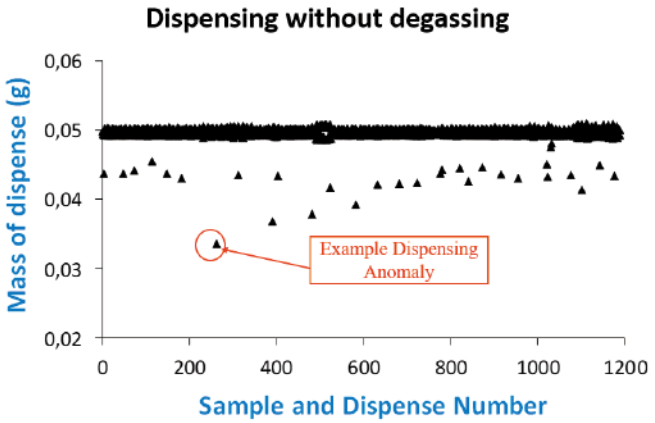

Figure 3a: Dispensing 1200 portions without degassing resulting in dispensing errors in 2% of the cases.

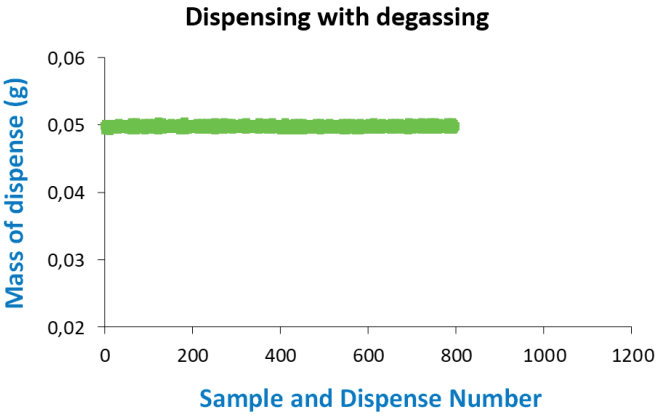

Figure 3b: Dispensing 800 portions with degassing without any dispensing errors.

from dispensing 800 portions of 50 µL water with active degassing is shown in Figure 3b. With the degasser active, no dispensing anomaly was observed and no sample deviated more than 2% by weight from the target weight.

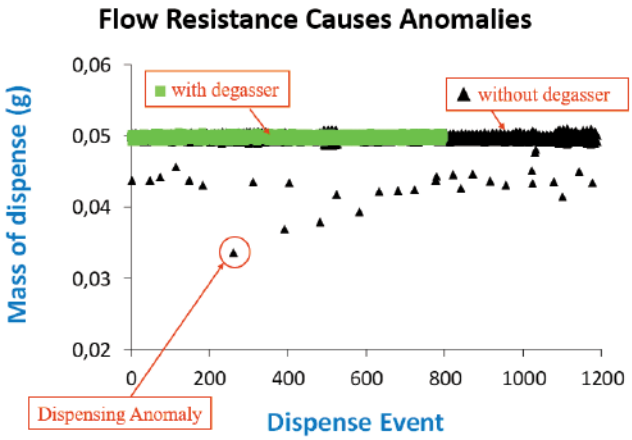

Figure 3c: Overlay of dispensing data with and without degassing. Proper degassing eliminated the dispensing errors and increased dispensing precision.

Figure 4: DEGASi® Plus Classic with tubular 480µL degassing chambers used in the dispensing experiment.

The difference between these experiments becomes even more apparent when an overlay is made (Figure 3c). In each of these experiments, the temperature was kept constant during the full procedure.

Summary

We have demonstrated the power and importance of in-line degassing on dispensing outcome without the additional driving force for out-gassing created by warming up the liquid. A chilled solution, saturated with air, gradually warming up during the process should be expected to cause even more errors from bubble formation during dispensing if proper degassing is not applied.

By proper degassing, not only can significant anomalies in data and dispensing be avoided, but the overall productivity of a manufacturing facility can increase. In this way, the root cause of dispensing anomalies is eliminated and precision is dramatically increased. The economic impact of this can outweigh the investment cost within weeks.

Biotech AB and Biotech USA are the leading providers of in-line degassing solutions for flow rates from <1 µL/min to L/min, and are available as standalone degassers (DEGASi®) as well as customised OEM solutions. These systems can handle a wide range of reagents, water-based solutions, and organic solvents[4].

We would like to express our gratitude to IDEX Health & Science for providing the data for the validation experiment.

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    2. Vacuum pumps for degassing https://www.biotechfluidics.com/products/degassing-debubbling/vacuum-pump-for-hplc-degassing/

BIOTECH

FRITIOF PONTÉN

Fritiof Pontén has been R&D Manager at Biotech AB since 2018. He has a PhD in synthetic organic chemistry from Lund University. In his professional career he has been heading early sale-up and process development of drug candidates at AstraZeneca in Gothenburg, where he also introduced flow chemistry and continuous processing. He is also a board member of SpinChem AB, Umeå, Sweden.

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BIOQUELL HELPING PHARMACEUTICAL COMPANIES RESUME OPERATIONS POST-COVID-19

Gay Turner, Director of Product Management for Bioquell

Bioquell Rapid Bio Decontamination Service (RBDS) enables businesses to quickly regain control of clean spaces and ramp up capacity.

As the world prepares to enter the next phase of the COVID-19 pandemic with the potential relaxation of lockdown restrictions, Bioquell, an Ecolab solution and leading manufacturer of high performance bio decontamination technology, is utilising its well-proven Rapid Bio Decontamination Service (RBDS) to help pharmaceutical companies ensure operational continuity and quickly ramp up capacity.

The fully managed and inclusive RBDS solution, which utilises the company's scientifically proven 35% Hydrogen Peroxide Vapour technology, provides microbiologically clean surfaces and spaces. It is backed by an excellent track record of use in spaces impacted by pathogens including SARS, Ebola, MERS-CoV and SARS CoV-2 across a range of life science and healthcare environments.

Bioquell RBDS can be used to effectively decontaminate newly constructed spaces prior to occupation or production areas after a scheduled maintenance to ensure there are no remaining contaminants that might impact operations.

As a result, it will enable pharmaceutical companies that have reduced production during the coronavirus pandemic to quickly gain control of clean spaces and return to full capacity. Bioquell RBDS is a fully managed service that enables pharmaceutical businesses to retain or recover the microbial integrity of critical areas such as cleanrooms and research laboratories.

Bioquell's Hydrogen Peroxide Vapour is a vapour-phase disinfection method that is virucidal on structurally distinct viruses dried on surfaces. It achieves a level of efficacy against a wide range of microorganisms unmatched by standard cleaning practices and other disinfection technologies. It is uniform across the entire target area and not limited to line-of-sight or easy-to-reach spaces. The process is residue-free, proven safe on sensitive electronics and shown to kill a broad spectrum of microorganisms including bacteria, viruses, fungi, spores and more.

Bioquell RBDS can be quickly called upon to eradicate coronavirus[1] and other bioburden from a single area, several locations within a facility or an entire building. The service is

fully operated by Bioquell's expert team of bio decontamination specialists allowing on-site staff to focus on the other activities need to restore operation. In some cases, decontamination can be completed in as little as 24 hours, enabling a rapid return to production.

It offers the flexibility to retain or recover the microbial integrity of critical areas with every deployment including planning, coordination, setup, equipment, and cycle validation and verification. It provides a complete final report confirming a 6-log kill of the spaces and surfaces that have been treated with the use of biological and chemical indicators.

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bioquell
An Ecolab Solution

GUY TURNER

Guy Turner is the Director of Product Management for Bioquell. He has been with Bioquell since 2008 holding roles in R&D, Sales and GM of Bioquell Asia Pacific. He holds a MSci in Chemistry from the University of Bristol.

CASE STUDY

BIOQUELL RAPID BIO DECONTAMINATION SERVICE

Decontamination of UK Hospital Wards Following Temporary Use for Treatment of COVID-19 Patients

"Bioquell RBDS Returns Converted COVID-19 Wards Back to Normal"

During the COVID-19 pandemic, many hospital wards were temporarily converted to solely treat COVID-19 patients. As these begin to revert back to 'regular' non-COVID-19 wards, a solution is required to manage the increased potential environmental contamination risk facing the patients admitted to these wards.

Eliminating SARS-CoV-2 from surfaces in the ward is extremely important in order to prevent further infections. With the high transmission rate of this pathogen and its ability to survive on surfaces for days[1], it is essential that any cleaning process used is able to fully eliminate surface contamination. With an efficient process, the areas can be back in operation quickly whilst ensuring the safety of patients and staff.

Bioquell Rapid Bio Decontamination Service (RBDS) Returning an Emergency COVID-19 Ward to General Use

Day 1 | 10:00 A vacated COVID-19 ward, including common areas, corridors, and staff rooms was readied for Bioquell.

