the Medicine Maker

# SPECIAL SERIES:

## *Sustainability*

SUPPORTED BY

ZETA

IN MY VIEW

# Embracing Enzymes

To meet increasing global demand for more efficient and greener processes, environmentally friendly catalyst technologies are on the rise

As pharma companies grow more mindful of the environmental impact of their products and supply chains, chemists and engineers are turning their attention to increasing efficiency and reducing waste in API synthesis. One attractive solution relies on nature's catalysts – enzymes – which can be used as highly specific and selective "biocatalysts." Notably, biocatalysts follow many of the principles of "green chemistry", making them an attractive alternative to chemocatalysts.

So why aren't more companies embracing enzymes? Put simply, the entire workflow of biocatalysis – from sourcing, development, and optimization of an enzyme, to finally delivering a biocatalyzed process – is a complex, multidisciplinary affair. And that's why, for the pharmaceutical industry to fully leverage the power of biocatalysis, it's vital to tap into advances across the key areas of enzyme screening, engineering, immobilization, and bioprocessing.

With the growing complexity of pharmaceutical APIs, the demand for biocatalysts that are active towards novel, non-natural substrates has also increased. However, this is at odds with natural evolution, which has produced an impressive library of powerful yet substrate-specific enzymes. As such, many industrial reactions do not have a process-ready natural biocatalyst because the enzyme's active site is suboptimal for accommodating the desired substrate.

To overcome this hurdle, scientists developed an approach that mimics natural evolution in a laboratory setting by randomly mutating, screening, and selecting thousands of enzyme variants. Using "directed evolution", enzyme development scientists can incrementally address inherent hurdles, such as substrate scope, undesirable selectivity and process stability of the natural enzyme starting point. The importance of this technique for the pharmaceutical and wider chemical industry was recognized by the 2018 Nobel Prize in Chemistry – awarded to Frances Arnold.

Though directed evolution showcased the power of engineered enzymes for industrial biocatalysis, the iterative cycles required to

*"Drug development suffers from a high attrition rate, making the return on investment for designing a new biocatalytic route uncertain."*

deliver a final process-ready biocatalyst is not always compatible with drug development timelines. Additionally, drug development suffers from a high attrition rate, making the return on investment for designing a new biocatalytic route uncertain. Therefore, for more biocatalyzed processes to be realized, we first need to enhance biocatalytic solutions for all desired routes and shorten enzyme engineering timelines.

Although the enzyme engineering field is synonymous with Arnold's directed evolution technique, the mounting understanding of protein sequence–structure relationships has allowed for rational design to mature. Rational design approaches rely on computational analysis of sequence alignments and protein structure/dynamics to predict the exact changes required to elicit a desirable effect in the enzyme. The strategy has more success when prior structural and experimental data is available for the specific candidate enzyme or family of enzymes. Although still prone to high failure rate, if successful, enzyme development timelines can be drastically reduced.

At the intersection of both these methods is semi-rational design. By rationally and accurately predicting favorable "hotspots" on the enzyme structure through proprietary computational workflows but also allowing for randomness at hotspots, we can create a smart library that increases our chance of finding vastly improved enzymes in reduced timelines.

Altering an enzyme's specificity or regioselectivity is usually determined by active site residues, while enzyme solubility and stability is often dictated by surface residues. However, in the pursuit of addressing one limitation, you may often affect another. As such, multiple compensatory mutations are required, which can be a long-process with full-gene random mutagenesis approaches.

Proprietary computational workflows are emerging that can be used to accelerate timelines by scanning millions of possibilities to identify the best enzyme for the target reaction. These workflows can traverse natural sequence space (public or metagenomic databases) and predictively find sequences that are as close as possible to an ideal biocatalyst for the transformation. In silico mutations can also be introduced if required.

But enzyme engineering is only one part of the equation. To deliver a robust biocatalyzed process, reaction engineering and enzyme formulation are equally important. For this reason, expertise should be drawn from a range of different specialists. This approach must operate throughout the entire process, starting with enzyme discovery, design and development through to the initial screening, process intensification, and scale-up stages. Especially as delivering the final industrially viable enzyme often relies on identifying the limitations of the biocatalyst in process conditions coupled with targeted enzyme engineering.

