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Interview

Mitochondria are small, but the upside for investors may be huge, says Alexander Schueller from cellvie AG.

FREE EXCERPT

Biopharma progress spares animal testing

Obesity Drugs
The Pharma Industry is in a gold-rush over weight-loss treatments

Rules & Regulations
European Commission conjures up an idealised biotech world

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The future of health biotech innovation in Europe

ADRIEN SAMSON is Healthcare Policy Senior Manager at EuropaBio, the European Biotech Industry Association. He leads the association's policy work on health biotech issues. He has expertise on EU pharmaceutical and industrial policies and works with a diverse range of stakeholders, including policymakers, regulators, industry representatives, patient groups, and research organisations, to promote the benefits and potential of biotech for health and society.

The 2023 State of the Union speech saw biotechnology rise as a priority for the European Union. It has been designated as a critical technology for Europe's economic security. In March 2024, the European Commission presented its biotechnology and biomanufacturing strategy with a clear leadership ambition for Europe's biotech industries. The Letta Report on the future of the Single Market, published April 2024, proposed a fifth freedom on research and innovation which would directly benefit biotech.

In a sign of how quickly policy priorities change in Brussels, six months before the European Commission published its much-anticipated revision of the EU General Pharmaceutical Legislation (GPL). The proposals make no reference to biotech and the impact on the biotech ecosystem was not specifically assessed. The revision proposed several welcomed improvements, including reducing the assessment periods and the creation of sandboxes for cutting edge products, but also proposed a lower baseline incentives and unpredictable modulation for novel medicines, including for rare diseases that will negatively impact the biotech ecosystem.

Within healthcare, biotech is increasingly the primary source of new therapies, bringing previously untreatable diseases within reach and transitioning from 'manage' to 'cure' with improvements to quality of life, freeing patients, families, and healthcare systems. Higher risk and long development timelines characterise the translation of biotech into therapies, with smaller companies being the primary vehicle for translation of Europe's research into development pipelines. The pathway to patients is a highly collaborative ecosystem between companies of all sizes. Innovators, especially emerging and small companies, are highly reliant on a strong and predictable incentives framework to secure early investment for long term programmes.

The GPL is a force for growth in EU biotech innovation and patient benefit. The Commission's proposals will negatively impact Europe's biotech ecosystem, with small innovators are at greatest risk and with them the EU's engine for novel medicines. Biotech companies are strongly inter-dependent for successful development of medicines. Proposed changes negatively impact partnerships and Europe's healthcare autonomy. Reducing incentives and certainty for early programmes is a barrier to the delivery of innovative medicines through biotech.

Despite the European Parliament having adopted its position on the proposals in record time, it must not be forgotten that GPL is legislation for future innovation and will only become law at the end of the decade. There is still time and opportunity for the Member States in the Council to ensure the GPL is aligned with Europe's priorities on competitiveness and open strategic autonomy, and delivers a more ambitious vision for the future of biotech innovation. ■

Picture: © EuroppaBio/Iris Haidau

FREE EXCERPT

COVER STORY

Organ-on-a-chip systems take off

The Three R (Replacement, Reduction and Refinement) principles developed over 60 years ago provide a framework for more humane lab animal testing and, more importantly, less of it. A range of in-vitro model systems that might one day replace animal-based programmes is now out there, but only recently has the use of multi-organ chips gained serious momentum. High-tech developments are increasingly allowing the replication of human tissues and organs for testing purposes.

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EU BIOTECH ACT

Principle hope

With the presentation of a biotech and biomanufacturing initiative shortly before its putative re-election, the EU Commission has raised hopes in the biotech sector for good framework conditions in Europe. However, in addition to the vague promise to draft by an EU Biotech Act, the non-binding paper contains many ifs and buts.

OBESITY

Eye on obesity drugs

Within a single year, new treatments for obesity – incretin agonists – have propelled Novo Nordisk and Eli Lilly to first and second place in the global ranks of top-selling pharma companies. In a global race, developers are now targeting hunger control with combination therapies that boost the effect.

