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**Medicine Maker**

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## IN MY VIEW

# A Reawakening of Small Molecule Drug Development

New technologies are driving a small molecule renaissance

Small molecule drugs are the mainstay of medicine, representing around 90 percent of all approved medicines and 75 percent of all new medicines approved in the US in 2020 (1). They also still make up the lion's share of prescriptions, and are useful in non-genetic, prevalent, and multifactorial diseases, which affect a broad spectrum of patients. With predictable properties, small molecule drugs can be manufactured cost-effectively with less complexity than biologics.

However, small molecules feel like yesterday's news to some industry players: lacking in glamor, excitement, and venture funding. One key reason small molecules have been forsaken is the perception that they have run their course. The yet-to-be drugged therapeutic targets are thought to be out of reach for small molecules because of the scarcity of identifiable druggable binding pockets. Consequently, drug developers pursue these targets with newer drug modalities, forcing an unattractive tradeoff – shifting to riskier, more complex, and more expensive drug modalities for biologically validated targets.

Nevertheless, many protein targets are, in fact, druggable with small molecules. New technologies that combine advanced protein dynamics and computational chemistry analyses are driving massive data iterations that identify binding pockets by shining a light on areas of the protein that were previously beyond the sight of conventional tools. What are some of these technologies and strategies allowing us to see proteins in a new light?

- **Exploring all possible protein conformations.** Although increased computational power allows broad sampling of protein

conformations, traditional approaches to process these data required significant user bias. Use of a completely unsupervised proprietary processing approach eliminates this bias. In this way, one can distinguish pockets that exist in some but not all conformations and are often not present in the most frequent conformations.

- **Determining dynamic hydration protein structures.** New technologies can be used to determine each conformation's accurate dynamic solvation structure, since pocket desolvation is the principal driving force of small molecule binding.
- **Correlating structure and function.** Dynamic attributes – protein dynamics, conformations, and water molecular dynamics – can then be correlated to protein function. In this manner, validated targets can be pursued with the predictability of small molecules.

Once new binding pockets are identified using these approaches, current technologies can conduct virtual binding screens in over 3 billion virtual compound libraries.

In my view, companies pursuing these approaches need to reach across the aisle – to not only conduct the computational modelling and virtual screens, but also to test and develop the molecules suggested by these screens in traditional wet labs to learn more about them. This information can then help inform all other phases of drug discovery – from binding site identification and lead identification to lead optimization in end-to-end, interactive, continuously improving processes that will progress until functional drug candidates are selected.

Why is this relevant? Well, a foremost advantage of small molecules is their suitability for polymorphic, prevalent diseases; their development must embody the same innovation and boldness as their discovery.



Most newer drug modalities, including gene therapy, RNAi, and CRISPR, are tested in rare monogenic diseases or genetically defined disease subsets, leaving prevalent diseases out of their scope. Our job as small molecule drug developers is to create new medicines for prevalent diseases, build a compelling case to investors by identifying patients with a higher chance of responding to therapies, and then implement rigorous decision points before advancing the most promising drug programs. As with new medicines of all types, success is also defined by embracing patient-centricity. And that means including virtual clinical trials, adopting patient-relevant endpoints, selecting pragmatic designs, and incorporating real-world evidence.

I believe that the importance of small molecule drugs in the armamentarium of innovative medicines will remain on the increase. But we need to capitalize on today's opportunities and so bring new technologies to the field of medicinal chemistry, driving the renaissance of small molecule medicines.

## REFERENCES AVAILABLE ONLINE

*Marcelo Bigal is CEO at Ventus Therapeutics*

## IN MY VIEW

## A Roadmap to Improved Drug Access in the Global South

We developed a safe and affordable hepatitis C antiviral to save lives in South-East Asia and beyond. One key to success? Alliance management.

The adage, “If you want to go fast, go alone; if you want to go far, go together,” is more salient for the pharmaceutical sector today than it has ever been – especially if we are to achieve global health objectives in a sustainable manner.

Our organization’s nearly 20-year experience in drug development has shown that sustainable access to essential medicines is greatly enhanced when drugs are developed, registered, manufactured, and distributed in partnership with stakeholders from a much wider geography; in our case, the Global South. Indeed, alliances are increasingly used in global health efforts – but managing them effectively is a key to success.