Day 1 | 14:00 The Bioquell team arrived on site to set up equipment, place biological indicators and chemical indicators (BIs/CIs) and seal vents.

Day 1 | 16:00 After hospital approval, the decontamination process was initiated.

Day 1 | 18:00 The ward was left sealed overnight to allow the aeration units to break down the hydrogen peroxide vapour.

Day 2 | 08:00 Bioquell engineers checked the results of the CI to verify the cycle's efficacy and confirmed the area was safe for immediate reoccupation. The CIs showed expected efficacy of over 6-log. In 24 hours an initial report regarding the BIs was delivered, followed by a comprehensive final report after a seven-day incubation.

The above process was then repeated on a second ward at the same hospital.

Outcomes

- **Two** wards, one per day, **successfully converted**
- **50** out of **50*** biological indicators receive a 6-log kill
- Common areas, corridors & staff rooms **decontaminated** for each ward
- Little to **no disruption** of surrounding areas during decontamination

Bioquell RBDS may be able to respond immediately in your region. Visit bioquell.com for additional details.

STIRRED-TANK BIOREACTORS AND HOW THEY ARE USED IN THE DEVELOPMENT AND PRODUCTION OF COVID-19 VACCINES

David Solbach, Scientific Communications Manager Bioprocess at Eppendorf AG

Increasing demands from governmental vaccination programmes and pandemic events such as the current COVID-19 outbreak require scientists to work under pressure to shorten the time-to-market of developed vaccines. The current global vaccine market valuation of approximately 50 Billion USD, with 80% of the market on human vaccines. Altogether, a need for new methods to increase speed and yield, and to produce new vaccines in a cost-effective manner in order to remain competitive is a constant concern for scientists. Although the competition on the vaccine market is high, a noteworthy effect of the current COVID-19 crisis is the fact that big vaccine manufacturers are forming and maintaining collaborations with comparably young companies, and former competitors are cooperating with each other in order to speed up vaccine development. And we see a trend towards collaboration in the biotechnology industry in order to accelerate the research, development and large-scale production of new vaccines.

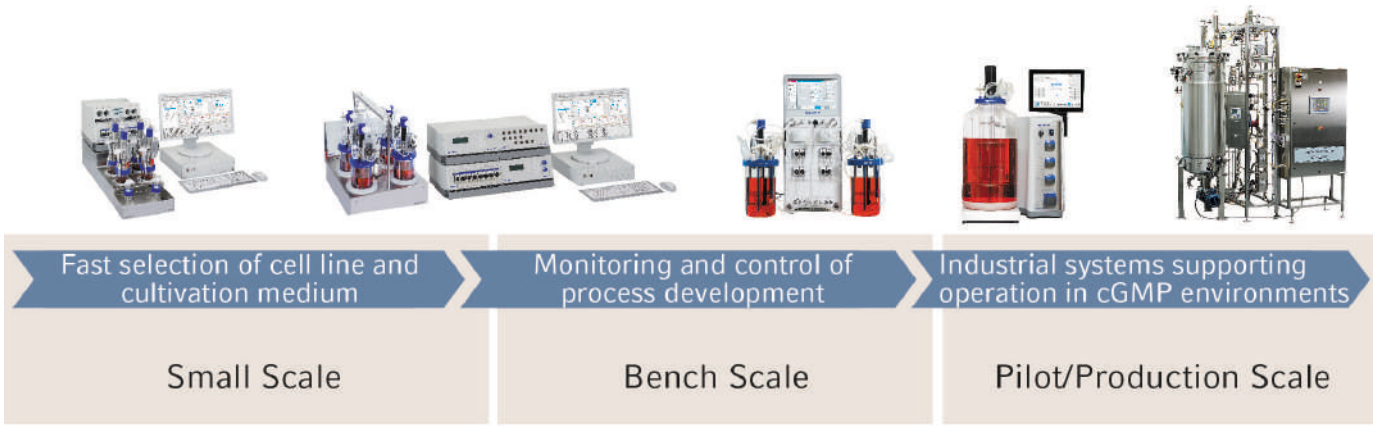
Bottlenecks for production arise from the use of two-dimensional T-flasks and roller bottles. Therefore, a shift to stirred-tank biological control systems is essential in order to increase productivity. By enabling the parallel control of several bioreactors at the same time, monitored and controlled by powerful software solutions, vaccine development processes can be optimised in small scales and the parameters transferred in order to scale-up to large production volumes.

Parallel Processing – Learn from Failures and Optimise the Bioprocess

Process optimisation consumes time when experiments are running individually and sequentially. And these experiments are very costly. By utilising scale-down strategies and single-use bioreactors, the consumption of resources can be reduced. Parallel bioprocess control systems are well suited for scale-down approaches and offer the possibility to change individual parameters in several bioreactors at the same time, while monitoring and comparing the effect of the changes in parallel (Figure 1).

Advanced technologies in upstream bioprocessing enhance the efficiency of vaccine development

Parallel processing	Single-use technology	Scalable systems	Process intensification	Efficient use of data



Single-use Solutions – A Step Ahead of Cross-contaminations

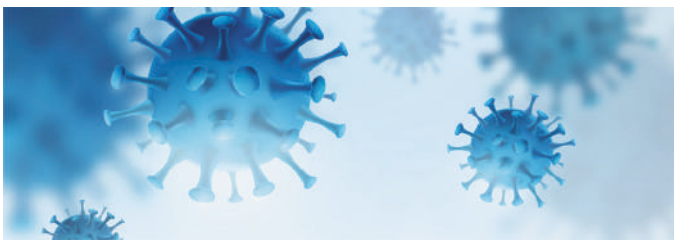
Process optimisation and development includes significant manual interactions, increasing the risk of contaminations. Traditional glass or stainless-steel bioreactors need to be carefully cleaned and sterilised after each run before they can be re-used. Especially nowadays, where time is crucial to find a cure against COVID-19, the use of single-use bioreactors offers the potential to speed up a bioprocess and prevent the loss of a whole run due to contamination.

Scalable Systems

Nearly five million people have been infected by the novel coronavirus so far. Due to its high infection rate, this number is expected to increase tremendously before a new vaccine will be available. In order to produce enough doses of vaccines to help develop immunity at a global scale, easy parameter and technology transfer is needed when scaling-up from bench to pilot and production. However, developing a scale-up strategy is time-consuming and cost-intensive. High titre, robustness of the process, constant product quality, fast turnaround times, and scalability are some of the success factors that need to be considered. It is important to work with bioreactors that are comparable at bench- and pilot- and production-sized bioreactors. Keeping in mind critical scalability-related engineering parameters like proportional vessel/impeller geometry, oxygen transfer rate (OTR), impeller power number (Np) and the impeller power consumption per volume (P/V) helps to optimise a scale-up strategy.

Experience the Power of Data

One of the major benefits of working with advanced bioreactor control systems is the use of powerful SCADA software. A powerful software suite, monitoring all critical parameters, automatically adapting feeding speed, gassing conditions, and many more parameters, is the heart of each process. With the help of software, limiting factors can be detected and eliminated to efficiently optimise a process. Thanks to the digitalisation, the global lockdown did not affect international collaboration of scientists and manufacturers. Like the scientists and manufacturers around the globe are communicating with each other, it is also important that the software is able to understand all the information delivered by the various sensors connected to a bioreactor. This is especially true when they are manufactured by different suppliers. Modern communication protocols such as OPC UA enable the seamless communication among devices, allowing the independent implementation into a process while being safe and stable.

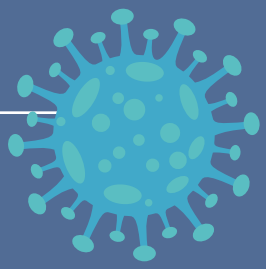


Conclusion

Stirred-tank bioreactors are one of the key technologies needed on the journey of developing and producing a new vaccine (Figure 2). They are optimal tools during each step in upstream biology. Working with bioreactors enables the parallel control of several bioreactors, resulting in a more efficient and reproducible optimisation of various process parameters. The quality of the produced product greatly benefits from the possibility to program automated responses such as feeding cycles or pH control. And finally, large systems are available on the market that are suitable to operate in cGMP environments in order to produce vaccines.

DAVID SOLBACH

David Solbach is the Scientific Communications Manager Bioprocess at Eppendorf AG since 2019. He holds a master's degree in molecular plant science and genetics from the Uppsala University. In his professional career, he has been conducting research on redox signalling pathways in plants, bacteria and yeast at the Rheinische Friedrich-Wilhelms-University in Bonn.