The enzyme development and process chemistry teams are closely linked with the bioprocessing team. Through the optimization of the molecular biology, fermentation, and downstream process, the bioprocessing team aim to reduce the final cost contribution of a biocatalyst. This can be done by maximizing expression in the host-organism, and thus, the specific activity of the final enzyme powder; however, it is also heavily dependent on the development team finding the right combination of plasmid, host, and codon-optimized DNA sequence.

Great headway has been made in biocatalysis – but, in my view, we need many more scientists and engineers working on the solution. The paradigm shift of "predictive biocatalysis" is not too far away, and with multiple academic groups, start-ups, and large corporates innovating across key aspects of the workflow. As such, the need for more efficient and sustainable approaches to pharmaceutical synthesis is not going away; the golden age of biocatalysis beckons.

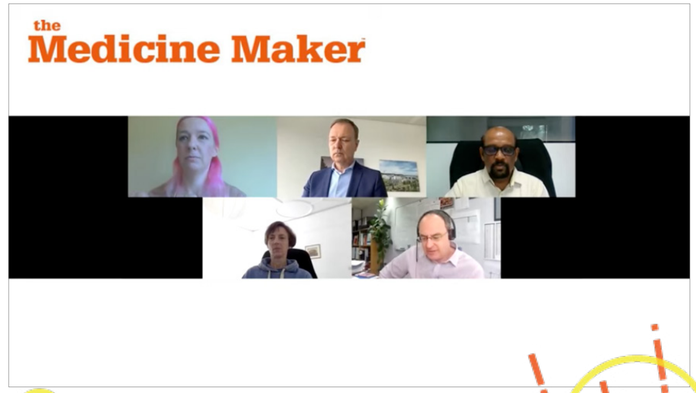
*By Ahir Pushpanath, Team Leader, Biocatalysis, at Johnson Matthey*

VIDEO DISCUSSION

# The Growing Importance of Sustainability in Pharma

A question of sustainability: how can pharma companies up their environmental game? Experts discuss in our video roundtable.

Sustainability is becoming an increasingly important topic for the entire world – and every industry – must play their part. What does this mean for pharma? I spoke with four experts from different corners of the industry to find out their thoughts on the importance of sustainability, protecting the planet, and what action companies can take – both small and large – to help make a difference.



IN MY VIEW

# Green Progress and Pitfalls

Where are pharma companies falling behind when it comes to the environment?

Historically, the pharma industry has been a heavy polluter. One notable study found that pharma's emissions intensity (a metric to fairly compare companies of different sizes) exceeded the automotive sector by 55 percent, despite being 28 percent smaller as a market. The study concluded that to meet targets outlined in the Paris Agreement, the industry would need to see a 58.6 percent reduction in 2015 emission levels by 2025 (1).

And the good news is that progress is being made in a number of areas – namely, air emissions, waste, water, and energy usage. However, an analysis by Owen Mumford Pharmaceutical Services of the top 25 companies reporting environmental, social, and corporate governance (ESG) scores found three critical issues that have yet to receive sufficient attention. Firstly, efforts to reduce packaging in the industry are well behind other industries. Secondly, addressing contamination through antibiotic manufacturing emissions must be a priority (particularly as endeavors to combat antimicrobial resistance become increasingly difficult). Thirdly, there is a large variance in sustainability performance across businesses in the industry. Let's look at these three areas in more detail.

Packaging in the pharmaceutical industry has been largely focused on safety and sterility, making efforts to move towards sustainability challenging. Though policies to improve packaging are in place in most companies included in the analysis (76 percent), hard targets have been set by just 13 percent. Other industries are advancing faster in this respect; for example, McDonalds plans to use completely renewable and recycled packaging as soon as 2025 (3). Where clinically feasible, the industry can convert to sustainable alternatives – ensuring that there is a net environmental gain when changing original materials. One sustainable alternative is polyolefin laminate packaging, which is 70 percent recyclable and can be used for unit dose packaging of solid formulations. There is also a commercial benefit; adopting this packaging can lower packaging-associated costs by up to 60 percent (4). Reducing weight and improving packing efficiency can also reduce shipping resources and cost.