SPECIAL

Biofairs Compass

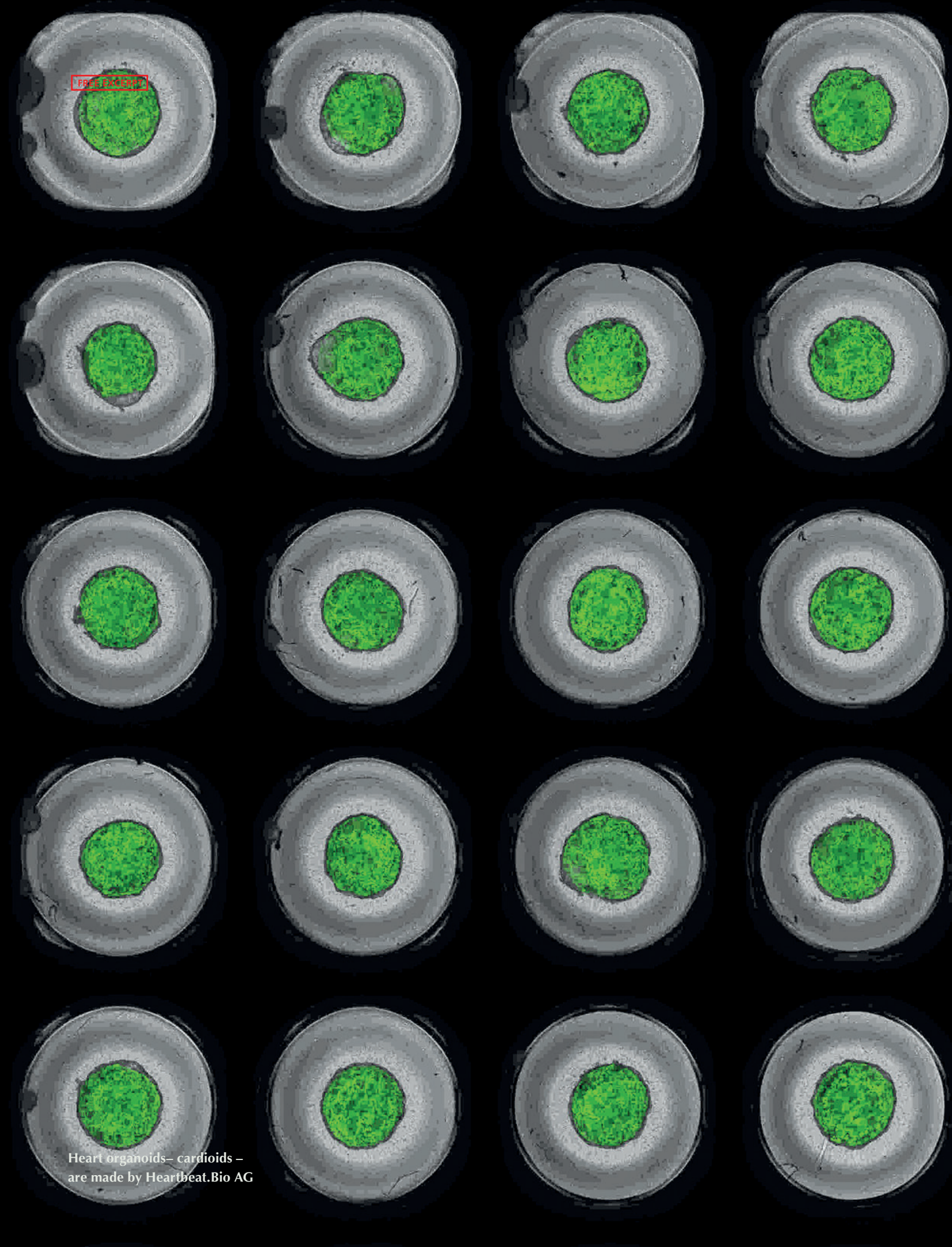
EDITORIAL

Against the flow

With a grand gesture, the European Court of Auditors (ECA) issued its first statement on the future of the internal combustion engine in the EU with a 'report' – and cast a clear vote against synthetic and biofuels and in favour of electric mobility in passenger transport. That would be all well and good, if only the statement of opinion disguised as an analysis were not riddled with outdated facts and errors that also politically obstruct the future of a sustainable solution to the fuel problem in heavy goods transport. The auditors are apparently unaware that, in addition to bio-based fuels, there are also fuels that can be produced directly from sunlight and a few minerals without any sourcing problems. Several European and US companies are also working on diesel from non-GM algae that are 70% oils that can be easily converted into certified diesel fuel.

The auditors also failed to realise that these and other biofuels are not overpriced, but can be produced at a price of €1.50/litre even before upscaling. There are just two problems. First, it will cost money to build the ponds for algae cultivation, and second, these would have to be located in places that get a lot of sunlight, such as Africa. Hopefully post-pandemic Europe has learnt from its mistakes in the past, as well as a thing or two about cooperation.

Thomas Gabrielczyk
Editor-in-Chief



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Organ-on-a-chip systems take off

MODELLING The Three R (Replacement, Reduction and Refinement) principles developed over 60 years ago provide a framework for more humane animal testing and, more importantly, less of it. A number of in-vitro model systems are now out there, but only recently has the use of multi-organ chips gained serious momentum. 3D printing technologies loaded with stem cells are increasingly allowing the replication of human tissues and organs for testing purposes.

The Three Rs were first defined in 1957 by Russell and Burch in their book *The Principles of Humane Experimental Technique*. Since then, the guidelines have been incorporated into national and international laws and regulations governing the use of animals in scientific procedures, as well as into the policies of organisations that fund or conduct animal experiments. But despite some headway, animal testing in the life sciences continues to decline slowly, if at all.