TOGETHER BEYOND COVID-19

Dr. Jürgen Hönig, Senior Director; Lisa Pascoe, Associate Director

We find ourselves in one of the most challenging situations in history. In a very short time, the world has been consumed by a virus that has proved to be both ruthless and deadly. Countries all over the world are battling an invisible enemy and yet remain resolute in the face of such adversity.

Whilst challenges create opportunity, never has such a spotlight been put on the pharmaceutical industry to react quickly and effectively and develop a cure or vaccine for COVID-19. However, despite the current crisis, product development continues and regulatory compliance, quality management and ongoing pharmacovigilance must be maintained.

As a leading provider of specialised services for the pharma, biotech and medical device industries, PharmaLex's expertise can really make a difference and we are committed to going above and beyond to fight this as an industry. We are proud that we continue to support our clients and provide the necessary backbone which allows our industry to deliver.

In this article we explore some of the key topics our clients are facing, and how the pharmaceutical industry is coming together to use this as an opportunity to learn, grow, innovate and increase in flexibility.

A Global Problem Requires a Global Effort

Historically more associated with academia and smaller pharma companies, there have been a number of prominent research and development (R&D) collaborations announced since the start of the pandemic, with stakeholders of all sizes understanding that working together will be key.

R&D collaboration facilitates pooling of complementary skills, learning from the partner as well as sharing risks and costs. Companies are forced to innovate at a faster rate to maintain their competitiveness in the market and, as a result, they see R&D alliances not as an option, but as a strategic need. Typically small and medium-sized pharma companies tend to benefit from collaboration through access to a broader and more diversified knowledge base. However, during these times, no single company is going to be able to solve this crisis alone, irrespective of their size, and so we are seeing collaboration at the highest level.

PharmaLex as a full-service provider offers its customers the possibility to access a broad network of independent R&D institutes. In more than 25 years PharmaLex has been involved in various stages of the development process of innovations and has gained extensive experience in different areas, be it galenic or clinical development.

We are currently working with a number of clients to ensure they can continue vital research, as they face practical issues such as laboratories closing for safety reasons. In one case PharmaLex supported the transfer of analytical method development studies to an alternative laboratory. The methods involved identification of co-compounds for a biologic medicinal product and were crucial in obtaining approval of a Phase I clinical study.

PharmaLex was also recently approached by a small biotech company seeking support for the identification of alternative laboratories for the qualification of non-genotoxic impurities (NGIs) regarding biological safety. During the search for a suitable partner for this very specific request, it became apparent that the client did not have sufficient capacity and, above all, experience to work efficiently with existing external partners. Subsequently the client requested PharmaLex take over the coordination and management of all external partners to enable their internal resource to focus on their core business.

The COVID-19 Clinical Trial Challenge, Today and Tomorrow

In response to the pandemic, clinical studies are emerging at an unprecedented rate with the EMA advising that, as of 14th May, they have been in discussion with the developers of around 115 potential COVID-19 treatments and 33 potential vaccines. However, when it comes to clinical trials, companies are facing challenges on numerous fronts. On one hand, clinical trials are needed for development of these potential treatments and vaccines, yet typically take many months or even years to set up. On the other hand, the development of pipeline products cannot be stopped, yet sponsors must safeguard the safety of trial participants, and research and regulatory affairs resource are being redeployed to frontline care.

Fortunately, health agencies have been quick to support in facing these challenges. Whilst the scientific and ethical evaluations are as stringent as ever, a number of initiatives have been launched for acceleration of development support

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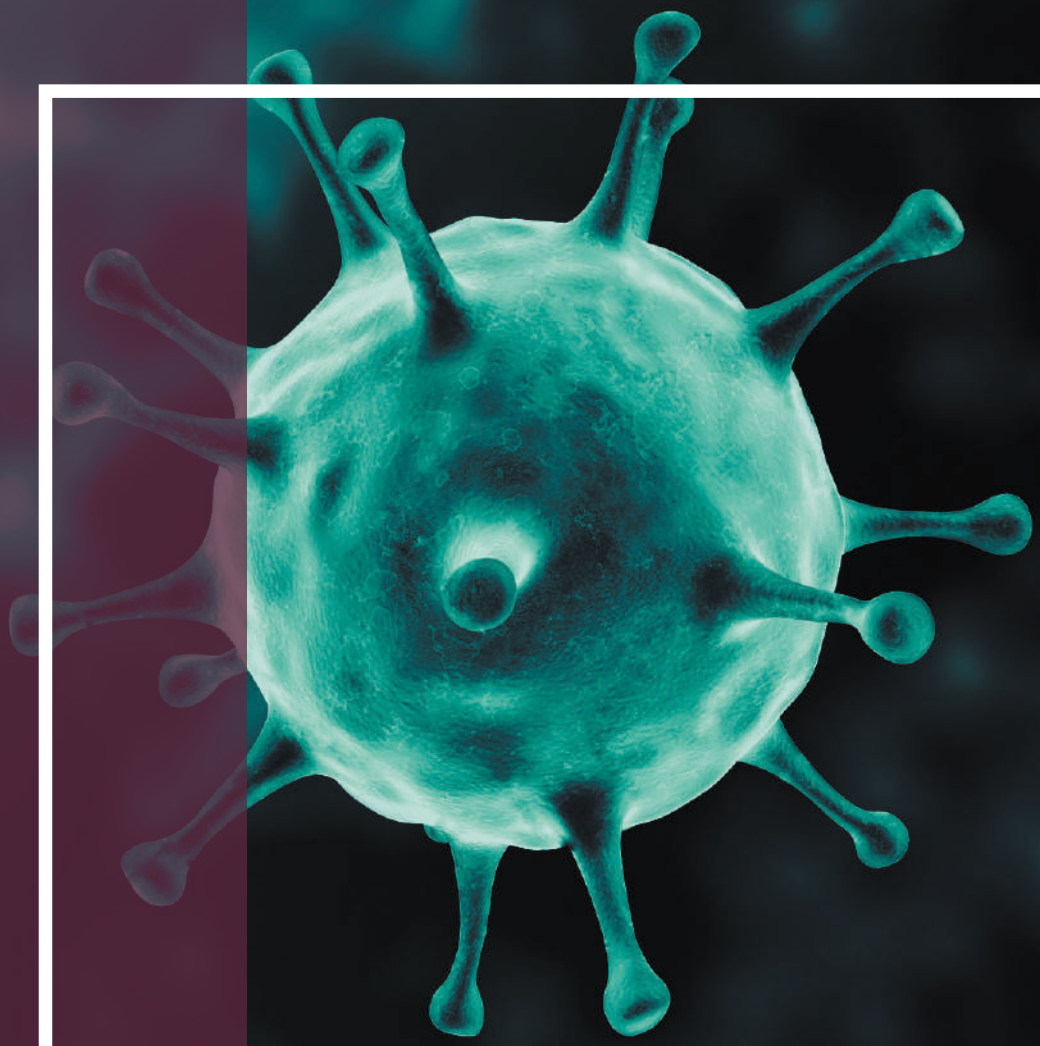

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and evaluation procedures for treatments and vaccines with the release of COVID-19 guidance including from the EMA, MHRA and FDA.

The EMA has established a dedicated task force; the COVID-19 EMA pandemic Task Force (COVID-ETF) who will, among other activities, support rapid scientific advice which can facilitate protocol authoring, and expedited assessment of paediatric investigation plans (PIP).

The FDA have created the Coronavirus Treatment Acceleration Program (CTAP) which 'uses every available method to move new treatments to patients as quickly as possible'. In order to get a first wave of studies underway, the CTAP has provided ultra-rapid protocol review, within 24 hours of submission in some cases.

PharmaLex has considerable experience in supporting scientific advice procedures and authoring of PIPs, as well as submission of clinical trial authorisation applications and investigational new drug applications across Europe and the US. With our local market PharmaLex experts, we are currently supporting the applications for a COVID-19 clinical trial in a multi-market EU study.

Whilst the world is focused on new clinical trials and the anticipation of a vaccine, sponsors of ongoing trials unrelated to COVID-19 have also needed to take rapid action. In response to the management of ongoing clinical trials and participants, and the potential impact of the pandemic, the agencies acknowledge there will be disruption and have put measures in place. The new guidance all has patient safety at the forefront and requires sponsors to conduct a critical evaluation of the risk/benefit regarding continuation of the trial for both ongoing participants and recruitment of new participants.

During the global pandemic, PharmaLex have successfully evaluated and submitted a number of regulatory activities in relation to ongoing clinical trials impacted by COVID-19. Sponsors should seek specialist regulatory advice to ensure their clinical studies remain compliant and value-added whilst the safety of trial participants is prioritised.

Maintaining Drug Safety

Despite the current crisis, ongoing pharmacovigilance must be maintained and later, monitoring the safety of new medicines remains an obvious top priority. Risk communication, difficult under normal circumstances without a global safety reporting system, is proving to be an even greater challenge given the amount of uncertainty that surrounds all aspects of the pandemic.