Contamination is a more challenging issue; 84 percent of companies analyzed have a policy on pharmaceuticals in the environment (PiE), and 36 percent on antimicrobial resistance (AMR). However, there is a lack of hard targets being set to enforce action. AMR has been identified by the United Nations Environment program as one of the greatest threats to global public health (5). In some countries, such as China and India, where there is a high level of pharmaceutical manufacturing, uncontrolled discharges can leak into water systems, consequently impacting the people and animals that come into contact with the resulting resistant bacteria. One study analyzed waste from a wastewater treatment factory in India and found concentrations of broad-spectrum antibiotic ciprofloxacin sufficient to treat 44,000 people daily (6). The complexity of tackling contamination could be one reason for slow progress in this area to date. But the longer the issue is not properly addressed, the more difficult it will become to solve. Responsible and informed policies are urgently needed.

Finally, the industry as a whole does not have a consistent approach to sustainability. Our study found a variance of over 40 percentage points between those committed to sustainable practices and others who had yet to make real inroads. Neither geography nor size seem to affect a company's ability to achieve impressive sustainability scores. One analysis shows that, despite selling similar products and generating similar revenues, one pharma company's CO2 emissions were five times greater than an industry counterpart (7). To that end, corporate will is just as important as a large budget. A further issue is that companies are not necessarily reporting progress in a standardized manner – an inconsistency that confounds tracking of progress and could be contributing to the high levels of variance we are currently seeing.

It's not all bad news. And we should acknowledge the efforts made by the pharmaceutical industry in other areas. A study by EcoAct analyzing top firms' sustainability commitments showed the pharmaceutical industry performed well compared with many industries, with an average score of 60 percent – comfortably above the overall average of 53 percent (8). Our own analysis shows that 70 percent of companies are pursuing targets to reduce air emissions, and 50 percent of companies are setting hard targets to optimize water use – a positive development for an industry that is a major consumer of water (9).

But the goal of sustainability is a multifaceted challenge – and a little success cannot lead to complacency. The sizable environmental impact of the industry means there is still plenty of work to be done. Hard targets ensure firms are taking action and remain accountable. These targets must be continually scrutinized and updated in a bid to set ambitious industry standards and motivate every player in the supply chain to make greater strides. At Owen Mumford Pharmaceutical Services, we have already made significant steps, such as becoming one of the first medical device manufacturers globally to receive a B Corp certification. We recognize the importance of ongoing action, and our next ambitious targets include achieving net zero carbon emissions by 2045.

*By Michael Earl, Director of Pharmaceutical Services, Owen Mumford.*

REFERENCES AVIALABLE ONLINE

INTERVIEW

# Winter is Coming: How the Energy Crisis Will Change Pharma in 2023

In the face of war and the lingering economic aftereffects of COVID-19, Europe is weathering an energy price storm. What does this mean for medicine makers?

As the war in Ukraine draws ever closer to the end of its first year and winter tightens its grip on the northern hemisphere, many of us – from ordinary families to corporate accountants – will be watching our energy bills in an entirely justified state of anxiety. Stacked on top of a prolonged period of COVID-19-induced economic disruption and surging inflation, this is a tremor in the market that nobody asked for, but almost everyone will have to deal with.

So what does it mean for the pharmaceutical industry? To help us consider where to even begin, we spoke to Naomi Ikeda, a tax consultant at Ayming with a PhD in molecular biology and years of experience working with small, medium, and large companies across medtech, biotech, and pharma. Recently, Ayming published its 2023 International Innovation Barometer, which devoted roughly one third of its pagecount to the energy crisis.

## What is the scope of the energy crisis right now?

The energy crisis is impacting the productivity and capabilities of many industries, not just those in the energy sector. Due to the interconnectedness of the world's industries and their reliance on fuel for production and trade, changes in one sector can have a significant impact on others, creating widespread instability across all industries. Over the years, numerous crises have had lasting effects on supply chains. Disruptions caused by the COVID-19 pandemic highlighted Europe's dependence on global suppliers and resulted in shortages of APIs and packaging materials. Continued lockdowns in China have exacerbated these shortages, while the war in Ukraine has increased the price of energy and we are still feeling the effects of COVID-19 on healthcare. This translates into simultaneous supply and cash flow shortages.

Some of these problems will affect the entire world but, in many cases, their effects will be concentrated in specific regions. The countries suffering from the energy crisis are predominantly in Europe due to their dependence on gas from the Baltic Sea pipeline – but there will also be countries outside Europe affected by the knock-on effects of the crisis. In addition, the continuing lockdowns in China have led to a significant global decrease in raw materials, increasing the costs of both consumables and manufacturing processes.

## What are the knock-on effects of the crisis?

This crisis will lead to upfront corporate investment in future-proofing. This involves short- and long-term strategies for fuel saving and the creation of contingencies for further supply volatility – so we can expect some innovative benefits for the economy and the environment.