Are numbers really falling?

For many years, the EU's statistical database ALURES (AnimaL Use REporting System) on the use of animals for scientific purposes in accordance with Directive 2010/63/EU has attempted to provide a numerical basis for animal testing in research and product approvals. However, the data framework changed in 2019 due to Brexit and new inclusion for Norway, leaving room for misinterpretation. In spite of those complicating factors, indications imply that the number of animal experiments in the EU has fallen. There were around 8.1 million lab animals in the bloc in 2019, and just 7.3 million in 2020. That's the first time the number of animals has dropped below 8 million since the introduction of Directive 2010/63/EU. There's an ongoing debate as to whether this fall might only be a result of pandemic-driven lockdowns. Viewed positively, however, it's hard to see why the number of animals involved in clinical testing might have actually dropped despite massive efforts to get vaccines and therapeutics against COVID-19 over the approval line.

FDA allows a little more wiggle

One way or the other, there is major interest in finding alternatives to animal testing, as animal data are not just costly, time-consuming and ethically questionable, but also often fail to predict results in human trials. A lack of human-relevant preclinical models – and the resulting high failure rates for therapeutics in the clinic – have led to unsustainable rises in healthcare costs and fewer effective medicines reaching patients. Pressure from societies and governments to find alternatives to animal testing is also growing harder to ignore, as evidenced by the US Food and Drug Administration (FDA) Modernisation Act of 2021 and the Humane Research and Testing Act (HR 1744) passed by the US Congress. This new law disperses with the requirement that drugs in development have to be tested on animals before being given to participants in human trials. Signed by US President Joe Biden in December as part of a larger spending package, however, the new legislation doesn't ban testing new drugs on animals completely. Instead, it simply removes the former hard requirement that pharma companies use animals to test new drugs before testing them on humans. Companies are still allowed to test drugs on animals if they wish. Even so, the act is a sign of how strongly the FDA is promoting the development of alternative testing methods.