Although many local health authorities have adopted electronic reporting, such as the E2B gateway, portal entry and email, many are reluctant or unable to implement such processes. Therefore, these authorities still require paper reporting or electronic reporting by means of electronic devices. This situation requires efficient management of pharmacovigilance teams, local legal representatives, shipment services and teams distributed across different geographical locations, which is just not practical at this current time. Health agencies are currently publishing new guidance on the management of pharmacovigilance systems to minimise the impact on safety reporting and to maintain patient safety. The aim is to establish a robust safety reporting environment.

Having a robust business continuity plan (BCP), ensuring a global footprint of drug safety specialists, efficient technology solutions and a strong and proactive intelligence management process are essential at this time.

PharmaLex's pharmacovigilance team is supporting a number of our clients with COVID-19 related matters, who have a high need for business continuity, for example with *ad hoc* support due to office shutdowns or sickness cover. With a global distribution of pharmacovigilance subject matter experts, thus avoiding resource bottlenecks in one region, PharmaLex can react immediately and flexibly to meet our clients' needs. Furthermore, PharmaLex offers technology solutions and intelligence management to ensure business continuity and fulfilment of requirements.

Manufacturing to Meet Changing Demands

The pharmaceutical industry is constantly dealing with the challenge of how a manufacturing process should be set up efficiently, and above all robustly, so that both up-scale and down-scale production can run smoothly and cost-effectively. Finding solutions is now more important than ever: COVID-19 is resulting in industry having to navigate severe disruptions in manufacturing, resulting from issues such as obtaining raw materials to ensuring employee safety, coupled with more pronounced changes in drug demand. As such, production time is very precious, especially when a company must support a portfolio of products across a wide variety of process formats or scale-up.

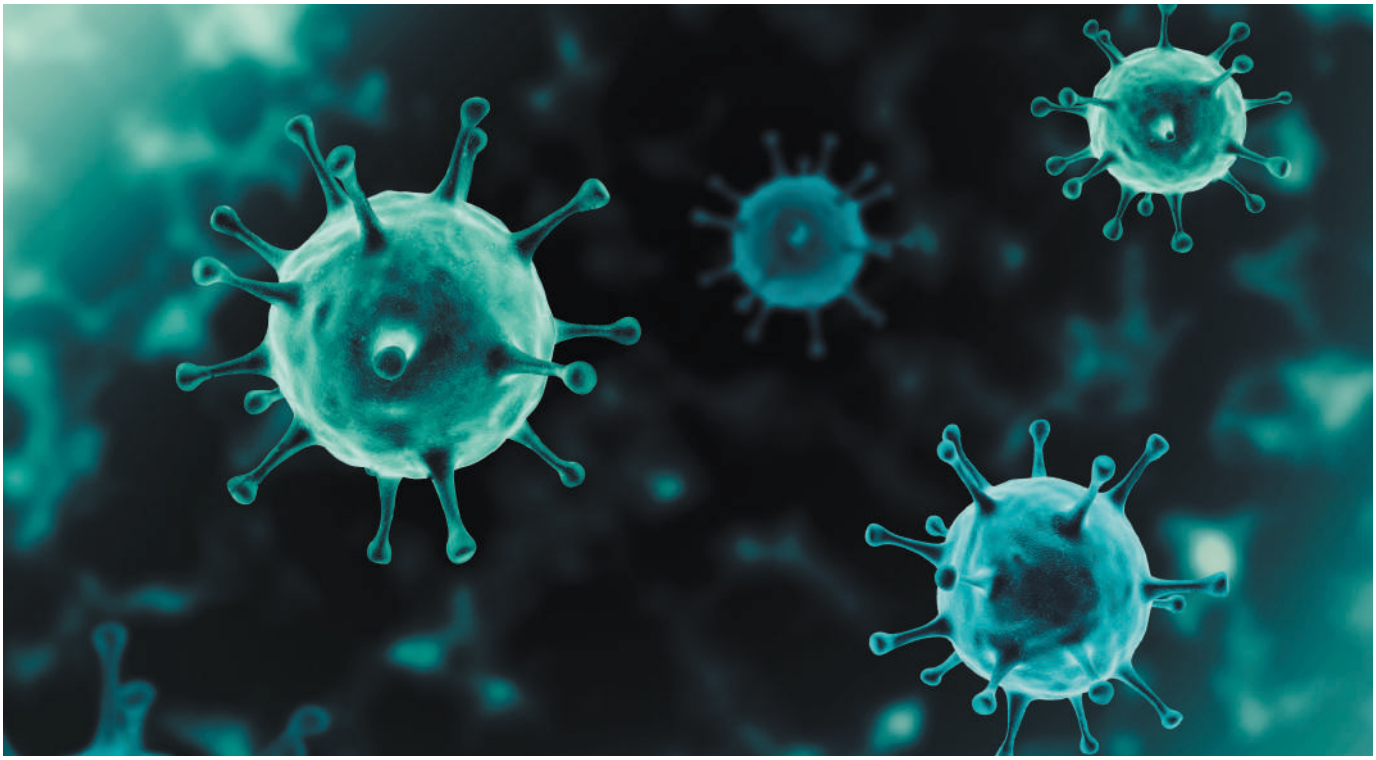
PharmaLex subject matter experts have many years of experience in the design of manufacturing models and have recently supported a client to up-scale the production of two medicinal products indicated for the treatment of COVID-19 patients. We can also discuss options around running a variety of operational platforms including batch, semi-continuous and continuous process platforms during the pandemic uncertainty. With any such review, we take into account the organisation's process landscape impacting critical and support utilities and the management of resource and infrastructure (control strategy) attributes.

De-risking the Supply Chain

Not only are our clients seeing changes in demand for existing drugs, COVID-19 is also testing the robustness of existing supply chains. De-risking supply of raw materials and finished products is an ever-present task for marketing authorisation holders. However, lockdown of countries has resulted in API shortages and finished product manufacturing capabilities, which have been combined with transport delays and restrictions and in some cases direct intervention from governments to stop material leaving their country.

As already discussed, many authorities have published guidelines which allow simplified procedures and, above all, shortened assessment periods to try and counteract this situation. Despite this, the technical and regulatory processes needed to register new suppliers can still quickly result in a stock-out situation if not carefully managed.

PharmaLex has been supporting a global consumer health pharmaceutical company with their de-risking initiatives for a number of years, registering secondary suppliers of APIs, excipients, containers, etc. wherever possible. However, for many key materials, suppliers chosen to close the single-source gap are based in countries that are now restricting exports due to COVID-19, meaning that previously 'de-risked' products are now back in scope as the new supply route was no longer secure. The timelines for resumption of supply are not yet clear and so urgent



action and increased resource are required to prevent supply issues.

A task force has been created by the client with PharmaLex providing the regulatory support following many years of managing global source change projects. The key ask from a regulatory perspective is two-fold: to assess supply chain proposals from a regulatory perspective to understand challenges they may present. And to explore the options of expedited submission routes to drive supply chain proposals, for example reduced data requirements at the point of dossier submission, expedited dossier review by authorities, implementation of 'do and tell' submissions where approval would usually be required before implementation, etc.

Working with the client's own local affiliates, we have collated the COVID-19 market-specific intelligence and facilitated discussions with health authorities at an early stage to share the hurdles being faced and request agency support.

Virtual Auditing for GxP Compliance

The essential containment measures being implemented globally due to COVID-19 require a dynamic, pragmatic and risk-based response to quality oversight and third-party audit. With the current uncertainty, it is likely to be some time before the impact of social distancing is lifted from the pharmaceutical industry and auditors will be allowed on-site. In addition, once restrictions are eased, companies need to be prepared for inaccessibility due to auditee capacity beyond the immediate COVID-19 constraints. QA teams will also experience increased workloads and QA capacity may be an issue.

In response, the EMA and FDA have released guidance and a series of measures to mitigate the impact of disruptions caused by the pandemic on the conduct of inspections of manufacturing facilities or other sites relevant for medicinal products.

Even before COVID-19, PharmaLex had developed and implemented a stepwise and risk-based methodology to deliver virtual audits for GxP compliance. This approach enables our clients to maintain oversight of supply chains and ensure the continuity of clinical and commercial operations. We are supporting clients with risk assessments to determine the criticality of the audit, and whether a deferral is acceptable, where the audit is essential, determine the feasibility of a virtual audit and identify the risks associated with a remote audit and mitigating actions.

Using tools such as video conferencing with key site personnel and subject matter experts (SMEs) and conducting virtual tours of facility areas, PharmaLex will prepare a comprehensive written report that details the areas covered during the audit, observations classified by risk and recommended remediation actions for each observation. Following this, we can also support the implementation or oversight of audit CAPAs and a focused on-site assessment once local restrictions have been lifted and site access is granted, if required.