The increase in energy costs is also leading to a significant decrease in margins for European pharmaceutical manufacturers, with reports in a letter addressed to the European Commission stating that electricity prices for drug manufacturers have risen 10-fold and that costs for raw materials are increasing between 50 and 160 percent. This particularly affects products such as antibiotics, whose manufacture is energy-intensive due to the fermentation processes and required sterility. The rising costs are leading to calls for the discontinuation of generics, which would push higher costs onto the customer. This would lead to production impacts for all medication and would limit the availability of medicines for patients in need.

All of this has led many companies to seek manufacturing methods that can alleviate the pressing cost challenges. During times like these, innovation will increase as companies seek new modes of operation to create a "new normal" that is less dependent on high energy requirements.

**What did the survey behind Ayming's 2023 report reveal about the energy crisis?**

Our survey encompassed 846 pharmaceutical businesses across 17 different countries in Europe, Asia, and North America, and revealed numerous insights into how people across different economic sectors are responding to the energy crisis. More than 80 percent of pharmaceutical companies have had to make changes to counter the rising energy bills, with 36 percent describing their changes as "radical."

Furthermore, the results showed us that pharma is less prone to inter-sector collaboration than other industries. This is most likely due to NDAs on products, which create a barrier to joint ventures and innovation. However, during this volatile period, it will be crucial for pharma to expand its collaborations.

Collaboration reduces the amount of energy each individual company requires and enables more efficient use of time and resources. During a period of ever more finite resources, the industry needs to recognize how and where redistribution of scant resources would be most useful.

More broadly, our survey showed that 41 percent of firms are looking at energy efficiency savings. Of those, 30 percent are looking at alternative energy sources, such as a new supplier or renewables, and 25 percent are looking for alternative materials that are not derived from fossil fuels. Surprisingly, only 58 percent of respondents said they were receiving the funding necessary to navigate the energy crisis, but 62 percent are expecting an increase in R&D budget. This underlines the rising importance of innovation that we can expect through 2023.

**Can major private sector investments offer a way out of (or at least through) the crisis?**

There are several key paths to navigate this crisis, including procurement-funded innovation within the private sector, government funding, and collaborative work within commercial sectors. However, governments must ensure that they have a wide range of support mechanisms to stimulate the energy transition, including R&D tax credits, grants, and subsidies. Effective solutions here will provide immediate benefits to both the economy and the environment and will begin to stabilize the market.

**Does pharma need special support to handle rising energy costs?**

During this crisis, we will need to view the interdependencies of the various sectors collectively. Pharma is just one part of a wider picture. At the height of the pandemic, pharma was the industry with the potential to save us – and it received increased attention and funding accordingly. But, in the case of the energy crisis, that responsibility is more distributed across a range of sectors. What we can say with certainty is that the danger posed by finite, geography-dependent fossil fuels has never been more real.

Across the 21st century, this danger will lead to starvation due to the lack of available resources for agriculture. We will also be faced with a lack of medicines and therapies that used to be commonplace among the general population. Ultimately, it cannot be said enough that fossil fuels contribute to increasing CO2 emissions and the rising temperature of the world, which in itself will have an ever more catastrophic impact on our way of life.

Companies that embrace greener practices reap double benefits: environmental sustainability and lower energy costs. Actioning such strategies commits funding to innovation and pays off in the long run through new savings and efficiencies. The greener a company is, the more green advances it will be able to make and the more easily it will secure additional government and commercial funding as a result.

Future-proofing by developing greener technologies is key for us all. It's these technologies that could spare us from a future riven by crises induced by our dependencies on fossil fuels and other finite resources.

*By Angus Stewart, Associate Editor of The Medicine Maker*

INTERVIEW

# With Great Power…

Every pharma company should have a robust environmental, social, and governance framework in place – but what does that really look like?

Environmental, social, and governance (ESG) plans should be an integral part of any company that aims to thrive in today's society; after all, the public (as well as other stakeholders) are increasingly holding businesses accountable for their actions in ways that weren't considered even a decade ago. People want the companies they support to care not only about their own interests but also those of their employees, the environment, and the communities they interact with.

We spoke with Elizabeth (EJ) Ashbourne, Executive Director of the Partnership for Quality Medical Donations (PQMD), to find out what good ESG looks like, and why medicine makers must spend time creating initiatives that work for all stakeholders.