Case in point: in June this year, following nearly five years of development, our organization and its partners celebrated the registration of a new safe and effective hepatitis C drug called ravidasvir in Malaysia – the very first hepatitis C drug delivered through South–South collaboration. Though hepatitis C is not usually counted as a neglected disease, the needs of people living with hep C are often overlooked. Breakthrough direct-acting antivirals (DAAs) for hep C, introduced in 2013, are safe and highly effective. Yet only about 13 percent of patients globally have received treatment. Though drug prices have come down in recent years, they still constitute a major barrier to access in many countries, especially those that are excluded from licensing agreements that enable access to generics.

And that’s why, in 2016, the Drugs for Neglected Diseases initiative (DNDi) established an alliance with Pharco Pharmaceuticals of Egypt, Pharmaniaga Berhad of Malaysia, Presidio Pharmaceuticals, and the Malaysian Ministry of Health to develop an affordable regimen that could boost access to treatment in low- and middle-income countries (LMICs).

Presidio Pharmaceuticals, the originator of ravidasvir, committed upfront to a pro-access vision, including an equitable licensing scheme to enable rapid scale-up of generics manufacturing. Pharco and Pharmaniaga Berhad committed to supporting the development and scale-up of the active pharmaceutical ingredient, manufacture of the tablets, complete toxicology studies to demonstrate safety, and preparation of the registration dossier. We coordinated the clinical trials and, together with Pharmaniaga, supported the registration process in Malaysia. The Malaysian government provided critical leadership and resolve throughout the lifecycle of the project. For example, it issued a government-use compulsory license that enabled it to purchase sofosbuvir (which is used in combination with Ravidasvir) for less than US\$300 per treatment.

We are now in discussions to register ravidasvir in other countries in South-East Asia and Latin America to reach even more neglected hepatitis C patients.



This alternative model of drug development – centered around affordability and public health priorities – was made possible through an alliance (as defined in Jeremy Ahouse’s ASAP Handbook of Alliance Management) that brought together players with very different skills and interests, and that provided a platform for all partners to share complementary assets and address financial risks together.

Building on the ravidasvir case – and to inform its own alliance management practice and offer support to others – DNDi’s Amalia Daka designed two surveys that were conducted in summer 2021. The first was conducted among non-profit product development partnerships (PDPs) similar to DNDi, and the second among pharmaceutical companies located in high-income countries as well as LMICs. We wanted to learn how alliance management has accelerated the development of other health technologies and to identify good practices. Seven of the 13 PDPs and 18 of the 25 pharmaceutical companies we reached out to completed the survey.

[READ THE FULL ARTICLE ONLINE](#)

*Greg S Garrett is the Director of Business Development & Alliance Management at the Drugs for Neglected Diseases initiative*

*Jean-Michel Piedagnel is the Director for South-East Asia at the Drugs for Neglected Diseases initiative*



# Your guide **today,** **tomorrow,** and for the **future**

We are the CDMO with the solutions you need now plus the agility and ambition to innovate and improve processes, technologies and science.

Let us be your guide so today's innovations become tomorrow's solutions.

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## VIDEO

## Why Does Pharma Need Novel Excipients?

With so many new dosage forms and breakthroughs being seen in the pharma industry, a problem is emerging: the need for unique formulation solutions – and novel excipients. In fact, the industry has needed novel excipients for years...

Many formulators continue to use old excipients that were developed decades ago – even though they aren't always well suited to the task at hand.

In this video discussion, experts from IPEC-Americas talk about the importance of novel excipients – and the problems facing their development. Fear of the unknown has made pharma companies reluctant to use novel excipients. And excipient manufacturers – due to uncertainty in realizing business benefits in developing new excipients for pharma – are reluctant to make significant investments. But in September 2021, the CDER launched a Novel Excipient Review Pilot Program to allow excipient manufacturers to obtain FDA review of certain novel excipients prior to their use in drug formulations. And hopefully this is the first step towards change.

Here are some quotes from the discussion that might whet your appetite:

“When you look at therapies today, there are new dosage forms and breakthrough therapies that simply didn't exist 20 years ago,

*“A good example is the mRNA COVID-19 vaccines. It was a novel, lipid nanoparticle type of excipient that had not been previously used that really facilitated some of the development work on the vaccines. It is a clear example of where a novel excipient helped the industry meet an unmet patient need in a critical situation.”*

such as targeted immunotherapy agents and certain combination products. They require unique formulation solutions – and that means more novel excipients.”