Regulatory Compliance as Usual

As the number of rules and regulations increases constantly, regulatory compliance management has emerged as a distinct function in pharma industry over the last ten years. For globally operating manufacturers and marketing authorisation holders, it is an increasing challenge to maintain the different regulatory or country-specific requirements for the fulfilment of regulatory compliance.

During the COVID-19 pandemic, we have seen many marketing authorisation holders adapt their business strategies to the situation or have even made significant corrections. Currently, globally acting pharma companies are focusing on production continuation and up-scaling, and with that comes the need to ensure regulatory compliance. Such lifecycle management of marketed products often requires a lot of resource, and our clients are therefore requesting support to manage these workload peaks on a headquarter and local level.

In order to react to the special challenges and to ensure the supply of the population, many authorities or official institutions (FDA, PDMA, EMA, CMDh, etc.) have published guidelines at

short notice, which allow simplified procedures and, above all, shortened assessment periods. In addition, approvals of new drugs are to be simplified and the corresponding approval procedures accelerated, particularly for medicinal products for the treatment of COVID-19 patients.

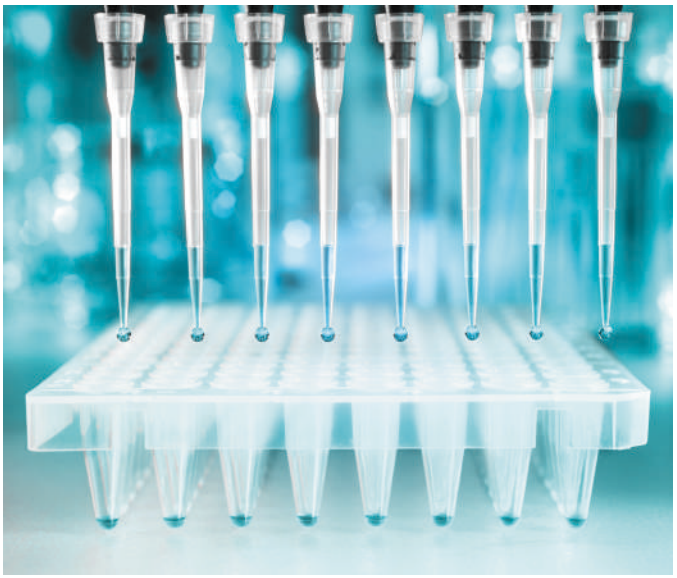
As a strategic partner, PharmaLex provides regulatory affairs support combining global reach with local presence for its global end-to-end full outsourcing solutions. With an outstanding track record and many years of experience, PharmaLex offers full portfolio outsourcing from global / headquarter to local affiliate activities including responsibilities in the area of global labelling, CMC (change control and writing), market expansion, worldwide renewals, line extensions and publishing. We help our clients maintain products throughout the lifecycle while ensuring the highest quality and compliance globally and locally. Near and offshoring models are available to support a variety of budgets and provide instant support in a time zone appropriate for the client.

As travel restrictions affect business continuity of pharma companies without a global infrastructure, PharmaLex's global presence and end-to-end service have also carried out submissions to local authorities through personal interactions on-site to prevent the delay of important regulatory activities.

The Ever-changing Regulatory Landscape

Regulatory intelligence (RI) is becoming one of the most valuable strategic tools for goal-oriented pharma. The regulatory landscape is evolving at such a rate that, from the start of a project to its completion, the compliance needs have often changed – with new policies created and regulations adapted.

Each year, regulatory bodies issue hundreds of new guidelines and regulations globally; however, these last few months have seen a huge increase in new guidance as agencies look to safeguard patients, as well as supporting industry in this uncertainty. Staying abreast of each relevant update and maintaining compliance standards for each market is a considerable undertaking, but one that is of vital importance given its potential impact on everything from pre-clinical research, to new drug approvals and the ongoing availability of existing products. The power of this knowledge is demonstrated during complex decision-making processes, especially development strategy and, importantly, chemistry, manufacturing and controls (CMC) maintenance.



In the context of the COVID-19 pandemic, PharmaLex recognised the need to inform our clients quickly and easily about current changes in the regulatory environment. PharmaLex has therefore configured a special website that provides quick access to knowledge on the current situation. In addition, we regularly publish information about the performance of health authorities in a global setting, e.g. closure or delayed response times.

Beyond COVID-19

Finally, it is important to also look beyond COVID-19 and have a strategy in place to manage this. Planning at a local level will help boost resources and ensure plans are aligned when the time comes. Now is the opportunity to put in place fail-safe measures that will ensure business can continue now and will continue and grow when the crisis is over.

At PharmaLex our approach is straightforward – we have experts across the globe who understand the current challenges and deliver solutions remotely. Whilst on-site services are inevitably affected, our flexible team of committed experts is tailoring our solutions to your changing circumstances and has adopted a virtual approach wherever possible to deliver now and #TOGETHERBEYONDCOVID19 – business continuity.

PHARMALEX
CONFIDENCE BEYOND COMPLIANCE

DR. JÜRGEN HÖNIG

Dr Jürgen Hönig is Senior Director, Regulatory Business Intelligence at PharmaLex. He obtained his pharmacist training at University of Heidelberg and has over 20 years' experience in regulatory strategy, regulatory operations, project management and business process optimization. He joined PharmaLex in 1999 after several years in hospital pharmacy and academic research, mainly focused on phytochemistry and biochemical/pharmacological models for proof of concept.

LISA PASCOE

Lisa Pascoe is Associate Director Regulatory Affairs and International Services Coordinator for Clinical Trial Authorizations at PharmaLex. She has over 10 years' experience in regulatory affairs specializing in CMC; drug products & APIs, OTC & Rx. She has successfully delivered large project portfolios for multi-national consumer healthcare clients. She has experience and understanding of new product development through to post-approval product lifecycle management. She joined PharmaLex in 2008 following completion of a BSc (Hons) in Biochemistry, MTOPRA at the University of Southampton.

IMPORTANCE OF THE LIMULUS AMEBOCYTE LYSATE (LAL) ASSAY IN THE DEVELOPMENT OF A COVID-19 VACCINE

Lisa Komski, Sales General Manager for the LAL Division

In December 2019, an outbreak of pneumonia was reported in the city of Wuhan, China. The causative agent behind the outbreak, a novel coronavirus called severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), was identified in January 2020. The World Health Organization (WHO) named this disease coronavirus disease 2019 (COVID-19). Since these initial reports, COVID-19 has rapidly spread to become a global pandemic. As of June 5, 2020, the WHO reported 6,535,354 confirmed infections and 387,155 deaths resulting from COVID-19 worldwide[1].

As laboratories across the globe focus their research efforts on the development of a vaccine for COVID-19, it is crucial that quality control standards are maintained throughout the research and development process. This report will focus on the risks that endotoxin contamination poses for COVID-19 vaccine research, as well as highlighting the utility of the Limulus Amebocyte Lysate (LAL) assay for endotoxin detection during vaccine research and manufacturing.

Gram-negative Bacteria, Endotoxin, and Sepsis

The Gram staining test was invented in 1884 by Hans Christian Gram. The test characterises bacteria based upon the thickness of the peptidoglycan layer within their cell wall. Gram-positive bacteria have a very thick peptidoglycan layer, ranging from 20 to 80 nm. In contrast, the peptidoglycan layer of Gram-negative bacteria is much thinner, around 8 nm[2].

Gram-negative bacteria are responsible for a multitude of infectious diseases, including many foodborne illnesses, cholera, gonorrhea, and urinary tract infections.