## What is PQMD?

The Partnership for Quality Medical Donations (PQMD) is a global network of nonprofit and corporate organizations that got its start by addressing the critical need for guidelines related to donation policies and practices. Our non-profit organization dates back to 1996, when an informal alliance of several non-governmental organizations (NGOs), pharmaceutical companies, and medical device firms joined together to develop guidance regarding medical donations.

Our mission is to promote sustainable health access in underserved communities and populations in crisis. Intimately tied to these objectives are the environmental, social, and governance (ESG) programs of our pharmaceutical industry members.

## Why is ESG so important?

ESG initiatives and increased disclosures are key contributors to sustainable access to quality healthcare and medicines, and they are moving out of the corporate periphery and into core business aspects. The reason for this shift? The ESG movement encompasses several factors critical to success and focuses on a blended long-term portfolio of purpose, planet, people – showcasing companies' social investments and proving their commitment to global medicines access and equity concerns.

This evolution in corporate responsibility has undoubtedly been hastened by the pandemic – and the suddenly unveiled fragility of global systems. The increased focus on ESG has been further heightened by the expectations and public demand of stakeholders, and has also emerged as a key part of investors' ability to assess the resilience of companies to public health threats.

## What is the difference between a successful ESG initiative and a poor one?

A critical success factor is leadership buy-in to ESG initiatives. If it doesn't exist, the headwinds are strong! With top-down support, ESG efforts become far easier to embrace, approach, and implement. ESG must also be aligned with the corporate mission and be part of the overall business strategy – not just a series of activities to be checked off a list. Building a strong governance committee or function is also essential. ESG is no longer the responsibility of one person with a particular title; instead, the function must be cross-departmental working throughout the enterprise with champions advocating for the integration of the ESG strategy into the business.

*"At the end of the day, it is important to remember that ESG initiatives are ultimately about mitigating risk across the business, building a resilient mindset, and contributing to the long-term sustainability of the communities they serve"*

In my opinion, some of the best (and simplest) advice on developing appropriate ESG initiatives came from Mark Chataway, Head of Hyderus Consulting, and Baird's Communications and Management Consultancy. In his words, we must "consider the value and impact of ESG initiatives through 'materiality assessments' – looking at which issues really matter to important stakeholders. An idea might sound good in the executive suite, but you need to ask stakeholders whether this is something they want you to do."

He and his colleagues were even surprised to find that pharma stakeholders in Africa were worried about the environmental impact of medicines, packaging, and medical waste – highlighting the importance of listening to all voices involved in the success of the industry.

In addition to the top-down approach and materiality assessments, I recommend learning from the experiences of your industry peers. PQMD produced an "ESG 101" session that was offered to members in advance of another event of ours – the 2021 Global Health Policy Forum. Panelists from both industry and the public health community gave their takes on ESG and shared best practices on how companies can get it right. These types of discussions are important for increasing awareness across the pharmaceutical community and creating the best possible initiatives.

At the end of the day, it is important to remember that ESG initiatives are ultimately about mitigating risk across the business, building a resilient mindset, and contributing to the long-term sustainability of the communities they serve; the importance of all three aspects has been amplified by the pandemic – perhaps beyond anyone's expectations. A focused approach to ESG can help us be better prepared for the next challenge.

It's no longer possible to sit on the sidelines when it comes to ESG, as business interests are increasingly intertwined with the outcomes of philanthropy and public accountability. It's an issue all pharma companies should be thinking about – today.

*By Maryam Mahdi, Deputy Editor of The Medicine Maker*


ZETA
“Ready to achieve the climate goals?
WITH ZETA TO ZERO EMISSION
► Customer-specific decarbonization strategies
► Cut energy consumption as well as emissions
► Reduction of interfaces – from concept to project execution
► Perfect alignment of process systems and building
► Expertise in clean room and HVAC engineering
WATCH THE VIDEO ON
WWW.ZETA.COM

INTERVIEW

# From Saving Patients to Saving the Planet

How can pharma help save the environment? We need to look at our processes – examining where we can apply green chemistry, reduce cleanroom sizes, and use less energy overall. If we're truly serious about patient health, we need to protect our home.

A handful of people (and corporations) still deny climate change, but it is happening. A report from NOAA and NASA showed that 2010 to 2019 was the hottest decade since records began 140 years ago (1). Polar ice is melting. Extreme weather, such as hurricanes, floods and droughts, is becoming more frequent.