The search for other options

The stage is thus set for other methods pharma companies can use to evaluate new treatments, such as computer modelling and "organs-on-a-chip" (OOCs) – microfluidic devices that can mimic how organ function is affected by drugs. And companies that provide technology or equipment for organoids and OOC models have indeed seen increased demand since the new FDA law was passed, according to Reyk Horland of Berlin-based TissUse GmbH.

Currently, however, genetically modified mice and other animal models continue to dominate both basic research and drug development. Aware of this fact, the FDA has not mandated an immediate end

›› Read the full story in the printed issue.

Without the Gila monster (*Heloderma suspectum*) there would probably be no GLP-1 receptor agonists today. In 1992, Dr. John Eng isolated and patented the enzyme exendin-4 – which has a sequence >50% homologous and significantly extended half-life compared to GLP-1 – from the venom of the big desert lizards. This laid the foundation for the first blood-sugar-level-lowering GLP-1RA treatment for diabetes from Amylin Pharmaceuticals, which received FDA approval in 2005. The observation that diabetes patients lost weight during therapy has led to the development of optimised GLP-1RA therapies for obesity.

Industry eyes the weight-loss prize

SLIMMING DOWN Within a single year, new treatments for obesity – incretin agonists – have propelled Novo Nordisk and Eli Lilly to first and second place in the global ranks of top-selling pharma companies. Demand for Novo's GLP-1 receptor agonist (semaglutide) and Lilly's GLP-1/GIP booster (tirzepatide) currently can't be met. The drugs reduced weight by 12.7% and 18% over 68 and 72 weeks respectively in patients with BMI>30 and BMI>27 in those with obesity-triggered diseases. In a global race, developers are now targeting hunger control with combinations that boost the effect.

Light is sometimes hard to differentiate from shadow, especially in high-risk sectors like biopharmaceuticals. One tried and tested PR rule is that there are always two pieces of news, and you have to put the good news out front and hide the bad. In the young growth market of obesity treatments, Amgen Inc did exactly the opposite. A day after announcing it had deprioritised its Phase I programme with the oral Delta-5 desaturase (D5D) blocker AMG 786, the multinational rolled out the golden news: not a single patient enrolled in the proof-of-concept Phase II study of its GLP-1RA/GIP blocker maridebart cafraglutide had discontinued treatment due to side effects, and all 11 study arms of the placebo-controlled trial will remain active. Within 24 hours of the conference call, Amgen's value on the market had ballooned by US$20bn. The company said details of the study will be presented at the end of this year. Some analysts have guessed the combination could reduce body weight by up to 24%.

There has been no stopping obesity therapies since FDA approval of Novo Nordisk A/S's GLP-1 (glucagone-like peptide 1) receptor agonist Wegovy in April 2021 and Eli Lilly Inc's GLP-1/GIP (Gastric inhibitory polypeptide) receptor agonist tirzepatide (Zepbound) in November 2023. Goldrush fever has seized the rapidly growing field. Analysts are predicting sales of at least US$90bn by 2030, and are already calling the two approved obesity drugs "blockbusters of the decade". As of May 9th, the pen-injected compounds have made Lilly the top pharma dog in terms of market capitalisation (US$756.56bn) and Novo number two (US$429.99bn). "We are in a new era for obesity pharmacotherapy where combinations of entero-pancreatic hormones approach the weight loss achieved with bariatric surgery," stresses diabetes and obesity expert Prof. Dr Melanie Davies from the Leicester Diabetes Centre. In addition, there are several agents with different mechanisms that can complement the effect of the incretin hormones, which lower blood glucose levels, the speed of digestion in the stomach and