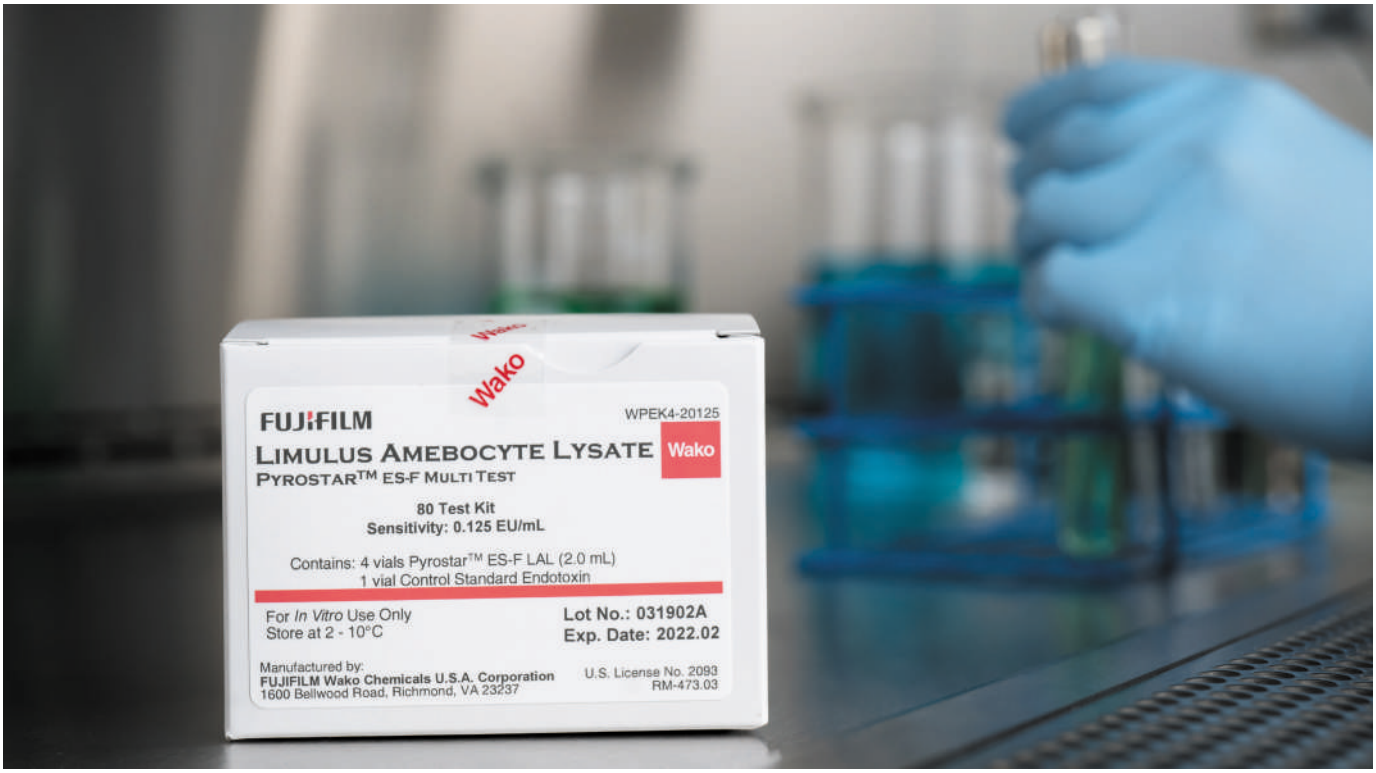
One of the distinguishing characteristics of Gram-negative bacteria is their ability to produce endotoxin. Endotoxin, also known as lipopolysaccharide (LPS), is a component of the outermost membrane found in Gram-negative bacteria. It is composed of a lipid group, which anchors the structure to the cell wall, and an oligosaccharide group, which extends from the bacterial surface. The lipid moiety, known as lipid A, is the main structure that is recognised by the immune system as a pathogen-associated molecular pattern (PAMP). Specifically, lipid A is recognised by a complex of two immune system proteins: Toll-like receptor 4 (TLR4) and MD-2. When activated, this complex triggers an innate immune cascade to combat the pathogen[3].

Endotoxin is a potent pyrogen and can activate immune cells at even picomolar concentrations[4]. The resulting release of pro-inflammatory cytokines into the bloodstream triggers a variety of downstream immune responses, including recruitment of leukocytes and activation of the complement system[5]. Normally, this immune response clears the infection without significant collateral damage; however, in cases of sepsis, the response is hyperactive and causes damage to healthy tissues throughout the body, greatly increasing the risk of mortality. A hospital mortality rate of 17% for sepsis and 26% for severe sepsis was reported for high-income countries between 2005 and 2015[6].

Endotoxin-induced sepsis can also progress to septic shock, which is characterised by hypotension and elevated serum lactate[7]. Septic shock results from the upregulation of tissue factor (TF) by pro-inflammatory cytokines. TF, in turn, initiates a cascade that leads to thrombin synthesis. Thrombin is an enzyme that promotes blood coagulation to prevent excessive bleeding. Its activation in sepsis causes the formation of clots in the bloodstream, leading to a sudden drop in blood pressure[8]. Septic shock is even more dangerous than sepsis, with an estimated hospital mortality rate of 39%[9].

Detecting Endotoxin Contamination Using the LAL Assay

Endotoxin is highly heat-stable. As a result, many common sterilisation methods, such as autoclaving or dry heat, can leave enough intact endotoxin behind to trigger an immune response,



even in the absence of viable bacteria[10]. Thus, reliable detection of endotoxin contamination is a chief concern in the pharmaceutical, biotechnology, and healthcare industries.

Current U.S. Food and Drug Administration (FDA) guidelines require endotoxin testing for all medical devices and drug products. Medical device extracts must contain below 0.5 endotoxin units (EU) per mL (20 EU/device) if they contact the cardiovascular or lymphatic systems, or 0.06 EU/mL (2.15 EU/device) if they contact cerebrospinal fluid[11]. The limit for drug products is calculated as K/N, where K is the threshold pyrogenic dose and M is the maximum dose of the drug. Standard values of K are provided in the table below[12].

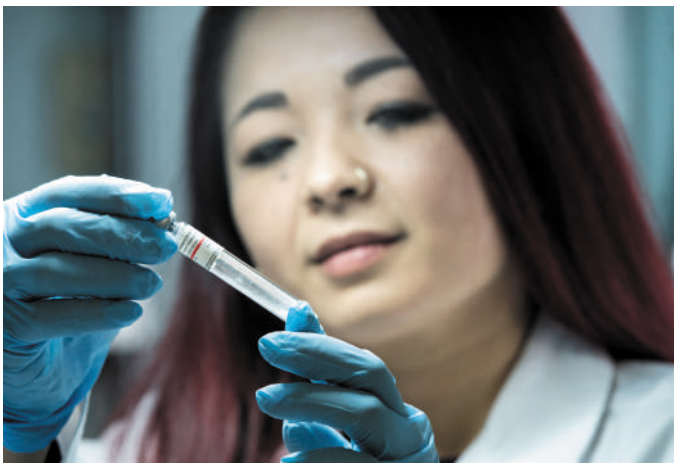
Route of administration	K for non-radiopharmaceuticals	K for radiopharmaceuticals
Non-intrathecal	5 EU/kg/hr	175 EU/kg/hr
Intrathecal	0.2 EU/kg/hr	14 EU/kg/hr

There are several methods for detecting endotoxin. During the early 1900s, the first endotoxin assays were performed using the rabbit pyrogen test (RBT). Rabbits are injected intravenously with the test solution, and a rise in body temperature is used as a basis for detecting potentially dangerous levels of endotoxin. However, this method presents practical challenges, being both expensive and time-consuming, in addition to having a relatively high rate of false positives. The assay has also raised ethical concerns regarding the treatment of animals[13].

The RBT was later replaced by the Limulus Ameboctye Lysate (LAL) test, which remains the industry standard to this day. The assay's active ingredient comes from the horseshoe crab (Limulidae). The crabs' hemolymph (a fluid analogous to blood) contains immune cells called amebocytes that undergo rapid clotting in response to endotoxin exposure. In the horseshoe crab, this mechanism serves to "wall off" or isolate potential pathogens and prevent them from spreading to the rest of the animal[14].

The key players in the clotting cascade are three serine protease proenzymes: factor C, factor B, and proclotting enzyme. Following endotoxin exposure, factor C cleaves itself, resulting in autoactivation. Factor C then cleaves and activates factor B, which in turn cleaves and activates the proclotting enzyme. Finally, the active clotting enzyme cleaves another protein called coagulogen. Many molecules of cleaved coagulogen then aggregate together to form a clot. The reaction is highly efficient, forming a clot in only 90 seconds[14].

The LAL assay takes advantage of this chemical cascade. The original form of the assay, called the gel clot method, is qualitative, relying on the presence of a visible clot to determine a positive result. The gel clot method has a lower detection limit between 0.01 and 0.03 EU/mL. In addition, quantitative versions of the LAL assay have been developed, which are also more sensitive than the gel clot method. One version uses a chromogenic readout, which relies on Boc-Leu-Gly-Arg-p-nitroanilide. This molecule's amino acid sequence matches that of the site cleaved on coagulogen by the clotting enzyme. As a result, when the clotting enzyme is active, it cleaves the Boc-Leu-Gly-Arg tag and releases chromogenic p-nitroanilide. The absorbance of free p-nitroanilide can then be detected at 405 nm. The chromogenic assay manufactured by FUJIFILM Wako is highly sensitive with an extremely low detection limit between 0.0002 and 0.0005 EU/mL[13]. Another LAL variety uses a turbidimetric readout. Turbidity refers to the loss of transparency in an aqueous solution due to the presence of suspended solids.



In the case of the LAL assay, the solids are gel clumps formed during the clotting reaction. The turbidity of the solution is then used to calculate endotoxin concentration. FUJIFILM Wako's high sensitivity turbidimetric assay has a lower detection limit of approximately 0.001 EU/mL[13].