Let's go back to 2010. When I used to ask medicine makers what they were doing to reduce their environmental footprint, I was often laughed at. Drug development is complicated enough, they would say. It's essential for human health, they would argue. Most companies didn't seem to feel compelled to consider the environmental impact of their operations.

Today, there is a growing realization that the planet is in danger, and – slowly – more companies are wanting to play their part. Company initiatives focused on the environment and sustainability are now commonplace in the pharma industry. And academic literature on the topic grows and grows.

Kristi Budzinski works for Roche Molecular Systems and is a member of the American Chemical Society Green Chemistry Institute Pharmaceutical Roundtable (Pharma Roundtable). The Pharma Roundtable was formed to encourage innovation in green

chemistry and engineering – and to help companies incorporate more sustainable approaches into their processes. Budzinski was recently the lead author on a paper, conducted by the Pharma Roundtable, examining the life cycle assessment of single use technologies in biopharma manufacturing (2). Here, Budzinski discusses the paper, the Pharma Roundtable's efforts to encourage the uptake of greener manufacturing, and her views on how the industry can improve sustainability in both small molecule and biopharmaceutical manufacturing.

**What's the story behind the Pharmaceutical Roundtable?**

The Pharmaceutical Roundtable started in 2005. It began as a collaboration between the ACS Green Institute and the pharma industry about how to include green chemistry in their processes. Initially, there were only around five companies involved; back then, one of the main discussion points was how to collaborate in a competitive setting – because it is not easy to talk about green chemistry and small molecules without potentially infringing on intellectual property!

As the initial hurdles were overcome, the Roundtable has also focused on how to measure and assess the impact of green chemistry, resulting in the development of the process mass intensity metric, which has become the industry standard for how to measure process efficiency. It works by summing the mass of all of the inputs that go into synthesizing a product and then dividing this by the output (amount of API) – giving a numerical value.

The Roundtable has grown a lot over the last decade. Today, there are 23 full members (innovators and pharma companies), 16 associate members, and 3 affiliate members. Most of the growth has come in the last five years or so – and we are seeing burgeoning interest in the topic of environmental sustainability.

**How have conversations and attitudes around green chemistry and sustainability changed over the years?**

I've been participating in the Pharma Roundtable for ten years and the conversations have evolved. The Roundtable remains focused on measuring impact and developing tools to help move the needle in manufacturing, but it has also focused on early stage research and development. For example, the Roundtable has contributed significant funding to academic research activities on green chemistry topics and connecting this to industry. More journals are also recognizing the importance of green chemistry – and there have been an explosion in the launch of new journals focusing on green chemistry implementation.

In 2012, when I joined the Roundtable, we formed a large molecule focus group which was challenging as biopharma has quite different challenges from traditional pharma manufacturing, but also a testament to the ability of the roundtable to adapt. The members welcomed the biopharma perspective and helped build on the existing tools for small molecules to develop similar approaches for biopharma. These tools and techniques are now being expanded to "medium" molecules, such as peptides and oligonucleotides.

**What aspect of small molecule manufacture produces the most waste?**

Solvents. The Roundtable performed a benchmarking exercise (3) to examine where most of the waste in small molecule manufacture comes from – and the answer was solvents, which is convenient because this is a very non-competitive space! The Roundtable has focused on guiding chemists towards choosing solvents that are better from an environmental, health and safety perspective, while also encouraging solvent providers to create new solvents, by using renewable raw materials and creating solvents with better environmental profiles.

The biggest hurdle in finding replacement solvents is a technical one; finding replacements for chlorinated solvents like dicholormethane, or for dipolar aprotic solvents like DMF, NMP, THF, etc. is extraordinarily difficult. The combination of physical and molecular properties of these solvents, such as their boiling point, or their solvation of higher molecular weight molecules, etc., are key determinants of reaction and overall process efficiency. If a chemical company finds a potential technical replacement, it then needs to meet stringent environmental, safety, health, and sustainability requirements in addition to passing regulatory requirements for residual solvents in the final drug product or for meeting GMP requirements. While the pharma industry is a big user of solvents, it is not the biggest user of solvents, and the types of solvents that are used are not always high-volume commodity solvents, such as in other industries. This makes the cost to develop a new solvent, document its EHS/Sustainability bona fides, and meet drug manufacturing and regulatory requirements a daunting prospect.