“A good example is the mRNA COVID-19 vaccines. It was a novel, lipid nanoparticle type of excipient that had not been previously used that really facilitated some of the development work on the vaccines. It is a clear example of where a novel excipient helped the industry meet an unmet patient need in a critical situation.”

“I know of circumstances where pharma companies have actually made decisions to avoid the use of a novel excipient, even though they've looked at the research and said, 'Wow, this would solve all of our problems!' Formulating with an existing excipient to produce a drug that is not as good as it could have been is not quality by design – it's quality by fear.”

[CLICK HERE TO WATCH THE VIDEO](#)

### Featuring:

*Kathy Ulman, President and owner of KLU Consulting, and Vice Chair of the Regulatory Affairs Committee at IPEC-Americas*

*Priscilla Zawislak, Global Regulatory Affairs Advocacy Manager at International Flavours and Fragrances (IFF), and the Immediate Past Chair of IPEC-Americas*

*Meera Raghuram, Director for Regulatory and Sustainability at Lubrizol, and Chair of IPEC-America's Regulatory Affairs Committee*

*Dave Schoneker, President and owner of Black Diamond Regulatory Consulting, and one of the original founders of IPEC-Americas.*

*Nigel Langley, Global Technology Director for BASF and current Chair of IPEC-Americas*



## Meet the CDMO of the Future

What does it take to be a CDMO of the future? It takes a solid foundation of expertise. An unwavering commitment to optimization. And perhaps most importantly, the experience and willingness to balance one against the other. At Asymchem, we realize that as strong and reliable as our current solutions are today, tomorrow's successful partnerships and healthcare breakthroughs rely on new technologies and improved methodologies.

### Seeking answers, dedicating resources

Our one-stop CMC services support the full lifecycle of drug development – from early clinical stage to commercial stage, including R&D and cGMP production of advanced intermediates, APIs, formulations, as well as clinical research services.

### Three-pronged approach to sustainable innovation

It's true that developing and manufacturing the drugs we need to cure or treat diseases, improve care, and decrease suffering can have unintended environmental impacts and hefty price tags. Today, both the US and Europe require pharmaceutical companies to take responsibility for environmental impacts across their entire drug development lifecycle and environmental standards have become more stringent everywhere. As a forward-looking CDMO, we anticipated this shift years ago and began intensive investment in three key areas: green chemistry, process efficiencies, and strategic collaborations.

### First, lead the way with green chemistry

For nearly a decade, we've been exploring and applying green chemistry advances for our customers' benefit. Today, those efforts fall into four key areas: flow chemistry, electrochemistry, enzymes, and photochemistry.

### Second, optimize production through process efficiencies

Like many of our customers, we're chemists. Guided by science we not only seek answers, we search for innovative, often overlooked, approaches to save our customers time and money, while increasing the safety and sustainability of each process. Today, our core process efficiencies center on five areas: catalyst screening, non-precious metal catalysis (NPMC), PPQ readiness, process intensification and solvent recovery.

### Third, collaborate for a brighter future

At Asymchem we believe that collaborating with our colleagues around the world – joining with them to share ideas and learn about new innovations – is how we'll grow our business and help to make the world a healthier, safer place. To that end, we consistently engage in strategic relationships with industry colleagues and academic researchers.

### Balancing what works... with what's next

Our mission is to accelerate the launch of new drugs, providing one-stop CMC services for the full lifecycle of drug development. And that requires going beyond what's tried and true to innovate for what's around the corner.

FIND OUT MORE ONLINE



## INTERVIEW

## Easy Film to Swallow, Hard Act to Follow?

Drug delivery to the esophagus has been underwhelming and overlooked for too long – but now a new device is going for the throat

Isabelle Racamier, CEO of EsoCap, a Swiss biotech dedicated to improving the lives of patients with serious diseases of the upper gastrointestinal tract, has seen a lot in her 25-year career. She has flown solo and been employed by some of the biggest pharma companies in the world, including Boehringer Mannheim (now part of Roche), Novartis, and Sanofi. We catch up with her to find out more about why esophageal disease is so important to tackle.