The LAL Assay in Vaccine Research and Manufacturing

Unlike other pharmaceutical products, vaccines are not required by the FDA to adhere to standard limits for endotoxin concentration. As such, endotoxin levels can vary widely between vaccines. Independent laboratory analyses of the endotoxin content of various vaccines have reported levels ranging from undetectable to 1,000,000 EU/mL. This topic is further complicated by the complexity of vaccine formulations, which can make it difficult to surmise whether a pyrogenic response is caused by endotoxin, as opposed to some other vaccine component or contaminant[15]. Currently, endotoxin testing is only required for polysaccharide vaccines, rabies vaccines, and tick-borne encephalitis vaccines, although exact endotoxin limits have still not been defined beyond the RPT[16].

Despite the lack of clear FDA guidelines, proper endotoxin monitoring throughout the vaccine manufacturing process is crucial to detect contamination that exceeds safe levels. Multiple cases of adverse events caused by endotoxin contamination in drug products and vaccines have been reported. In one instance, the antibiotic gentamicin resulted in 210 reports of pyrogenic reactions. It was later discovered that 10% of gentamicin lots had endotoxin levels exceeding 5 EU/kg[17,18]. In another case, the whole cell pertussis vaccine was found to have high immunogenicity, which decreased after switching to an acellular vaccine[19]. The endotoxin levels in the whole cell vaccine were found to be considerably higher than in the acellular vaccine[20]; therefore, it is likely that endotoxin contamination was at least partially responsible for the higher immunogenicity of the whole

cell vaccine, though the complexity of its formulation makes this difficult to determine for sure[15].

A 2011 commentary by Brito and Singh provided unofficial recommendations for endotoxin limits in preclinical vaccine research[15]. These limits were calculated based on previous reports of safe endotoxin levels in different types of vaccines. The recommended limits are summarised in the table below.

Vaccine type	Recommended endotoxin limit (EU/mL)
Gene vector	< 10
Recombinant subunit	< 20
Polysaccharide	< 20
Live attenuated	< 200
Inactivated	< 500
Toxoid	< 200,000

While the first vaccines were tested for endotoxin contamination using the RBT, many modern vaccines are now tested using the LAL assay. One study reported that that the gel clot version of the LAL assay was equally reliable and sensitive as the RBT for testing hepatitis B vaccines[21]. Another group found that the LAL assay was effective for endotoxin detection in 39 different porcine vaccines[22]. So far, the LAL assay has been successfully applied to commercial vaccines for hepatitis A, Haemophilus influenza type b, influenza, rabies, typhoid, and yellow fever[16].

When considering the LAL assay for vaccine quality control, it is critical to first test for assay interference by any components of the vaccine formulation. In particular, aluminum hydroxide is a common vaccine additive that can lead to false positive results[23]. Dilution of the samples may be sufficient to eliminate this interference and allow for successful application of the LAL assay[21]. Today, the LAL assay remains the best option for testing most types of vaccines in terms of cost, sensitivity, and accuracy, and may also be utilised in combination with the RPT or other pyrogen/endotoxin assays.

Conclusion

Endotoxin is a highly potent pyrogen that can lead to fatal immune reactions, including sepsis and septic shock. Due to its high heat stability, it cannot be deactivated by most common sterilisation techniques. The presence of endotoxin contamination in a potential COVID-19 vaccine would greatly impair preclinical or clinical research by inducing adverse pyrogenic events. The LAL assay offers a fast and inexpensive method to ensure that endotoxin levels are below recommended limits. The assay has been extensively validated and characterised since its initial development in the 1960s, and today it remains the most popular option for endotoxin testing. Incorporating the LAL assay at multiple checkpoints in the vaccine research and manufacturing process will minimise the risk of adverse events and maximise its therapeutic window.

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FUJIFILM
Value from Innovation

LISA KOMSKI

Lisa Komski is the Sales General Manager for the LAL Division of FUJIFILM Wako Chemicals U.S.A. Corporation. With a nearly 30-year career of working in the Chemicals and Life Science industries, she has established herself as a strong business development professional skilled in U.S. Food and Drug Administration (FDA) requirements and cGMP. Lisa holds degrees in Biology and Medical Technology.

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PASS-THROUGH AUTOCLAVES FOR IMPROVED CONTAINMENT

Lee Oakley,Sales Director Priorclave

When Brunel University required a double-door/pass-through steam steriliser as part of a new CAT III containment laboratory suite, it was sourced from dedicated laboratory autoclave manufacturer, Priorclave, a British company with many years' experience in bespoke design and build of steam sterilisers. A 350l double-door autoclave was supplied and installed within the Heinz Wolff building, Centre for Infection, Immunity and Disease Mechanisms and School of Health Sciences with a CAT II and CAT III research facility, for secure decontamination of hazardous waste.

Pass-through or double-entry autoclaves are used in relatively small numbers and require often complicated building work as part of the installation process. For this reason, double-entry units are considered bespoke, to satisfy specific application requirements, raising additional points for consideration, such as cleanroom or containment, direction of workflow, door swing profile, thermocouple entry ports, etc.

It is also important when specifying any large autoclave to have a clear delivery site map since there can be many obstacles just waiting to create delivery difficulties. If these can be anticipated early, measures can be taken during manufacture and at the point of delivery to minimise or eliminate costly and nasty surprises. At Brunel University, it was impossible to do a full site survey as the would-be laboratory was a building site with no walls. Nevertheless, the Priorclave representative was able to walk the route from entry into the building to the laboratory. The route required the use of a goods lift and passing through single doorways as narrow as 900mm, then through another laboratory whose entrance lay between a sink and a bench.

A Containment Suite

The company contracted to source the autoclave based on the Brunel brief was Cleanroom Design and Construction Limited (CDC), based in Stourbridge. As CDC have considerable experience in the type of laboratories Brunel University require, they were chosen as the specialist contractor to design and build the turnkey, laboratory containment facility from start to finish. This included:

- the demolition and alteration of the building structure;
- the selection of the pass-through autoclave and other laboratory capital equipment and furniture;
- the organisation of the full commissioning and validation of all the capital equipment they sourced for the containment suite.

Priorclave's already proven track record with Brunel University had secured them as the preferred supplier of the laboratory autoclave in the new containment suite.

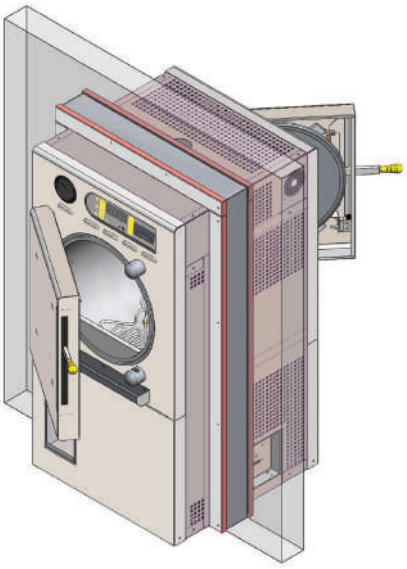
Performance and Build

Priorclave designed and built the autoclave to the specifications requested by CDC and the end users at Brunel University, supplying a 350l double-ended autoclave with electrical heating, vacuum facility, a printer and an exhaust filtration system for the containment of any hazardous pathogens. The design gave Brunel University a more cost-effective solution. The benefit of an electrically heated machine over one with a steam generator is that it uses less power, only switched on when in use. Also it would streamline the installation of the through-wall machine, since all elements are contained within the actual autoclave design.

Since the autoclave is used for de-contamination of hazardous material prior to its release from the containment suite, it was imperative that the double-door design had both ends of the autoclave isolated, and sealed at the point of passing through the wall by means of a bulkhead. Additionally, interlocks were necessary to prevent both doors being open at the same time, as this would obviously breach the integrity of the site. An interlock prevents the door at the unloading end from being opened until the sterilisation cycle has been successfully completed and the load is safe to pass into the unloading end. It is also standard with Priorclave machines that it is not possible to release the loading door until the unloading door has been opened and subsequently closed and locked. The steriliser supplied to Brunel's Centre for Infection, Immunity and Disease Mechanisms has an added benefit of a programmable key-lock that gives the facility the ability to use the autoclave as a single door autoclave at any end.

As Brunel's autoclave was a containment suite autoclave, most of it was located within the unloading room, with just the door section of the autoclave protruding into the containment area. This allows the majority of the maintenance tasks to be completed without the need for an engineer to enter the containment area or for the area to be decontaminated and temporarily disabled. CDC was instructed to install the drains and services at this end, thus minimising the number of pipes, wires, etc., that need to pass through the wall or bulkhead.