There are also regulatory concerns with integrating a new solvent into GMP processes. Companies generally need a key reason and strong motivation to change an existing process. If it is a really inefficient process with a lot of waste for example, there may be cause to make improvements. But most companies would likely only use a new solvent for a new development – and it could take a while before a company hits on a commercially viable target that uses a particular solvent. And why should chemical companies make a new solvent that likely won't be used for years?

Despite the challenges, some new solvents have come to market but maintaining adoption is difficult. Some people may try it, get interested, and want to buy – only to find out there's a six month backlog… And then everybody forgets about it.

We also have to acknowledge that solvents aren't "sexy." Not all companies have the staff available to test new solvents, although larger companies may perform solvent screening in process development. Here, they may not only be looking at the reaction and process efficiency, but also looking to identify different polymorphs and protect IP.

To help ease the adoption of new solvents for the industry, we need to get creative. And that's why it's really important to get this kind of work into academic settings. A great project for an up-and-coming student could be to explore where new solvents could be used and to help make it easier for industry adoption. Some companies are using interns for this type of work. For example, Genentech hosted a summer intern to look at solvent application – and the work was published so that it could be shared more broadly (4). However, just because a student does this work for a company, there is usually no mechanism to facilitate acceptance of alternative solvents in an academic setting. Secondly, investigation of new solvents isn't something of mainstream academic interest with the exception of ionic liquids and deep eutectic salts, both of which are non-starters in the Pharma industry.

**Tell us about your recent paper on sustainability and bioprocessing…**

Many of the same companies using green chemistry for small molecules also have a biopharmaceutical arm. Around one quarter of our Pharmaceutical Roundtable members also participate in our biopharma focus groups. Some of the tools and metrics we've developed for small molecules aren't necessarily applicable in biopharma, but we can at least look at how they were created, adopted, and accepted – to help us apply similar approaches to biopharmaceuticals.

We developed a process mass intensity metric for biologics (4) and used this metric to benchmark bioprocess manufacturing across companies and bioreactor scales and the resulting number was quite large, mainly because biopharmaceuticals use a great deal of water (water accounts for around 90 percent of the intensity of the process). As a group, we then looked for opportunities to reduce this number, which included collecting and sharing engineering best practices and cleaning best practices (5). While we were investigating this area, the industry started to significantly ramp up the adoption of single-use technology. The conversation evolved from only looking at process efficiency to also looking at single-use technology implementation, which generates increased plastic waste. The Roundtable wanted to assess, scientifically,

*"It was interesting to see how little the single-use lifecycle (production and disposal) mattered compared with the actual biopharmaceutical manufacturing process."*

the implementation of single use technology to understand trade-offs that arise from the use of plastics and environmental hotspots. Thus, we partnered with a consultancy to perform a streamlined life-cycle assessment (LCA) of single use biopharmaceutical manufacture (6).

With process mass intensity, one considers all the process inputs but not the environmental impact of those inputs and their supply chain. It also does not account for energy consumed or the impact of any waste generated. This information becomes very important when you think about moving from traditional stainless steel vessels to single use; how else can you properly compare a stainless steel tank – and all the water required– to a plastic bag?

Having this study conducted through the Pharma Roundtable was great because it allowed us to look at the issue from an industry-wide perspective. We started with the standard platform for a monoclonal antibody production, and had the member companies agree on standard input values for the number of steps, chemicals, amount of time required, and amount of energy and water consumed, and so on.

*By Stephanie Sutton, Editor of The Medicine Maker*

READ THE FULL ARTICLE ONLINE

SITTING DOWN WITH

# The Greener, Cleaner Path

Sitting Down With… Thomas Otto, Managing Director of Vetter Pharma-Fertigung, Ravensburg, Germany

**Have you always wanted to work in pharma?**

As a child, I wanted to drive trucks! Later, I thought I might like to be a teacher or to work in a technical role of some kind. I was working as a bus driver to pay my way through college with those goals in mind when a passenger asked what I was doing. I explained my story and she told me that her company was looking for people like me.

She was the head of HR at Vetter and that was the starting point. I didn't plan to work in the pharmaceutical industry, but I'm very glad I'm here.

**What was your first role at Vetter?**

I started as a project engineer in packaging development. Back then – in 1990 – Vetter was pretty small, with about 300 employees. In fact, there was nobody in the packaging development group, so I helped launch it. Five years later, I took over the responsibility of the whole development group and in 2002 I became a managing director.