GLP-1 and the gut-brain axis

In the field of obesity drugs – which has seen a string of failures since the 1980s – the hormone GLP-1 has now taken center stage. It's released by L-cells in the small intestine after meals and has a variety of effects on the brain-gut axis (see p. 56). The rapidly degraded natural hormone not only lowers blood glucose levels, but also intervenes in lipid metabolism, hunger control and gastric acid production, which are all centrally controlled by the hypothalamus. With GLP-1 receptor agonists, it has for the first time been possible to potentiate the amount of GLP-1 attaching to receptors in the brain in such a way that the chronic feeling of hunger many obese people experience disappears. Chyme remains in the stomach for longer and – in combination with a change in diet and exercise – significant weight loss occurs. Although the molecular mechanisms are not fully understood, and the long-term effects of GLP-1 receptor agonists are unknown, what is clear is that weight is regained when the therapy is discontinued. Novo Nordisk, Eli Lilly and competitors are currently all working feverishly on new combination therapies that promise to reduce

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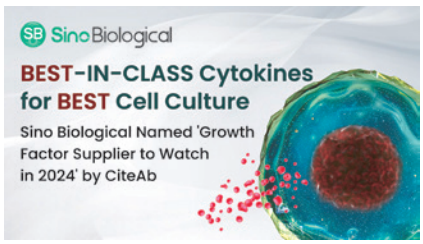

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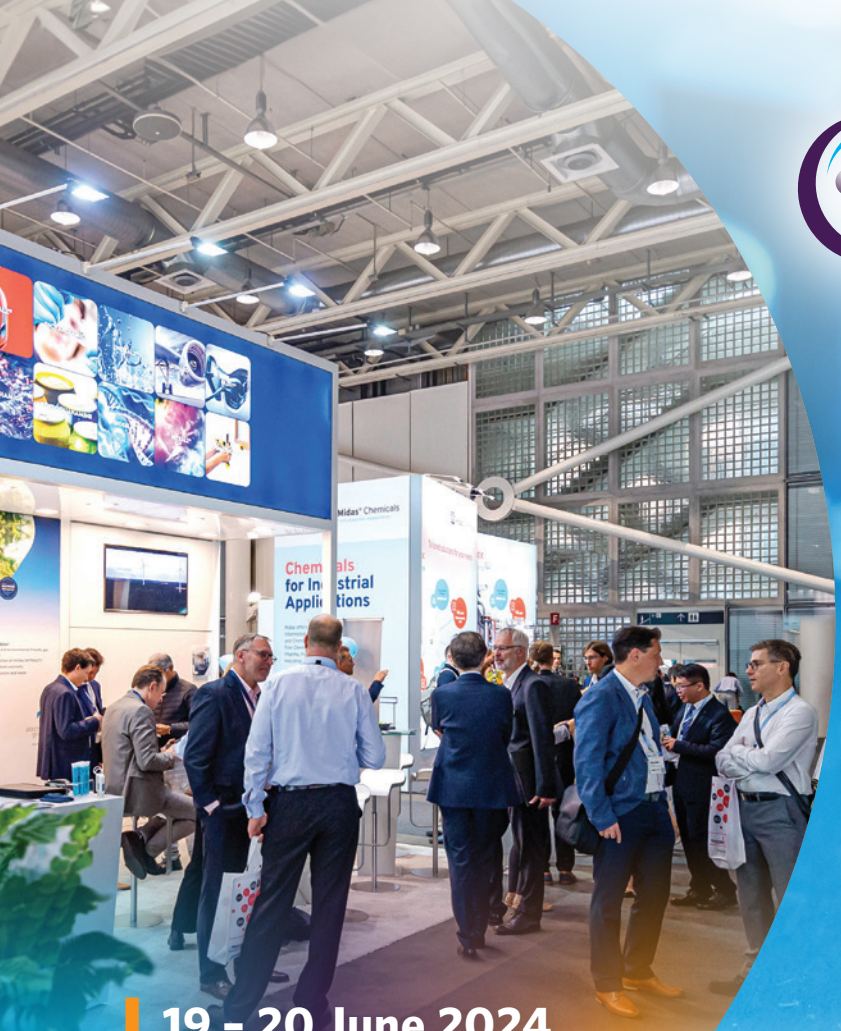

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