A printer was essential to produce a permanent record of each autoclave cycle, whether an integral part of the autoclave system or a separate and independent chart recorder device. It is normally desirable for the operator unloading the autoclave to be able to examine the record before opening the autoclave. For this reason and the fact that it is often not permissible to remove a paper record from a containment area, the printer was put on the non-containment end of the autoclave.



Schematic illustrating pass-through autoclave design.

A view of the autoclave from within the containment room.

The service end showing the effluent retention filter protruding from the top and the TACTROL® data print-out record on the right of the facia panel.

Following installation, Priorclave engineers returned to Brunel University to test the autoclave with actual loads and make adjustments to the autoclave and software to ensure optimum performance. Performance testing was done to UKAS accreditation and a full report and certification was given to the University on completion.

The service end showing the autoclave and water softener in-situ.

Easy-Clean Beneath Priorclave Benchtop Autoclave
With increased pressure to disinfect worksurfaces, the C40 benchtop autoclaves from Priorclave are the ideal steriliser. These research laboratory autoclaves can be supplied with short legs making it far easier to disinfect directly beneath the actual autoclave.

Initially introduced by Priorclave for laboratories looking to implement Cat 3 standards, their design is now just as essential in research and general laboratories where improved lab cleanliness and disinfection of the work surface is paramount to prevent cross contamination and spread of viruses.

Another added benefit of investing in Priorclave benchtop autoclaves is the Biomaster antimicrobial surface protection given to all steriliser. Biomaster is a proven effective means of reducing the growth of MRSA, E.Coli, Salmonella, Listeria, Campylobacter and over 50 other bacteria by up to 99.99%.

As an autoclave design and manufacturing centre, Priorclave developed both standard and vacuum models, which are available with a host of options enabling this British company to match unique application criteria.

One of the first models developed for such stringent lab requirements was the Priorclave C40 front-loading, vacuum laboratory autoclave. This is a wide-format benchtop autoclave with a 40l, front-loading chamber and is available with pre-vacuum and post-vacuum cycles. This adds to its versatility, the vacuum phases make the C40 autoclave ideal for sterilising laboratory waste, glassware, instruments as well as porous and wrapped goods.

The pre-vacuum mode efficiently removes ambient air from the chamber and load, allowing steam to completely penetrate the product whilst the post-vacuum cycle pulls steam and condensate out of the autoclave during this drying phase, the longer the vacuum runs the cooler and dryer the load. The overall benefit is a faster cycle time, making the C40 Priorclave suited to applications where a higher daily throughput is required or where delays in sterilisation are of concern.

As this model is ideally suited for installation in a CAT 3 laboratory it is available with an optional exhaust filtration system so that all autoclave exhaust is filtered.

In addition to the new C40 with short stand-off legs, all Priorclave Compact C40 autoclaves are available with an extended range of optional features normally found only on much larger steam sterilisers. This creates a brand that can turn its steam sterilisation capability to many business sectors including food, drink, dairy, pharmaceutical, veterinary, agricultural, education, healthcare, research establishments as well as industrial laboratories.

This latest compact benchtop steriliser is part of an impressive autoclave range, a range that also includes free-standing front-loading cylindrical and rectangular machines, power-door, double-door and stackable sterilisers. Standard models and those with vacuum including vacuum options offer capacities from 40L up to 850L; however, as a dedicated autoclave design and manufacturing company Priorclave have produced bespoke designs with chambers in excess of 7500 litres.

With years of experience in the design, manufacture and use of research-grade laboratory autoclaves, Priorclave is justifiably proud of its reputation as one of Europe's leading manufacturers. The company has a network of trained and certified technicians both in the UK and through accredited distributors throughout the world.

Priorclave is truly an international company, supplying and servicing laboratory autoclaves worldwide. In addition to its well-established standard range of benchtop, compact top-loading and front-loading sterilisers, the company provides in-house design and production facilities, enabling it to tailor the build of research-grade laboratory autoclaves to a client's particular requirements. They offer, in addition, a support service to help users get the very best from their laboratory autoclave.

Priorclave
"autoclaves are our business"

LEE OAKLEY

Lee Oakley was appointed Sales Director in April 2013. He joined the company in November 2005, a few years later was appointed Sales Manager, and made a significant impact in developing and motivating UK distributor sales, helping increase turnover year-on-year. As Sale Director, he takes on overall responsible for managing and developing UK sales, primarily through the established distributor network and service support, as well as exploring new business opportunities world-wide.

COVID-19: THE REAL-WORLD APPLICATIONS OF PHOTONICS EQUIPMENT

Tina Urbanek, Sales Engineer

Techniques such as PCR and medical imaging are vital in the fight against the coronavirus, and rely on the continued supply of components by manufacturers such as Hamamatsu Photonics.

The novel coronavirus (Sars-Cov-2) continues to spread across the world, impacting everything from daily life to the global economy. In these challenging times, the healthcare sector plays a particularly important role. In addition to protective clothing, respiratory masks and respirators, the ability to test rapidly and accurately is vital. However, rapid testing demands the availability of various laboratory analysers. Meeting the demand for analytical instruments requires that manufacturers continue production, to ensure the continuous supply of critical components across the world. Hamamatsu Photonics is part of the supply chain for products and devices used in the fight against the virus. Our products are integrated into many laboratory analysers and we also work closely with point of care diagnostic manufacturers to develop new instrumentation for rapid testing. But never forget: The safety and well-being of our employees is our top priority. We are monitoring the guidance of the World Health Organisation and other public health bodies closely and are taking appropriate measures to provide our employees with a safe and healthy working environment.

How to fight the virus? Researchers around the globe are striving to develop an effective vaccine against Sars-Cov-2, but this still requires time. To combat the further spread of the coronavirus efficiently, immediate detection of the virus is of crucial importance. The aim is to reduce the chain of infection and thus the infection rate. But to identify who is and who is not infected requires as many tests as possible performed. Tedros Adhanom Ghebreyesus, head of the World Health Organisation (WHO), famously said during a press conference in March: 'Test, test, test.'

Rapid tests and test analysers to test thousands of people, thousands of rapid tests are required, which in turn calls for great numbers of analytical devices for their evaluation. One common analysis method of these devices is the polymerase chain reaction (PCR). This method is widely used in molecular biology to multiply the patient's DNA.

How does the PCR test work? First, a smear is taken from the patient's mouth, nose, or throat. This sample is then sent to a laboratory. Each virus can be identified by a specific characteristic section of its genetic material. However, the quantity of the genetic material from the smear must be multiplied in order for there to be sufficient material to determine whether the pathogen is present or not. For this purpose, so-called thermocyclers are used, which initiate the polymerase chain reaction. In 30 to 50 cycles, the DNA is amplified exponentially. If the pathogen is present in the sample, its genetic material will multiply and will be detected. If there is no genome of the pathogen, it will not go through the multiplication process and therefore not be detected. Using a fluorescence dye, the amplification of the pathogen genome can be monitored in real time. This is called real-time PCR. It usually takes several days before the patient receives the test result. To send the sample to the laboratory takes the longest time, the test itself takes up to five hours.

Hamamatsu Photonics has decades of expertise in the development and manufacture of optical technologies. Several manufacturers of laboratory devices choose Hamamatsu Photonics for products such as photomultiplier tubes (PMTs), photodiodes and cameras that allow the optical detection of the target DNA sequence. We are proud to supply our products to manufacturers of laboratory analysers all over the world that are contributing to fighting the virus.

Medical Imaging as a Further Diagnostic Tool

Severe cases of Covid-19 are associated with pneumonia, which can lead to changes in lung tissue. As a further diagnostic tool of coronavirus, medical imaging techniques such as computed tomography (CT) and conventional radiography of the thorax are used. Changes of lung tissue are visible in the images obtained through these methods. In some cases, the changes of lung tissue are already visible despite the test results of PCR being negative. However, a negative CT result does not mean the patient is negative for coronavirus. With computed tomography or thorax x-rays, the severity of the disease can be assessed and the clinical indication in severe cases monitored. Compared to PCR, an advantage of medical imaging is that the results are available immediately. On the other hand, ionising radiation is used in CT and x-rays, so the health benefit for the patient must outweigh the radiation risk. Hamamatsu Photonics' contribution in the field of x-ray detection is apparent by a portfolio of suitable x-ray detectors, which it supplies to numerous medical equipment manufacturers around the globe.

TINA URBANEK

Tina Urbanek, Sales Engineer, Hamamatsu Photonics Deutschland GmbH

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AD INDEX

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LAL REAGENT PRODUCTS

For the Detection of Bacterial Endotoxins in the Battle Against COVID-19

As laboratories across the globe focus their research efforts on the development of a vaccine for COVID-19, it is crucial that quality control standards are maintained throughout the research and development process. The Limulus Amebocyte Lysate (LAL) assay for endotoxin detection helps reduce the risk of contamination during vaccine research and manufacturing.

Wako