Whenever I talk shop with my old college classmates, they tell me changing jobs and companies is necessary for a good career. But this has never been necessary for me thanks to Vetter's strong growth. I've had the chance to witness so much and take over so many responsibilities. I'm fortunate that the company has been expanding quickly enough to accommodate all my growth as a professional. It's been exciting to be a part of that growth story!

**What are the day-to-day responsibilities of your role?**

We do not have a CEO position in Vetter. I run the operational business together with my colleague, Peter Soelkner. Each of us is responsible for a certain part of the company; I'm responsible for development, pharmaceutical production, quality, technical services, and internal project management – including all of the investment projects, as well as finance and controlling.

I like to say I'm the "inside minister" and my colleague Peter – who took over functions such as key account management, HR, IT, and the supply chain – is responsible for "the outside."

**Vetter has embarked on a number of sustainability initiatives. Why is this so important to you?**

Today, sustainability should be paramount. And that means adopting a culture of responsibility and acting in a sustainable manner. It's important to us, it's important to our employees, and it's important for the world community and its future. Obviously, some investment is necessary to achieve sustainability. But, in the long term, the company will not only grow in a stable manner – it will profit as well. When I talk about "savings," I'm not just thinking of reductions in carbon and kilowatts. Environmentalism is an investment with returns!

**What sustainability milestones has the company hit over the years?**

Vetter has invested in various energy efficient and environmentally friendly technologies. Greenhouse gas is one of the main drivers of global warming, and so we put a lot of work into that area. At all our sites, we have worked to reduce emissions. Since 2014, these technologies have resulted in an overall saving of more than 15,000 tons of carbon dioxide, which I think is remarkable.

We have also realized more than 100 efficiency projects over the past 10 years, investing more than €6.5 million along the way. Through this work – and strategic spending, we have been able to realize savings of more than 30 million kilowatt hours – roughly equivalent to the electricity, natural gas, and biogas used by 7,000 family houses per year. I think that's remarkable, too.

One huge milestone became reality in 2020, when our German sites turned climate neutral. We are very proud of the fact we no longer have a carbon footprint. In 2021, our international production sites and offices also achieved CO2 neutrality – made possible by the interaction of many components all working within the scope of a long-term CO2 strategy within the company.

Another significant sustainability project was the construction of our center for visual inspection and logistics. I believe it is a unique facility! It has environmentally friendly block-heating, harnesses geothermal energy, makes comprehensive use of excess energy, and runs photovoltaic systems. All of this runs in together to make it really efficient.

**How have customers reacted to Vetter's focus on sustainability?**

We find that sustainability is increasingly a focus and concern for our customers. Green factories are important to them – and we see many more inspections with this in mind. We are really pleased and proud that we began the necessary work years ago – otherwise we would be behind rather than ahead of the curve!

**What other big changes are you seeing in the industry right now?**

We live in extremely dynamic times. Over the last decade, we have seen high global demand combined with a great deal of unmet needs. There is a strong demand for specialized, targeted, precision therapies, and biotech is preparing to meet these demands with a wide variety of complex medications. But that means we must also deal with greater manufacturing complexity. There are also challenges in drug delivery. Although we are still producing drugs using syringes, cartridges, and vials, there remains a high degree of pressure to develop innovative and more efficient delivery systems.

*"We find that sustainability is increasingly a focus and concern for our customers."*

This all goes hand-in-hand with other trends, such as providing patients with convenient solutions to obtain a high degree of patient adherence, particularly where patients need to self-administer medication on a daily basis.

**As we start a new year, where do you think the industry's priorities should lie?**

If a company wishes to determine its future, it must understand its past. Success necessitates an understanding of who you are, how you became who you are, and continuous investment in your future. We must have the right infrastructure, capacities, and people to meet growing global demand, and be as flexible as needed for the contract development and manufacturing sector.

Because of the complexity of the new molecules on the horizon, we also recognize the importance of viable partnerships. Collaboration is essential and leads to successful projects and valued customer relationships. Many of our clients still look for a one-stop shop so we need to collaborate to meet their needs. In the end, the most important thing is bringing high-quality, life-critical medications to patients in need in the fastest way possible and collaboration can help us all to do this.

*By Stephanie Sutton, Editor of The Medicine Maker*

READ THE FULL ARTICLE ONLINE