### Why has esophageal disease treatment seen such neglect, in terms of localized therapy?

Many people don't realize how wide the spectrum of esophageal diseases actually is – think 370 million patients worldwide. The largest sub-group within this are those suffering from reflux – a condition for which there are proton pump inhibitors, but insufficient therapeutic alternatives beyond that. Another 50 million patients have Barrett's disease, a condition that carries a risk of developing into esophageal cancer. Barrett's disease is a tough one because despite a very poor prognosis, it simply does not garner the same level of attention as cancers of other organs. And then there is eosinophilic esophagitis, the disease that EsoCap has set out to tackle first. Eosinophilic esophagitis, is a rare, chronic, immune-mediated esophageal disease. The symptoms include swallowing disorders, vomiting, and food impactions.

The treatment of esophageal diseases is plagued by one fundamental problem: whatever one swallows passes through the organ almost immediately. From mouth to stomach, nature asks no more than a couple of seconds. Even viscous syrups and orally dispersible tablets fare poorly, scoring a maximum of 45 seconds of exposure at the desired point of delivery – the esophageal mucosa. The only extant workarounds are invasive methods like endoscopic cross-section or ablation, and these are far from ideal.

In fact, there is currently only one approved medication for eosinophilic esophagitis – a tablet – and it is approved only in Europe and in Canada. There are no other therapeutic alternatives. That's why we are trying to change things.

### What is EsoCap working on?

Our treatment approach began in the mind of Werner Weitschies, a professor at the University of Greifswald, Germany. Back in 2017, he pitched a concept to the future president of our board, Werner Tschollar – and the two Werners joined forces to create EsoCap.

Essentially, our technology is a piece of mucoadhesive film – loaded with APIs to treat the target disease – that is rolled up tight and



*“By 2019, we had determined that our first indication would be eosinophilic esophagitis.”*

contained within a capsule (alongside a weight that ensures quick swallowing). The capsule is placed into a specifically designed mouthpiece (a special drinking cup) and attached by an API-free “retainer” (think string) that triggers the mechanism. As the capsule descends, the film unrolls and sticks to the patient’s esophageal mucosa. To make Werner’s ambitious dream a reality, each component had to be developed, tested, and adjusted to work harmoniously with each other. That work was completed in 2019.

We conducted our first feasibility study that same year, with 12 healthy volunteers swallowing a test capsule six times each – all monitored with magnetic resonance imaging. These 72 images showed us that our drug delivery film consistently rolls out and onto the esophagus properly, where it remains visible for over 15 minutes (1, 2). The results were a huge milestone for us, but the study also signaled a quantum leap for drug delivery in this part of the body. It is important to remember that we were aiming to beat the 2 seconds of drug exposure provided by conventional tablets or syrups, and the 45 seconds offered by orodispersible tablets. Our delivery platform has been proven to manage a far superior 900 seconds, and with refinement I believe we can manage even longer than that.

In terms of our most current work, earlier this month we signed an exclusive licensing agreement with Upadia, a company that designed specific antibodies for the treatment of Barrett’s disease esophagus and was founded by Sheila Krishnadath, a gastroenterologist and Principal Investigator at Antwerp University Hospital. We plan to

combine EsoCap’s technology with Upadia’s antibodies to advance this promising treatment approach into clinical development.

**How far through the drug approval process are you?**

By 2019, we had determined that our first indication would be eosinophilic esophagitis. We obtained an accelerative orphan drug designation from the FDA, and in 2020 began preparing to launch the first clinical trial. We also submitted dossiers that were accepted by the authorities in four countries: Spain, Germany, Switzerland, and the Netherlands. We are running that phase II trial as a double blind placebo-controlled study on a 42-patient cohort (28 of the participants are taking the drug, and 14 are on placebo). We are also conducting further feasibility work in other indications that we consider to be strategic priorities, such as reflux and Barrett’s disease.

**Will EsoCap be going global?**

EsoCap’s first patents have already been granted in key countries, including the US and Japan. We are also in regular contact with large partners in the industry, and we know they are impressed by our work. They say that our tech is not only unique and unexpected, but also elegant. This is all deeply gratifying, but I want more than praise for our platform. I want it to be used. After all, millions of patients are waiting.

REFERENCES AVAILABLE ONLINE

INTERVIEW

## Join the Resistance

Tackling the issue of antimicrobial resistance

*With Professor Janet Hemingway,  
founding Director of iiCON*

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INTERVIEW

## Prizewinning Pillmaster

What does it take to win awards? For one young scientist, it was quantity, quality, and excellent excipients

*With Alberto Berardi,  
Product Application Specialist  
at DFE Pharma*

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VIDEO

## The Manipulation of Genetic Machinery

How an RNA targeting approach helped patients living with spinal muscular atrophy

Muscle weakness. Joint pain. Breathing difficulties. Spinal muscular atrophy (SMA) is a rare disease that presents patients with myriad physical challenges. But patients and their carers must also deal with the emotional and psychological burden of the condition.

Though a cure does not currently exist, pharma companies are in pursuit of treatments to simplify disease management. Roche's recently approved RNA-targeting small molecule Evrysdi (risdiplam) was designed to manipulate the genetic machinery of cells to restore lost function. Paulo Fontoura, Global Head and SVP of Neuroscience and Rare Diseases Clinical Development at Roche, acknowledges that the approach sounds like science fiction – but it's very real. SMA is caused by a deficiency in survival motor neuron (SMN) protein – the result of a mutation in the SMN1 gene. Evrysdi acts as a splicing modifier of a second gene, called SMN2, which boosts the levels of functional SMN protein (SMN2) in the central nervous system and peripheral tissues.

Bringing this approach to reality alongside partners at PTC Therapeutics has meant that patients worldwide have been able to access treatment. And for its considerable impact on the SMA community, the drug received the British Pharmacological Society's

Drug Discovery of the Year Award. Small molecule drugs are, after all, easier to manufacture than their bio counterparts, potentially increasing accessibility.

In this video, Fontoura shares his views about the company's approach to the production of Evrysdi, as well as his thoughts on the future of small molecule development.

[CLICK HERE TO WATCH THE VIDEO](#)



SITTING DOWN WITH

## Leadership Star

Sitting Down With... Andrew Moore, General Manager of Pfizer CentreOne, Pittsburgh, Pennsylvania, USA

### Did you always want to be a leader?

I thought I wanted to be a lawyer, but I couldn't afford law school. I decided to join the military because my family has a long history of military service. After that, all I knew was that I wanted to be a leader in something... I've always enjoyed leadership roles; at college, I was captain of the university track and field team.

The military is the foundation of my leadership skills. To me, the definition of pure leadership is the ability to get things done through others. This is what the military teaches young officers. When you join, you don't know very much. You have to listen to your sergeants and learn from them, so that you are prepared when the time comes for you to lead in the field.

### How did you get into pharma?

I like to tell this story! In the army, my specialty was nuclear, chemical, and biological warfare, so people associate that with a link to pharma. But the truth is that I fell into the industry in a very different way. One of my soldiers married the daughter of the international president for Baxter. I attended the wedding and the father of the bride and I got along well. In fact, he convinced me to consider working for pharma... and then he actually offered me my first job in the industry! I did some research and realized that it was interesting and could really help people – which was important to me. Pharma also seemed to be at the cutting edge of technology. I wanted to be part of it.

### What was your first role?

It was in sales. I did my whole year's budget in the first nine months and was promoted to product manager. From there, I moved up the rungs of the marketing ladder. I eventually left to work for Becton Dickinson, where I ran North American operations for the hypodermic business. I spent seven years at Pfizer before leading the Northeast region of pharmaceutical distribution and business operations at McKesson. In time, I became CEO of CogxVision and then, in 2020, I joined Pfizer CentreOne. Pfizer is where I experienced the most personal growth in business. It was nice to come home.

### What was it like to start a new role during the pandemic?

I was interviewed via WebEx, joined the team the same way, and still have not met many of my colleagues face-to-face. It is a challenge, but this new environment has also, in some ways, made us more productive. WebEx meetings can help get things done in terms of driving decisions. Previously, you'd be trying to get people from all over the world to come together at one location for a meeting. There is nothing better than face-to-face contact, but there can also be a lot of wasted time. Without COVID-19, I would still be travelling around the world meeting team members globally. Instead, it is all done via WebEx. I've missed out on the opportunity to bond outside of work, but I've met more people across the organization than I would have if I'd been in the office every day.

[READ THE FULL INTERVIEW ONLINE](#)

